

# THE PROMISE OF PRIORITY REVIEW VOUCHERS AS A LEGISLATIVE TOOL TO ENCOURAGE DRUGS FOR NEGLECTED DISEASES

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## ABSTRACT

*Despite the intellectual property system's success in promoting the economic well-being of the United States, this system has not achieved all socially valuable ends. Insufficient treatments are applied both to diseases endemic in developing countries, such as malaria, and rare diseases, such as rare childhood cancers. Several legislative tools aim to promote socially valuable drugs and biologics through market incentives. The priority review voucher (PRV) program is the latest and most unique of these legislative tools aimed at encouraging the development of drugs for neglected diseases without burdening taxpayers. The Creating Hope Act—recently signed into law as part of the Food & Drug Administration Safety & Innovation Act—extends the PRV program to rare pediatric diseases. This Issue Brief argues that some provisions in this new legislation may result in undesirable collateral effects that could prevent the legislation from fulfilling its objective of encouraging investment in treatments for rare pediatric diseases.*

## INTRODUCTION

“Everybody wins,” President Reagan declared from the Rose Garden on the day he signed the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act) into law.<sup>1</sup> The Hatch-Waxman Act sought to carefully “strike[] a balance between two potentially competing policy interests—inducing pioneering development of pharmaceutical formulations and methods and facilitating efficient transition to a market with low-cost, generic copies

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<sup>1</sup> Remarks on Signing S. 1538 into Law, 20 WEEKLY COMP. PRES. DOC. 1359 (Sept. 24, 1984).

of those pioneering inventions at the close of a patent term.”<sup>2</sup> The legislation sought to accomplish this objective by offering distinct incentives for generic manufacturers, pharmaceutical companies, and consumers. For generic manufacturers, the Hatch-Waxman Act promised to hasten generic entry with a mechanism for abbreviated applications for drugs with active ingredients that the FDA had already approved.<sup>3</sup> For pharmaceutical companies, the Hatch-Waxman Act granted up to five additional years of patent protection for new drugs to make up for time spent under regulatory review.<sup>4</sup> Finally, President Reagan estimated that consumers would “save more than a billion dollars over the next 10 years.”<sup>5</sup>

Civilized society has long grappled with the challenge of balancing individual reward with the public good.<sup>6</sup> The Hatch-Waxman Act has achieved much of this balance through meeting its primary goal of bringing low-cost generic drugs to market without burdening consumers.<sup>7</sup> In fact, President Reagan’s estimate that consumers would

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<sup>2</sup> *Novo Nordisk A/S v. Caraco Pharm. Lab., Ltd.*, 601 F.3d 1359, 1360 (Fed. Cir. 2010), *cert. granted*, 131 S. Ct. 3057, 180 L. Ed. 2d 884 (2011), *and rev’d*, 132 S. Ct. 1670, 182 L. Ed. 2d 678 (2012).

<sup>3</sup> Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, § 101, 98 Stat. 1585 (codified as amended at 21 U.S.C. § 355 (2012) and 35 U.S.C. § 156)

<sup>4</sup> *Id.* at § 201.

<sup>5</sup> Remarks on Signing S. 1538 into Law, *supra* note 2.

<sup>6</sup> In Aristotle’s *Politics*, Aristotle condemns as unsafe Hippodamus’s idea of rewarding individuals for discovering things useful to the state. ROBERT PATRICK MERGES & JOHN FITZGERALD DUFFY, *PATENT LAW AND POLICY: CASES AND MATERIALS 1–2* (5th ed. 2011). The United States Constitution also embodies the tension between individual self-interest and social benefit by granting the Congress the power to give inventors exclusive rights to their discoveries overlaid with the objective “To promote the Progress of Science and useful Arts . . .” U.S. CONST. art. I, § 8, cl. 8.

<sup>7</sup> See *GPhA Says New Study Shows that Hatch-Waxman is a Successful Model for Biogenerics Legislation Exclusivity Provisions Similar to Those in Hatch-Waxman Would Promote Competition and Innovation*, GENERIC PHARM. ASS’N (Sept. 17, 2008), <http://www.gphaonline.org/media/press-releases/2009/02/12/gpha-says-new-study-shows-hatch-waxman-successful-model-biogenerics> (“Generics represent 65% of the total prescriptions dispensed in the United States, but only 20% of all dollars spent on prescription drugs.”). *But see, e.g.*, C. Scott Hemphill, *Paying for Delay: Pharmaceutical Patent Settlement As A Regulatory Design Problem*, 81 N.Y.U. L. REV. 1553, 1553 (2006) (“First, certain features of the Act widen, often by subtle means, the potential for anticompetitive harm from pay-for-delay settlements. Second, the Act reflects a congressional judgment favoring litigated challenges, contrary to arguments

save \$1 billion dollars in the first ten years after enactment of the Hatch-Waxman Act may have been considerably understated. The Congressional Budget Office estimated that, in 1994 alone, consumers saved between \$8 and \$10 billion from substituting generic drugs for brand-name drugs.<sup>8</sup>

The U.S. regulatory and patent system, however, has not achieved all socially valuable ends. Social deficiencies are particularly pronounced for diseases endemic in developing countries. Pharmaceutical firms are under a fiduciary responsibility to maximize profits and to recoup their research and development costs (estimated to be \$800 million up to \$12 billion).<sup>9</sup> Consequently, executives often choose to develop more profitable drugs rather than drugs designed to treat diseases endemic in developing countries.<sup>10</sup> For example, as a result of the low per capita income and weak patent protection in developing tropical countries, less than ten percent of global research and development expenditures are focused on neglected tropical diseases. Nevertheless, these diseases “account for over ninety percent of the global disease burden.”<sup>11</sup> This discrepancy between research expenditures and disease burden is known as the “10/90 gap.”<sup>12</sup>

The profound impact that the high risk-to-return ratio for drugs to treat tropical diseases has on deterring investment is even more salient when the category of neglected tropical diseases is subdivided. Some tropical diseases (such as HIV/AIDS and tuberculosis) affect people in

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employed to justify these settlements.”); Matthew Avery, Note, *Continuing Abuse of the Hatch-Waxman Act by Pharmaceutical Patent Holders and the Failure of the 2003 Amendments*, 60 HASTINGS L.J. 171, 173 (2008) (“But the original Act also contained provisions that were exploited by patent holders to delay generic competition, thereby extending their monopoly sales.”).

<sup>8</sup> CONG. BUDGET OFFICE, HOW INCREASED COMPETITION FROM GENERIC DRUGS HAS AFFECTED PRICES AND RETURNS IN THE PHARMACEUTICAL INDUSTRY, at ix (1998), available at <http://www.cbo.gov/publication/10938>.

<sup>9</sup> Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151, 180 (2003) (“[W]e estimated that total R&D cost per new drug is US\$ 802 million in 2000 dollars.”); 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> (“AstraZeneca has spent \$12 billion in research money for every new drug approved . . .”).

<sup>10</sup> James Love & Tim Hubbard, *The Big Idea: Prizes to Stimulate R&D for New Medicines*, 82 CHI.-KENT L. REV. 1519, 1527 (2007).

<sup>11</sup> Ann Weilbaeher, Comment, *Diseases Endemic in Developing Countries: How to Incentivize Innovation*, 18 ANNALS HEALTH L. 281, 284 (2009).

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

both developed and developing countries and therefore receive moderate private investment.<sup>13</sup> Other tropical diseases (such as leishmaniasis, schistosomiasis, and trichuriasis), however, overwhelmingly appear in developing countries and therefore receive little private investment.<sup>14</sup>

Various entities have implemented strategies designed to correct market failures in the patent system and promote the public good. Broadly defined, two strategies have emerged to increase investment in treatments for neglected diseases. The first strategy involves “push” mechanisms. Push mechanisms provide research dollars *ex ante* to reduce initial investment risk.<sup>15</sup> These mechanisms include grants for research and development (R&D), tax credits, and fast-track approval.<sup>16</sup> For example, donors in product development partnerships (PDPs), such as the Bill and Melinda Gates Foundation, will fund a drug developer at the outset or on a stage-by-stage basis.<sup>17</sup> In contrast, the second strategy involves the use of “pull” mechanisms. These mechanisms reward innovation with economic benefits *ex post*,<sup>18</sup> including advanced market commitments (AMCs), market exclusivity provisions, patent term extensions, priority review vouchers, and prizes.<sup>19</sup> The United States Patent and Trademark Office, for example, recently instituted a prize of accelerated processing of future patent applications for patent owners who have used their patents for humanitarian needs.<sup>20</sup>

The U.S. government has instituted several push and pull mechanisms to address the unique market failures in the pharmaceutical industry. These push and pull legislative tools—each of which are aimed at impacting drug development for neglected diseases—include the Orphan Drug Act (ODA),<sup>21</sup> Pediatric Exclusivity Provision in the Food and Drug Administration Modernization Act of 1997 (FDAMA),<sup>22</sup> Best

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<sup>13</sup> ADRIAN TOWSE ET AL., OFFICE OF HEALTH ECON., DRUGS AND VACCINES FOR DEVELOPING COUNTRIES 6 (2011), <http://faculty.fuqua.duke.edu/~dbr1/research/developing-Oxford.pdf>.

<sup>14</sup> *Id.*

<sup>15</sup> *Id.* at 5.

<sup>16</sup> *Id.* at 21.

<sup>17</sup> *Id.* at 22.

<sup>18</sup> *Id.* at 5.

<sup>19</sup> *Id.* at 21.

<sup>20</sup> *Patents for Humanity*, UNITED STATES PATENT AND TRADEMARK OFFICE, [http://www.uspto.gov/patents/init\\_events/patents\\_for\\_humanity.jsp](http://www.uspto.gov/patents/init_events/patents_for_humanity.jsp) (last updated Aug. 20, 2012).

<sup>21</sup> Orphan Drug Act of 1983, Pub. L. No. 97-414, 96 Stat. 2049 (codified as amended in scattered sections of 21 U.S.C., 26 U.S.C., 35 U.S.C., 42 U.S.C.).

<sup>22</sup> Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 111, 111 Stat. 2296 (codified as amended in 21 U.S.C. § 351).

Pharmaceutical Practices for Children Act,<sup>23</sup> Pediatric Research Equity Act,<sup>24</sup> and the Food and Drug Administration Amendments Act of 2007, which instituted a priority review voucher (PRV) program.<sup>25</sup> The PRV program rewards developers of neglected tropical disease products *ex post*. The reward consists of transferable vouchers for future priority review on a subsequent drug or biologic before the Food and Drug Administration (FDA).<sup>26</sup> By promising to incentivize the development of tropical disease products without burdening taxpayers or delaying generic entry, the PRV program seeks to benefit all constituents including disease sufferers, innovators, and taxpayers.<sup>27</sup>

The latest legislative pull mechanism aimed at encouraging investment in drugs for neglected diseases is the Creating Hope Act of 2011, which was enacted in July 2012 as part of the Food and Drug Administration Safety and Innovation Act (FDASIA). The Act was specifically designed to extend the PRV program from simply rewarding developers of tropical disease drugs to rewarding developers of rare pediatric disease products.<sup>28</sup> A rare disease, or “orphan disease,” is a disease that affects less than 2-7 individuals per 10,000 in a country.<sup>29</sup> Companies tend to invest little in drugs to treat these rare diseases because they are unlikely to recoup their development costs. Drug developers’ hesitancy is manifest: the FDA last approved a new molecular entity for treating pediatric cancer over twenty years ago.<sup>30</sup> Although the PRV program, like the Hatch-Waxman Act, has great potential to ensure that “everybody wins,” several provisions in the new legislation may actually undermine that objective.

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<sup>23</sup> Best Pharmaceuticals for Children Act, Pub. L. No. 107-109, 115 Stat. 1408 (2002) (codified as amended in scattered sections of 21 U.S.C. and 42 U.S.C.).

<sup>24</sup> Pediatric Research Equity Act of 2003, Pub. L. No. 108-155, 117 Stat. 1936 (codified as amended in scattered sections of 21 U.S.C. and 42 U.S.C.).

<sup>25</sup> Pub. L. No. 110-85, 121 Stat. 823 (codified as amended in scattered sections of 21 U.S.C. and 42 U.S.C.).

<sup>26</sup> David B. Ridley, Henry G. Grabowski & Jeffrey L. Moe, *Developing Drugs for Developing Countries*, 25 HEALTH AFF. 313, 313-15 (2006).

<sup>27</sup> *Id.* at 319-21.

<sup>28</sup> Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112—144, § 908, 126 Stat. 993 (2012) (codified in 21 U.S.C. § 360ff).

<sup>29</sup> D.A. Hughes et al., *Drugs for Exceptionally Rare Diseases: Do They Deserve Special Status for Funding?*, 98 QJM 829, 829 (2005).

<sup>30</sup> Steven Hirschfeld et al., *Regulatory Approvals of Pediatric Oncology Drugs: Previous Experience and New Initiatives*, 21 J. CLIN. ONCOLOGY 1066 (2003) (FDA approved teniposide for childhood leukemia in 1992).

## I. EXISTING LEGISLATIVE TOOLS FOR PROMOTING SOCIALLY VALUABLE DRUGS AND BIOLOGICS

### A. Orphan Drug Act of 1983

The Orphan Drug Act (ODA) seeks to encourage the development of drugs for neglected diseases through providing market incentives. “The ODA was enacted in order to provide drug manufacturers with incentives to develop ‘orphan’ drugs—that is, drugs for the treatment of rare diseases or disorders that affect only small patient populations.”<sup>31</sup> The FDA deems a condition “rare” if it “affects less than 200,000 persons in the United States” or if “there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug.”<sup>32</sup> Even a disease like cholera, with 3–5 million cases worldwide, may qualify as an orphan disease under the ODA because it affects only approximately ten individuals living within the United States each year.<sup>33</sup>

The market incentives provided by the ODA include seven years of market exclusivity—even without a patent—tax credits for up to fifty percent of qualified clinical testing expenses, and research grants for clinical testing of new drugs for rare diseases.<sup>34</sup> Of these market incentives, the Office of Health and Human Services (HHS) concluded—based on interviews with thirty-six biotechnology and pharmaceutical companies—that drug-producing entities valued market exclusivity as the most important incentive in the ODA.<sup>35</sup> Despite the fact that competition for most orphan products is sparse, these entities believed that the assurance of market exclusivity helped them secure public and private capital.<sup>36</sup>

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<sup>31</sup> *Sigma-Tau Pharm., Inc. v. Schwetz*, 288 F.3d 141, 144 (4th Cir. 2002).

<sup>32</sup> 21 U.S.C. § 360bb(a)(2) (2008).

<sup>33</sup> *Cholera*, WORLD HEALTH ORG. (July 2012), <http://www.who.int/media/centre/factsheets/fs107/en/>; E. Steinberg, et al., *Cholera in the United States, 1995-2000: Trends at the End of the Twentieth Century*, 184 J. INFECTIOUS DISEASES 799, 800 (2001).

<sup>34</sup> Orphan Drug Act of 1983, Pub. L. No. 97-414, §§ 2(a), 3, 5, 96 Stat. 2049 (codified as amended in scattered sections of 21 U.S.C., 26 U.S.C., 35 U.S.C., and 42 U.S.C.).

<sup>35</sup> OFFICE OF INSPECTOR GEN., DEP’T OF HEALTH & HUMAN SERV., THE ORPHAN DRUG ACT – IMPLEMENTATION AND IMPACT 8 (2001).

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

HHS concluded that the ODA “unquestionably stimulated the development [of new drugs] for rare diseases.”<sup>37</sup> During the ten years preceding the ODA’s enactment, only ten drugs for rare diseases were approved by the FDA and brought to market.<sup>38</sup> In the seventeen years following the ODA’s enactment in 1983, however, approximately 200 drugs for rare diseases were approved by the FDA.<sup>39</sup> Moreover, from 1979 to 1998, the number of available drugs for rare diseases increased by over 500 percent, dwarfing the 200 percent growth of non-orphan drugs.<sup>40</sup> Further highlighting the success of the ODA in increasing the availability of orphan drugs, patient groups report experiencing few shortages of these orphan drugs even though the ODA makes no requirement that the sponsors market and distribute the drugs.<sup>41</sup>

## B. Pediatric Exclusivity Provision and Subsequent Legislation

Although the ODA led to breakthroughs in treating some rare diseases,<sup>42</sup> the pharmaceutical industry still lacked pediatric formulations for treating a broad range of diseases. Many companies had no incentive to test their drugs on pediatric populations.<sup>43</sup> As a result, physicians had little choice but to prescribe drugs to children that had only been tested in adults. Because children have markedly different physiology than adults, prescribing adult drugs to children put them at risk for adverse reactions.<sup>44</sup> A recent study found, for example, that extrapolating pediatric dosages from adult dosages with weight-based calculations could be both harmful and ineffective.<sup>45</sup> These harmful effects may occur because children’s bodies clear drugs at different rates than adults depending on their maturation stage.<sup>46</sup>

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<sup>37</sup> *Id.* at 7.

<sup>38</sup> Marlene E. Haffner, *Adopting orphan drugs—Two Dozen Years of Treating Rare Diseases*, 354 NEW ENG. J. MED. 445, 445 (2006).

<sup>39</sup> OFFICE OF INSPECTOR GEN., *supra* note 36, at 7.

<sup>40</sup> Frank R. Lichtenberg & Joel Waldfogel, *Does Misery Love Company? Evidence from Pharmaceutical Markets Before and After the Orphan Drug Act* 3 Fig.1 (Nat’l Bureau of Econ. Research, Working Paper No. W9750, 2003), available at <http://www.nber.org/papers/w9750>.

<sup>41</sup> OFFICE OF INSPECTOR GEN., *supra* note 36, at 9.

<sup>42</sup> *Id.* at 7.

<sup>43</sup> Aaron S. Kesselheim, *Using Market-Exclusivity Incentives to Promote Pharmaceutical Innovation*, 363 NEW ENG. J. MED. 1855, 1859 (2010).

<sup>44</sup> *Id.*

<sup>45</sup> William Rodriguez et al., *Improving Pediatric Dosing Through Pediatric Initiatives: What We Have Learned*, 121 PEDIATRICS 530, 530 (2008).

<sup>46</sup> *Id.*

Congress has passed several legislative acts to ameliorate the deficiency in drugs to treat pediatric diseases. The Pediatric Exclusivity Provision in the Food and Drug Administration Modernization Act of 1997 (FDAMA) awards a drug sponsor with six months of additional marketing exclusivity when the sponsor conducts timely pediatric studies.<sup>47</sup> The Best Pharmaceuticals for Children Act (BPCA) encourages more research on drugs for children.<sup>48</sup> In 2007, Congress passed legislation requiring the National Institutes of Health (NIH) to publish a priority list of needs in pediatric pharmaceuticals.<sup>49</sup> The Pediatric Research Equity Act (PREA) of 2003 granted the FDA authority to require research for certain drugs used in pediatric populations.<sup>50</sup> Finally, in 2009, the Biologics Price Competition and Innovation Act extended the BPCA to biologics, as well as substances derived from biological sources used to treat diseases.<sup>51</sup>

These legislative acts provide strong incentives to drug sponsors to conduct pediatric studies. The Institute of Medicine—the health arm of the National Academy of Sciences—has concluded that these legislative acts have been largely successful.<sup>52</sup> In 1998, the year just after FDAMA’s passage, drug labels were changed to reflect pediatric dosing information for only three products.<sup>53</sup> In 2009, however, the FDAMA resulted in over forty drug labels changing to reflect pediatric information.<sup>54</sup> Furthermore, by 2005, approximately 108 drug products

<sup>47</sup> Pub. L. No. 105-115, § 111, 111 Stat. 2296 (codified as amended in scattered sections of 21 U.S.C.).

<sup>48</sup> Pub. L. No. 107-109, § 3, 115 Stat. 1408 (2002) (codified as amended in scattered sections of 42 U.S.C.).

<sup>49</sup> Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 502, 121 Stat. 823 (codified as amended in scattered sections of 21 U.S.C. and 42 U.S.C.) (“[T]he Secretary, acting through the Director of the National Institutes of Health . . . shall develop and publish a priority list of needs in pediatric therapeutics, including drugs or indications that require study.”).

<sup>50</sup> Pediatric Research Equity Act of 2003, Pub. L. No. 108-155, § 2, 117 Stat. 1936 (codified as amended in scattered sections of 21 U.S.C. and 42 U.S.C.).

<sup>51</sup> Biologics Price Competition & Innovation Act of 2009, Pub. L. No. 111-148, § 7002(a), (b), (g)(1), 124 Stat. 119 (2010) (codified as amended in 42 U.S.C. § 262(a)(2)(B)).

<sup>52</sup> See INST. OF MED. OF NAT’L ACAD., REPORT BRIEF: SAFE AND EFFECTIVE MEDICINES FOR CHILDREN: PEDIATRIC STUDIES CONDUCTED UNDER THE BEST PHARMACEUTICALS FOR CHILDREN ACT AND THE PEDIATRIC RESEARCH EQUITY ACT 1 (2012), available at <http://www.iom.edu/Reports/2012/Safe-and-Effective-Medicines-for-Children.aspx>. But see Kesselheim, *supra* note 43, at 1859.

<sup>53</sup> *Id.* at 2 fig.

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



had undergone pediatric testing largely because of the FDAMA.<sup>55</sup> Approximately one-fifth of these pediatric tests resulted in significant label changes because of younger patients' lower or higher rates of clearing drugs from their systems.<sup>56</sup>

### C. Priority Review Vouchers (PRV) in the Food & Drug Administration Amendments Act of 2007

#### 1. *The idea behind Priority Review Vouchers (PRVs)*

Recognizing the financial barriers to developing drugs for neglected tropical diseases, Professors Ridley, Grabowski, and Moe (hereinafter Ridley et al.) at Duke University proposed a plan to link the development of essential drugs for diseases endemic in developing countries with priority FDA approval for more profitable drugs.<sup>57</sup> Under Ridley et al.'s novel proposal, a drug sponsor earns a PRV when it develops a drug to treat a neglected tropical disease.<sup>58</sup> The drug sponsor can then redeem the PRV for expedited FDA review of any other drug, even non-essential or mass-market medicines that are potentially highly profitable.<sup>59</sup> Before PRVs existed, the FDA only granted priority review in limited circumstances such as for drug products "where no satisfactory alternative therapy exists" or that represented "significant improvement compared to marketed products."<sup>60</sup> Priority review itself provides a significant advantage to drug manufacturers, as it can reduce regulatory review by up to seven months.<sup>61</sup> Ridley et al. estimated that a PRV "would be worth more than \$300 million for a potential blockbuster

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<sup>55</sup> Rodriguez, *supra* note 45, at 531.

<sup>56</sup> *Id.*

<sup>57</sup> Ridley, *supra* note 26, at 313.

<sup>58</sup> *Id.* at 313–314.

<sup>59</sup> *Id.* at 314.

<sup>60</sup> OFFICE OF NEW DRUGS, CTR. FOR DRUG EVALUATION & RESEARCH, MAPP 6020.3, REVIEW CLASSIFICATION POLICY: PRIORITY (P) AND STANDARD (S) 5 (2007).

<sup>61</sup> SUSAN THAUL, CONG. RESEARCH SERV., RS 22814, FDA FAST TRACK AND PRIORITY REVIEW PROGRAMS 5 tbl.2 (2008) (finding that the median approval time for all standard NDAs and BLAs was 13 months in 2006 and for all priority NDAs and BLAs was 6 months in 2006).

drug, because it would shorten the time the FDA takes to analyze data from an average of eighteen months to about six months.”<sup>62</sup>

PRV’s estimated monetary value can be illustrated by applying a hypothetical PRV to a past “blockbuster” drug that had undergone only standard review. The FDA approved the antihistamine Allegra, produced by Hoechst Marion Roussel, Inc., in July 1996 through standard review.<sup>63</sup> Allegra achieved sales of at least \$1 billion by its fifth year after product launch.<sup>64</sup> If Hoechst had used a PRV for Allegra, however, it might have received FDA approval in July of 1995, and consequently reaped the benefit of entering the market one year earlier than with standard review.<sup>65</sup> According to Ridley et al., not only would pharmaceutical companies like Hoechst financially benefit from priority review, but consumers would also benefit by gaining access to the drug earlier.<sup>66</sup> Perhaps most significant, priority review rewards the pharmaceutical company without harming consumers because PRVs do not increase patent terms or delay generic pharmaceutical entry.<sup>67</sup>

Ridley et al. proposed two ways drug sponsors like Hoechst could obtain a PRV.<sup>68</sup> First, the FDA could award a PRV to drug sponsors for developing a drug to treat a neglected tropical disease, such as dengue fever. Because PRVs do not expire, the drug sponsor can save its PRV for expedited review of any future drug. Second, one drug sponsor can purchase a PRV from another drug sponsor, which allows drug sponsors with few drug products in their product pipeline to sell their PRVs to those better positioned to use them. In either scenario, the market incentive provides both social and private welfare gains.<sup>69</sup>

The PRV program adeptly seeks these economic and social benefits without requiring public financing or delaying generic entry. Ridley et al.’s article proposed that the FDA charge drug sponsors a PRV user fee to cover the extra costs of the program so the burden does not

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<sup>62</sup> In the 1990s, about half of drugs that went on to become “blockbuster drugs” had received priority review. The other half received standard review. See Ridley, *supra* note 26, at 315. *But see* THAUL, *supra* note 62.

<sup>63</sup> Ridley, *supra* note 26, at 314.

<sup>64</sup> *Id.*

<sup>65</sup> See *id.* at 315. *But see* THAUL, *supra* note 61, at 4 (noting that the decision time for FDA approval can vary greatly, and therefore may not be one year longer than for priority review, depending on various factors such as staff constraints at the FDA and completeness of the application).

<sup>66</sup> Ridley, *supra* note 26, at 315.

<sup>67</sup> *Id.* at 320.

<sup>68</sup> *Id.* at 313.

<sup>69</sup> See *id.* at 315.

fall on taxpayers.<sup>70</sup> Partly due to strong bipartisan support because of the budget-neutral promise, Congress enacted the PRV provision in the Food & Drug Administration Amendments Act of 2007 (FDAAA), just a year and a half after Ridley et al. first published their proposal.<sup>71</sup>

## 2. The legislation creating PRVs

Section 360n of the Food & Drug Administration Amendments Act of 2007 (FDAAA) includes several important limitations on the granting of PRVs. First, the Secretary of Health and Human Services may only grant a PRV for a drug that treats a tropical disease such as tuberculosis, malaria, cholera, dengue haemorrhagic fever, leprosy or “[a]ny other infectious disease for which there is no significant market in developed nations and that disproportionately affects poor and marginalized populations, designated by regulation by the Secretary.”<sup>72</sup> Second, the Secretary may only grant a PRV for a drug with an active ingredient that has never been approved in any other New Drug Application (NDA) or Biologics License Application (BLA).<sup>73</sup> Third, the tropical disease product must qualify for priority review to have a chance of winning a PRV.<sup>74</sup> Although the drug treating a tropical disease must qualify for priority review to win a PRV, once the drug sponsor wins the PRV it gains priority review for any subsequent drug that would otherwise qualify only for standard review.

In addition to limits on the grant of PRVs, § 360n also includes limits on the use of PRVs. To redeem a PRV, a drug sponsor must do two things. First, the drug sponsor must notify the FDA of its intent to redeem the voucher one year before it submits a NDA.<sup>75</sup> Second, a drug sponsor must pay a user fee to cover the extra costs incurred by the FDA’s priority review.<sup>76</sup> For fiscal year 2013, this user fee is \$3.6 million.<sup>77</sup> The drug sponsor becomes “legally committed” to pay the user fee when it notifies the FDA of its intent to use the PRV one year

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<sup>70</sup> *Id.* at 315.

<sup>71</sup> Food & Drug Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (codified as amended in scattered sections of 21 U.S.C.).

<sup>72</sup> 21 U.S.C. § 360n(a)(3) (2011).

<sup>73</sup> § 360n(a)(4)(C).

<sup>74</sup> FOOD & DRUG ADMIN., DRAFT GUIDANCE FOR TROPICAL DISEASE PRIORITY REVIEW VOUCHERS 2 (2008) [hereinafter *Draft Guidance*].

<sup>75</sup> § 360n(b)(4).

<sup>76</sup> § 360n(c)(1).

<sup>77</sup> Fee for Using a Priority Review Voucher in Fiscal Year 2013, 77 Fed. Reg. 56649-01 (Sept. 13, 2012).

before applying.<sup>78</sup> To make the voucher attractive to even small drug sponsors that do not have any potential “blockbusters” in their pipeline, a drug sponsor that receives a PRV may “transfer (including by sale) the entitlement to such voucher” to another entity.<sup>79</sup> This right to transfer the PRV promotes economic efficiency by allowing a drug sponsor to sell the PRV to an entity better situated to profit from its use.

Under § 360n of the FDAAA, a PRV “entitles the holder of such voucher to priority review of a single human drug application . . . .”<sup>80</sup> When a drug sponsor redeems the voucher, the Secretary of Health and Human Services must “review and take action on” the application within six months.<sup>81</sup> The phrase “review and take action on” does not guarantee approval. Instead, within six months, an applicant will receive either approval or an action letter “set[ting] forth in detail the specific deficiencies that need to be addressed before the application can be approved.”<sup>82</sup> The FDA aims for, but does not guarantee, priority review in six months—four months faster than its goal for standard review<sup>83</sup> and seven months faster than its median standard approval time in 2006.<sup>84</sup>

Although § 360n largely followed Ridley et al.’s proposal for granting and using PRVs, the legislation included a few important differences. Both Ridley et al.’s proposal and § 360n limit the grant of PRVs to drugs that treat neglected tropical diseases. Ridley et al.’s proposal, however, included more provisions aimed at maximizing the social benefit of these drugs. The proposal envisioned limiting the grant of PRVs to companies that developed drugs or biologics exhibiting clinical superiority to existing treatments, companies that had foregone patent rights to the product, and companies that had identified at least one manufacturer for the tropical disease product. The impetus behind this limitation was a desire to increase the odds that the awardee would actually make the drug available.<sup>85</sup> Furthermore, Ridley et al.’s proposal also suggested that the FDA adjust the incentive for developing treatments for neglected tropical diseases as needed by offering multiple PRVs.<sup>86</sup> Despite these suggestions, no such flexibility exists in the

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<sup>78</sup> DRAFT GUIDANCE, *supra* note 75, at 2.

<sup>79</sup> 21 U.S.C. § 360n(b)(2).

<sup>80</sup> § 360n(a)(2).

<sup>81</sup> § 360n(a)(1).

<sup>82</sup> DRAFT GUIDANCE, *supra* note 75, at 4.

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

<sup>84</sup> THAUL, *supra* note 61, at 5 tbl.2.

<sup>85</sup> Ridley, *supra* note 26, at 314.

<sup>86</sup> *Id.* at 319.

current legislation,<sup>87</sup> and it is unclear why these provisions were not included.

The PRV program, developed from Ridley et al.'s proposal, works in tandem with other legislative tools toward promoting investment in neglected disease products. The FDA's 2008 Guidance for the PRV program indicated that a tropical disease product qualifying for a PRV would likely also qualify for benefits under the Orphan Drug Act (ODA).<sup>88</sup> The incentive to develop a drug for a rare tropical disease under the PRV program should be even greater when paired with ODA incentives, such as tax credits on R&D costs. Based on Ridley et al.'s calculations, the drug sponsor would receive a net benefit of approximately \$570 million from a PRV. This includes approximately \$321 million from the PRV itself, plus approximately \$252 million in tax credits from the ODA. Together, the benefit from the PRV and the ODA exceed the mean clinical trial cost of \$504 million of all drugs (in 2004 dollars).<sup>89</sup> Additionally, a drug sponsor would receive goodwill for developing a drug that treats a neglected tropical disease.<sup>90</sup>

### 3. Criticism of the PRV program

Although the PRV program seeks to promote the development of drugs with social value, some scholars argue that the PRV program is inefficient at best and dangerous at worst.<sup>91</sup> For example, Kesselheim, a research associate in Harvard's School of Public Health, opines that the PRV program "is inefficient because the program does not directly connect the incentive with the innovation."<sup>92</sup> Furthermore, although companies without "blockbuster" drugs in their pipeline can sell the voucher to companies that are better situated to use it, Kesselheim claims that such deals will lack transparency and "raise the cost or restrict the future availability of the products."<sup>93</sup> Other potential inefficiencies include the criticism that the PRV legislation does not allow the FDA to vary the reward based upon the utility of the drug.<sup>94</sup>

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<sup>87</sup> See 21 U.S.C. § 360n (2011).

<sup>88</sup> DRAFT GUIDANCE, *supra* note 75, at 7.

<sup>89</sup> Ridley, *supra* note 26, at 319.

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

<sup>91</sup> Aaron S. Kesselheim, *Drug Development for Neglected Diseases — The Trouble with FDA Review Vouchers*, 359 NEW ENG. J. MED. 1981, 1981 (2008).

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

<sup>93</sup> *Id.*

<sup>94</sup> See *id.*

Some scholars also fear that PRVs will compromise drug safety.<sup>95</sup> Traditionally, the FDA only granted priority review when a drug was a “[m]ajor advancement in treatment or treatment where no adequate therapy exists.”<sup>96</sup> Conversely, with a PRV, a company may obtain priority review for drugs with little clinical value. Kesselheim argues that the safety risks inherent in priority FDA review are justified only for drugs treating “serious problems.”<sup>97</sup> Ridley et al., however, argue that drugs that underwent expedited FDA review did not have a higher rate of safety problems than drugs that underwent standard review.<sup>98</sup> Therefore, as demonstrated by Ridley et al., the PRV program will not compromise drug safety.

The FDA’s *Draft Guidance for Priority Review Vouchers* highlights other possible limits of the PRV program. First, a sponsor may win a PRV whether or not it markets the product.<sup>99</sup> Without guaranteed marketing of the product, the program may not fulfill its goal of increasing the availability of drugs for the developing world. Second, drugs that have already been approved for another indication<sup>100</sup> or already approved for adults cannot receive a PRV.<sup>101</sup> By forbidding PRV grants to drugs with active ingredients that the FDA previously approved, the program may fail to incentivize new pediatric formulations or new combination products that include known drugs. Another legislative shortcoming is manifest within the requirement that the drug sponsor notify the FDA of its intent to use a PRV one year before it submits its application.<sup>102</sup> Once the sponsor notifies the FDA, it is legally bound to pay the user fee.<sup>103</sup> Considering the uncertainties that accompany drug development and the magnitude of the user fee (\$3.6

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<sup>95</sup> See *id.* at 1982.

<sup>96</sup> THAUL, *supra* note 62, at 3 tbl.1.

<sup>97</sup> See Kesselheim, *supra* note 92, at 1982.

<sup>98</sup> Ridley, *supra* note 26, at 321–22.

<sup>99</sup> DRAFT GUIDANCE, *supra* note 74, at 5 (“Q6. Would eligibility to receive a priority review voucher be affected in any way by whether the sponsor intends to market or distribute the qualifying tropical disease product after approval? No, it does not matter if the sponsor decides not to market the product.”).

<sup>100</sup> *Id.* at 7 (“For an application to qualify, it must be for a human drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application . . .”).

<sup>101</sup> *Id.* (“Q18. Would a new pediatric formulation for a drug already approved for adults be eligible? No. . . . [A]n application for a product containing a previously approved drug is not eligible to receive a tropical disease priority review voucher.”).

<sup>102</sup> *Id.* at 5.

<sup>103</sup> *Id.*

million for Fiscal Year 2013), committing to using a PRV one year in advance is a financially precarious prospect for the drug sponsor.

#### 4. *The first grant and use of a PRV*

Because the PRV program is relatively new, “the actions of the FDA in how it handles the priority review vouchers will help shape the success of the tropical disease incentive program.”<sup>104</sup> Since the PRV program’s inception, the pharmaceutical industry has had the chance to observe only one PRV grant and one redemption of a PRV. The first grant and use of a PRV answered some questions, but many remain.

Swiss-based Novartis received the first priority review voucher in 2009 for its anti-malarial drug Coartem (a combination of two existing drugs: artemether and lumefantrine).<sup>105</sup> Coartem met all of the PRV grant requirements: it treated a tropical disease, qualified for priority review, and had never before been approved by the FDA. However, even though the FDA had never before approved the active ingredients in Coartem, these active ingredients had been in use in the developing world since 2001.<sup>106</sup> Critics of the PRV program argued that the FDA provided an “undeserved windfall” to Novartis because the active ingredients were not novel.<sup>107</sup> Supporters of the PRV program acknowledged that the first awardee may have received the PRV simply through serendipity, but argued that the program would still incentivize the development of novel drugs over time.<sup>108</sup>

Novartis waited until 2011 to redeem its voucher for priority review on its supplemental biologics license application (sBLA) for Ilaris

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<sup>104</sup> Kyle Wamstad, Note, *Priority Review Vouchers — A Piece of the Incentive Puzzle*, 14 VA. J.L. & TECH. 126, 144 (2009).

<sup>105</sup> *First FDA Priority Review Voucher Awarded*, 8.5 NATURE REVIEWS: DRUG DISCOVERY 347, 347 (2009).

<sup>106</sup> *First Priority Review Voucher Wasted*, 10 NATURE REVIEWS: DRUG DISCOVERY 721, 721 (2011).

<sup>107</sup> Aaron S. Kesselheim, *Priority Review Vouchers: An Inefficient and Dangerous Way to Promote Neglected-Disease Drug Development*, 85 CLINICAL PHARMACOLOGY AND THERAPEUTICS 573, 574 (2009); Wamstad, *supra* note 105, at 127–28 (“Herein lies the problem: there is no need to encourage an innovation already in wide use throughout the developing world.”).

<sup>108</sup> Wamstad, *supra* note 105, at 128 (“One of the original authors of the policy paper, Jeffrey Moe, acknowledges that the first applicants for a qualifying voucher ‘will get them essentially by serendipity’ . . .”).

(canakinub) to treat gouty arthritis.<sup>109</sup> However, rather than the early approval Novartis hoped for, the FDA requested additional clinical data on the risks to patients.<sup>110</sup> After this result, critics of the PRV program pointed out that Novartis paid a \$5,280,000 priority voucher user fee on top of the sBLA fee without receiving any benefit.<sup>111</sup>

The criticisms of the first PRV award to Novartis for Coartem and the subsequent first use of the PRV for Ilaris may be greatly exaggerated. Regardless of the request for more clinical data, the total review time for Coartem still outpaced standard review.<sup>112</sup> BIO Ventures for Global Health points out that “[i]t is important to keep in mind that the PRV program was never designed to produce a *different* outcome upon FDA review, but simply a *faster* outcome.”<sup>113</sup> The claimed “failures” of the first grant and use of a PRV may actually be successes, demonstrating the FDA’s commitment to honoring the vouchers without compromising safety and providing future voucher holders with more guidance on how to maximize the voucher’s value.<sup>114</sup>

A recent survey shed light on certain reservations held by drug companies with regard to the PRV program.<sup>115</sup> The survey revealed that most companies viewed the PRV program as an additional factor, but not the deciding factor, in their decision to pursue drugs or vaccines for neglected tropical diseases.<sup>116</sup> The potential market value of the drug or vaccine was still the overriding factor in a company’s decision to instigate research.<sup>117</sup> Companies expressed concern over not knowing the true value of the voucher and also worried that the FDA would not support the program.<sup>118</sup> Companies said they would consider the PRV program more of an incentive after “a demonstrated sale of a voucher, with the purchase price disclosed to developers.”<sup>119</sup> However, given the

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<sup>109</sup> Bethany Hughes, *Priority Voucher Flops*, 29 NATURE BIOTECHNOLOGY 958, 958 (2011).

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

<sup>111</sup> *Id.*

<sup>112</sup> *Novartis Plays its PRV Card*, BIO VENTURES FOR GLOBAL HEALTH (July 8, 2011), <http://www.bvgh.org/News/Dispatches-from-the-Crossroads/PostID/71.aspx>.

<sup>113</sup> *Id.*

<sup>114</sup> *First Priority Review Voucher Wasted*, *supra* note 106, at 721.

<sup>115</sup> Andrew S. Robertson et al., *The Impact of the US Priority Review Voucher on Private-Sector Investment in Global Health Research and Development*, 6 PLOS NEGLECTED TROPICAL DISEASE 1 (2012).

<sup>116</sup> *Id.* at 5.

<sup>117</sup> *Id.* at 2.

<sup>118</sup> *Id.* at 3.

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



fact that drug development takes several years, the PRV program's success or failure cannot be evaluated so quickly.<sup>120</sup> In fact, the potential benefits of the PRV program are still so attractive that Congress recently extended the program to rare pediatric diseases.<sup>121</sup>

## II. CREATING HOPE ACT

President Obama signed the Creating Hope Act (CHA) into law as part of the Food & Drug Administration Safety & Innovation Act (FDASIA) on July 9, 2012.<sup>122</sup> The CHA aims to ameliorate perceived weaknesses in the original PRV program and extend the program to drugs for rare pediatric diseases.<sup>123</sup> A rare pediatric disease is one that “primarily affects individuals from birth to 18 years, including age groups often called neonates, infants, children and adolescents.”<sup>124</sup> In March 2011, Senator Bob Casey introduced the bill to “strengthen a cost-neutral FDA program giving biopharmaceutical companies an incentive to develop treatments for rare diseases that are often less profitable than treatments for more common medical conditions.”<sup>125</sup> Nancy Goodman, founder of the *Kids v. Cancer* advocacy organization and a champion for the Creating Hope Act, similarly believes the Act will “encourage the creation of new drugs for underserved children who suffer from serious and rare medical conditions, including life-threatening cancers . . . .”<sup>126</sup>

### A. Differences Between the PRV Legislation for Rare Pediatric Diseases and the PRV Legislation for Neglected Tropical Diseases

The legislation for rare pediatric diseases largely mirrors the original PRV legislation for neglected tropical diseases, but with some important differences. First, new 21 U.S.C. § 360ff will increase economic efficiency by making explicit that entities may transfer a PRV

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<sup>120</sup> Hughes, *supra* note 110, at 958.

<sup>121</sup> Creating Hope Act, H.R. 3059, 112th Cong. § 2 (2011).

<sup>122</sup> Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, § 908, 126 Stat. 993 (2012) (codified in 21 U.S.C. § 360ff).

<sup>123</sup> Creating Hope Act, H.R. 3059, 112th Cong. § 2 (2011).

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

<sup>125</sup> *Casey Introduces Bipartisan Bill to Help Develop Treatments for Rare Diseases*, ROBERT P. CASEY JR., UNITED STATES SENATOR FOR PENNSYLVANIA (Mar. 17, 2011), <http://www.casey.senate.gov/newsroom/press/release/?id=a8deb1ac-6ffd-424b-84b9-c166b4d6ff73>.

<sup>126</sup> *Creating Hope Act of 2011 – A Priority Review Voucher for Pediatric Rare Diseases*, KIDS V. CANCER, <http://www.kidsvcancer.org/thecreatinghopeact/> (last visited Oct. 21, 2012).

an unlimited number of times.<sup>127</sup> The original PRV program, codified in § 360n, left open the question of whether the voucher could be sold to another entity.<sup>128</sup> By making explicit that entities may sell the voucher an unlimited number of times, the CHC reduces the perceived risk for the voucher's would-be purchaser.

Second, new § 360ff reduces the period required for notifying the FDA of intent to use the voucher from 365 days to 90 days before use.<sup>129</sup> This change makes voucher use less risky for a drug sponsor. Because the notification of a drug sponsor's intent to redeem the voucher is "a legally binding commitment"<sup>130</sup> to pay a \$3.6 million fee,<sup>131</sup> drug sponsors desire as much clinical data as possible before committing to redeem the voucher. The ninety-day requirement balances the drug sponsor's need for gathering data before committing and the FDA's need for adequate advanced notice to gather enough resources for the priority review process.

Third, the CHA allows the new drug sponsor to obtain a designation at the beginning of the application process that the drug is an eligible treatment for a rare pediatric disease.<sup>132</sup> With this early designation, the drug sponsor is assured that it will receive a voucher if the drug is approved. By contrast, under the original PRV legislation, drug sponsors remain uncertain about whether the drug is even eligible

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<sup>127</sup> Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, § 908, 126 Stat. 993 (2012) ("There is no limit on the number of times a priority review voucher may be transferred before such voucher is used.").

<sup>128</sup> 21 U.S.C. § 360n(b)(2) (2011) ("The sponsor of the tropical disease product that receives a priority review voucher under this section may transfer (including by sale) the entitlement to such voucher to a sponsor of a human drug for which an application . . . will be submitted . . .").

<sup>129</sup> Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, § 908, 126 Stat. 993 (2012) ("The sponsor of a human drug application shall notify the Secretary not later than 90 days prior to submission of the human drug application that is the subject of a priority review voucher of an intent to submit the human drug application . . .").

<sup>130</sup> 21 U.S.C. § 360n(b)(4) (2011).

<sup>131</sup> Fee for Using a Priority Review Voucher in Fiscal Year 2013, 77 Fed. Reg. 56649-01 (Sept. 13, 2012).

<sup>132</sup> Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, § 908, 126 Stat. 993 (2012) ("Upon the request of the manufacturer or the sponsor of a new drug, the Secretary may designate . . . the application for the new drug as a rare pediatric disease product application.").

for a PRV until the FDA grants or denies approval.<sup>133</sup> Like the provisions for clarifying transferability and reducing the length of notification, the early designation provision makes the PRV program less risky for a drug sponsor.

Fourth, the CHA requires an assessment of the PRV program after the FDA has awarded three PRVs, and allows termination of the PRV program at that time.<sup>134</sup> The Government Accountability Office is instructed to “conduct a study of the effectiveness of awarding rare pediatric disease priority vouchers under this section in the development of human drug products that treat or prevent such diseases.”<sup>135</sup> This provision allows an independent assessment of the efficacy of the program, which was lacking from the original PRV legislation.

## B. Collateral Effects of the CHA

Although the transfer, notification, and designation provisions in the CHA go a long way toward encouraging the use of PRVs, some provisions may have collateral effects.<sup>136</sup> First, the CHA may fail to incentivize the development of the most promising new treatments for rare pediatric diseases. The CHA prohibits drug sponsors from receiving a PRV for a rare pediatric disease product with active ingredients that the FDA has approved in any other application.<sup>137</sup> Although such a provision is helpful for preventing gamesmanship when applied to tropical disease

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<sup>133</sup> 21 U.S.C. § 360n(b)(1) (2011) (“The Secretary shall award a priority review voucher to the sponsor of a tropical disease product application *upon approval* by the Secretary . . .”) (emphasis added).

<sup>134</sup> Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, § 908, 126 Stat. 993 (2012) (“The Secretary may not award any priority review vouchers under paragraph (1) after the last day of the 1-year period that begins on the date that the Secretary awards the third rare pediatric disease priority voucher under this section.”).

<sup>135</sup> *Id.*

<sup>136</sup> *Legislative and Regulatory Responses to the FTC Study on Barriers to Entry in the Pharmaceutical Marketplace: Hearing Before the S. Comm. on the Judiciary*, 108th Cong. 8, 14 (2003) (statement of Daniel E. Troy, Chief Counsel, FDA) (“FDA has tried to maintain a balance between protecting innovation in drug development and in expediting the approval of lower-cost generic drugs . . . . But let me say that there is no way, through rulemaking or through legislation, to avoid all opportunities for gaming . . . . [T]here are unforeseen circumstances and unintended consequences.”).

<sup>137</sup> Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, § 908, 126 Stat. 993 (2012) (“The term ‘rare pediatric disease product application’ means a human drug application, as defined in section 735(1), that . . . contains no active ingredient (including any ester or salt of the active ingredient) that has been previously approved in any other application . . . .”).

products, the provision may actually compromise the incentive for the most promising innovations for rare pediatric diseases involving cancer.

For example, this amendment in the Creating Hope Act would exclude from reward a promising innovation in cancer therapy that involves conjugating known chemotherapy drugs to “drug delivery vehicles” such as nanoparticles, stem cells or T cells.<sup>138</sup> These drug delivery vehicles help the known chemotherapy agents bypass biological barriers (such as the blood-brain barrier), minimize side effects of chemotherapy drugs by specifically delivering the known drugs to cancer sites rather than having the drugs released into the entire body, and aid in preventing drug resistance and monitoring treatment.<sup>139</sup> Nanoparticles attached to a standard chemotherapy drug, docetaxel, have been shown to cause complete remission of lymphoma in mice.<sup>140</sup> Furthermore, self-assembling antibody nanorings and other nanoparticles conjugated to known chemotherapy drugs have shown promise in treating leukemia, a deadly cancer in children.<sup>141</sup> Similar strides have been made using iron oxide nanovehicles to transport the known cancer drug, doxorubicin, to prevent multidrug resistance in a sort of ‘Trojan Horse’ mechanism.<sup>142</sup>

If the promise of a PRV is limited to drugs that contain no active ingredients previously approved by the FDA, the PRV program will not work to incentivize companies to use known chemotherapy drugs with these novel delivery vehicles. Legislatures should not tailor the requirements of obtaining a PRV too narrowly to traditional notions of drug development while inadvertently excluding the most promising mechanisms of innovation.

Even without considering the next wave of cancer therapy innovation, many successful treatments for rare pediatric diseases have historically involved finding new uses for known drugs. In 2011, for example, the FDA approved Soliris (eculizumab) for the rare pediatric blood disorder of atypical Hemolytic Uremic Syndrome (aHUS). The

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<sup>138</sup> See Forrest M. Kievit & Miqin Zhang, *Cancer Nanotheranostics: Improving Imaging and Therapy by Targeted Delivery Across Biological Barriers*, 23 *ADVANCED MATERIALS* H217, H217 (2011).

<sup>139</sup> *Id.*

<sup>140</sup> *Id.* at H238 (2011).

<sup>141</sup> *Id.*

<sup>142</sup> The known chemotherapy drug conjugated to the nanoparticle prevents multidrug resistance by waiting to release the chemotherapy drug until the nanoparticle is inside the cancer cell. *Id.* In standard treatments, chemotherapy drugs are freely released into the body before reaching the cancerous site allowing “a small proportion of cells that are resistant to the therapy [to] survive to form a resistant tumor. *Id.*

FDA had previously approved Soliris for the rare adult condition of Paroxysmal Nocturnal Hemoglobinuria (PNH).<sup>143</sup> Under the CHA, Soliris would not receive a PRV because the drug had already been approved for adults. Arguably, the PRV program should encourage investigation into using known adult drugs to treat rare pediatric diseases.

Second, the CHA may hasten the entry of pediatric applications at the needless expense of delaying adult treatments. Under the CHA, a rare pediatric disease product application is ineligible for a PRV if it “seek[s] approval for an adult indication *in the original* rare pediatric disease product application.”<sup>144</sup> Preventing drug sponsors from applying for both adult and pediatric indications simultaneously will simply delay adult treatments rather than encourage pediatric developments. Such a provision will also increase total regulatory costs by encouraging companies to seek approval for pediatric and adult indications at different times without the benefit of economies of scale in the regulatory process. Empirical evidence may elucidate how often treatments for pediatric and adult diseases overlap and what benefit, if any, pediatric patients would receive by delaying adult treatment.

Third, the CHA may disproportionately burden universities and small companies. The CHA’s marketing requirement is aimed at encouraging drug sponsors to manufacture and market drugs post approval.<sup>145</sup> For rare pediatric disease products, the provision allows the Secretary of Health and Human Services to revoke a priority review voucher if the product is not marketed in the United States within a year of FDA approval.<sup>146</sup> For all its good intentions, this marketing requirement may disproportionately affect universities and small businesses. Because a university’s expertise exists primarily in creating knowledge and conducting research, it is unreasonable for these entities to be required to take on the burden of marketing the drug. Congress should consider other options of encouraging drug sponsors to market the drug, such as creating an exemption for universities, requiring entities to give up or sell their intellectual property rights if they do not intend to market the drug, or providing a second reward or recognition five years

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<sup>143</sup> FOOD & DRUG ADMIN., FDA APPROVES SOLIRIS FOR RARE PEDIATRIC BLOOD DISORDER (Sept. 23, 2011), <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm272990.htm> (see rule 14.2(d)).

<sup>144</sup> Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, § 908, 126 Stat. 993 (2012) (emphasis added).

<sup>145</sup> *Id.*

<sup>146</sup> *Id.*

after initial approval for entities that do succeed in promoting access to the drug.

Fourth, the Creating Hope Act fails to create a nexus between the magnitude of the reward and the drug's improvement over existing therapies. One criticism of the PRV program for neglected tropical disease products is the lack of a link between the reward and utility of the drug.<sup>147</sup> The Creating Hope Act fails to rectify this problem. Section 360n(b) orders the Secretary to award a PRV upon approval of *any* tropical disease product application, with no regard to the extent that the drug will improve human health.<sup>148</sup> Congress should consider whether this one-size-fits-all reward system best advances its objective of improving the lives of people suffering from neglected tropical diseases or rare pediatric diseases. The PRV program may encourage the development of more desirable drugs if sponsors could receive a second PRV five years after approval for drugs found to significantly impact the Quality-Adjusted Life year (QALY) or Disability-Adjusted Life year (DALY) of the target population. QALY and DALY are standard calculations for the economic value of medical treatments.

Finally, extending the PRV program to rare pediatric diseases may actually undermine the PRV program for neglected tropical diseases. On one hand, the PRV program for neglected tropical diseases has resulted in only one grant and use of a PRV in the last five years. Thus, awarding a PRV for a rare pediatric disease drug product may help jumpstart the program for neglected tropical diseases by resolving some of the current legislation's ambiguity. On the other hand, the transfer value of a PRV depends on the number of vouchers on the market. If the market is flooded with PRVs, the value of each will decline. Congress should therefore evaluate whether extending the program to rare pediatric diseases will actually result in a reduced value for PRVs and reduced incentives for sponsors.

#### CONCLUSION

The priority review voucher (PRV) program holds great promise as a tool to both increase investment in drugs used to treat neglected diseases and reward sponsors for their innovations without burdening taxpayers. However, Congress may have prematurely extended the program to rare pediatric diseases by signing the Creating Hope Act into

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<sup>147</sup> See Kesselheim, *supra* note 92 (“[A]n effective novel antimalarial drug that degrades in the heat and must be taken six times a day would earn its sponsor a voucher, but no voucher would be granted for a follow-on formulation that might be more useful in resource-poor settings.”).

<sup>148</sup> Creating Hope Act, H.R. 3059, 112th Cong. § 2(c)(1) (2011).

law under the Food and Drug Administration Safety and Innovation Act of 2012. Although founded on the best intentions, the Creating Hope Act may exclude some of the most promising research areas for pediatric drug development, needlessly delay adult treatments at only a marginal benefit for pediatric patients, disproportionately burden small businesses and universities, fail to link the utility of the drug to the magnitude of the reward, and possibly even undermine the PRV program that already exists for tropical disease products. The GAO should consider all these possible collateral effects when it evaluates the program.<sup>149</sup> The GAO's evaluation will elucidate whether these concerns are valid and will help guide the drafting of future legislation seeking to expand the PRV program to other classes of neglected diseases.

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<sup>149</sup> Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, § 908, 126 Stat. 993 (2012) (“Beginning on the date that the Secretary awards the third rare pediatric disease priority voucher under this section, the Comptroller General of the United States shall conduct a study of the effectiveness of awarding rare pediatric disease priority vouchers . . .”).