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# The Priority Review Voucher Program at the FDA: From Neglected Tropical Diseases to the 21st Century Cures Act

*Ana Santos Rutschman\**

## I. INTRODUCTION

The priority review voucher program at the Food and Drug Administration (FDA) was established in 2007 to incentivize research and development (R&D) in traditionally underfunded diseases.<sup>1</sup> While shrouded in controversy and criticism, the program has recently been bolstered by the passage of the 21<sup>st</sup> Century Cures Act,<sup>2</sup> which prevented the vouchers from sunseting in late 2016 and furthered the overall scope of the program.<sup>3</sup> As it reaches the end of its first decade, this Article discusses the impact of the program, with a focus on recent developments. The Article builds on literature suggesting that the voucher program has been ineffective in incentivizing research in neglected diseases. It is the first to consider the expansion of the vouchers to cover R&D on Ebola and Zika, arguing that the expansion was attributable to misguided bipartisan political support and is likely to result in further cross-subsidization benefiting R&D on mainstream diseases. Finally, this is also the first scholarly piece to describe and assess the likely impact the 21<sup>st</sup> Century Cures Act has on the program.

The process of developing and getting regulatory approval for a drug is especially costly.<sup>4</sup> The default mechanism for incentivizing innovation in

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\* Jaharis Faculty Fellow in Health Law and Intellectual Property, DePaul University College of Law. For helpful comments, I would like to thank Wendy Netter Epstein, Sam Halabi, Katherine Macfarlane, Josh Sarnoff and Nadia Sawicki, as well as the participants in the Tenth Annual Symposium on Health Law & Policy at Loyola University Chicago School of Law. All errors remain my own.

1. Ridley et al., *infra* note 16, at 313; *Priority Review Vouchers: Overview*, <http://priorityreviewvoucher.org/> (last visited Apr. 6, 2017).

2. Jennifer Steinhauer & Robert Pear, *Sweeping Health Measure, Backed by Obama, Passes Senate*, N.Y. TIMES (Dec. 7, 2016), [https://www.nytimes.com/2016/12/07/us/politics/21st-century-cures-act-senate.html?\\_r=0](https://www.nytimes.com/2016/12/07/us/politics/21st-century-cures-act-senate.html?_r=0).

3. *Infra*, Part IV.A.1.

4. A 2015 study puts this number at as high as \$2.56 billion. See TUFTS UNIV., CTR. FOR THE STUDY OF DRUG DEV., OUTLOOK 2015, 3 (2015), <http://csdd.tufts.edu/files/uploads/Outlook-2015.pdf> [hereinafter TUFTS]. This might be an overestimation. There is however no consensus on what the exact figures are, and the numbers

capital-intensive areas is the patent system, which has consistently been regarded and lobbied for as a *sine qua non* of pharmaceutical innovation.<sup>5</sup> But even the ability to set monopolistic prices for on-patent drugs is of little avail in certain areas.<sup>6</sup> The patent model reinforces the tendency of pharmaceutical companies to focus R&D on drugs destined for markets with “attractive investment returns.”<sup>7</sup> Diseases that, in spite of a high social cost and medical burden, affect small populations or that primarily affect populations with limited resources receive scant R&D attention.<sup>8</sup>

However, other organizations and governmental agencies have provided additional research incentives in the form of grants, exclusivities, vouchers, and tax credits.<sup>9</sup> For example, the FDA administers the priority review voucher program. Congress designed the program and similar incentives to help cure market failures in pharmaceutical innovation when patent incentives alone are insufficient. The design of the program, however, is idiosyncratic. The FDA awards vouchers to drug sponsors who obtain regulatory approval for drugs treating qualifying, underfunded diseases.<sup>10</sup> Sponsors can redeem vouchers to speed up the approval process for a separate drug application.<sup>11</sup> The vouchers help sponsors get their drugs on the market faster and, in turn, collect larger profits.<sup>12</sup>

Critics argue that the program fails to generate the type of innovative R&D it purports to foster or to ensure the affordability of—and access to—drugs approved under the program.<sup>13</sup> Nevertheless, from a political point of view it has cyclically enjoyed the bipartisan support that is so elusive nowadays, and

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will vary according to type of drug or therapy. See Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent Law*, 89 VA. L. REV. 1575, 1581, 1616, 1676 (2003) (noting how the “precise statistics” of the costs associated with pharmaceutical R&D remain disputed).

5. See Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345, 346 (2007) (noting the role of the pharmaceutical industry in perpetuating a patent-based system for drug innovation: “[t]he pharmaceutical industry, lobbying for stronger patent laws throughout the world, has sung the praises of the patent system as a means of promoting costly and risky investments in research and development (‘R&D’).”).

6. Ezekiel Emanuel, *Don’t Only Blame Mylan for \$600 EpiPens*, FORTUNE INSIDERS (Sept. 8, 2016), <https://insiders.fortune.com/dont-only-blame-mylan-for-600-epipens-6ad0065373e0#p3gwrms23>.

7. TUFTS, *supra* note 4, at 3.

8. Ridley et al., *infra* note 16, at 313.

9. See generally Daniel J. Hemel & Lisa Larrimore Ouellette, *Beyond the Patents-Prizes Debate*, 92 TEX. L. REV. 303 (2013) (discussing the role of tax incentives in innovation policy); Benjamin N. Roin, *Intellectual Property versus Prizes: Reframing the Debate*, 81 U. CHI. L. REV. 999 (2014) (discussing the government’s various rewards for innovation).

10. See *infra* Part II.A.2 (discussing the FDA’s voucher program as an incentives mechanism).

11. See *infra* Part II.A.1 (explaining the R&D incentive of “blockbuster drug” sales).

12. See *infra* Part II.A.1.

13. See *infra* Part II.A.2.b.

was legislatively expanded over time in both scope and duration.<sup>14</sup> Moreover, Congress recently passed the 21<sup>st</sup> Century Cures Act, which provides funding for early-stage and “high-risk, high-reward” biomedical research and further expands the priority review voucher program.<sup>15</sup>

Part I of the Article introduces the voucher program in the context of innovation policy. Part II surveys the genesis, growth and shortcomings of the program. Part III shows how the expansion of the program—following the recent Ebola and Zika outbreaks, and into new fields—accentuates misalignments between the vouchers and R&D incentives strategies. Part IV explores the future of the program as affected by recent legislative changes, as well as the emerging role of the FDA as a catalyst for innovation policy as dictated by the voucher program.

## II. THE FDA’S VOUCHER PROGRAM AS AN INCENTIVES MECHANISM

### A. The Priority Review Voucher Program

#### 1. The Voucher Program in the Context of Incentives Mechanisms

David Ridley, Henry Grabowski, and Jeffrey Moe first proposed the priority review voucher program in Health Affairs article in 2006.<sup>16</sup> The catalyst for the proposal was the generalized lack of medicines available to patients with infectious and parasitic diseases in the developing world.<sup>17</sup> The authors suggest that the FDA could be the touchstone of an incentives scheme that would have pharmaceutical companies self-fund increased R&D in

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14. See *infra* Part III.

15. See 21st Century Cures Act, Pub.L. No. 114 – 255, § 2036 (2016) [hereinafter 21st Century Cures Act]; see also Elaine Schattner, *Why Patients Support the 21st Century Cures Act*, FORBES (Nov. 30, 2016, 9:54 AM), <http://www.forbes.com/sites/elaineschattner/2016/11/30/why-patients-support-the-21st-century-cures-act/#9143ceaac373> (citing funding for Precision Medicine Initiative and the Cancer Moonshot as one of the main reasons for supporting the 21st Century Cures Act). While both initiatives have been regarded favorably by patient advocacy groups and the general public, the potential and actual efficacy of the Precision Medicine Initiative and the Cancer Moonshot has been contested. Tabitha M. Powledge, *That ‘Precision Medicine’ Initiative? A Reality Check*, GENETIC LITERACY PROJECT (Feb. 3, 2015), <https://www.geneticliteracyproject.org/2015/02/03/that-precision-medicine-initiative-a-reality-check/>; Jamie Condliffe, *The Best—and Worst—Things About Joe Biden’s Cancer Moonshot*, TECH. REV. (Oct. 17, 2016), <https://www.technologyreview.com/s/602679/the-best-and-worst-things-about-joe-bidens-cancer-moonshot/>.

16. David B. Ridley et al., *Developing Drugs for Developing Countries*, 25 HEALTH AFF. 313, 313 (2006).

17. *Id.* For a discussion of the market failures surrounding R&D for neglected diseases, see Patrice Trouiller et al., *Drug Development for Neglected Diseases: A Deficient Market and A Public-Health Policy Failure*, 359 THE LANCET 2188, 2188–91 (2002).

neglected tropical diseases.<sup>18</sup>

With most companies engage in pharmaceutical R&D in the developed world, particularly in the United States and Europe,<sup>19</sup> Ridley et alia reasoned that a way to bolster the development and commercialization of new drugs and therapies for tropical diseases would be to tie the incentives for orphan drugs to strategic and financial benefits for “blockbuster” drugs which receive most funding for R&D. The scheme would partially add to R&D funding for diseases prevalent in economically unattractive markets (the markets of the developing world) from the traditional patent-based model in which innovator companies recoup R&D costs through the sale of drugs priced for more affluent populations.<sup>20</sup>

To implement the program in the United States, Congress created a list of voucher-eligible diseases.<sup>21</sup> When the sponsor of an eligible drug obtains FDA approval, a voucher is issued granting “priority review” to a second drug for which the sponsor might seek regulatory approval at a later time.<sup>22</sup> Under standard review, the FDA takes around ten months<sup>23</sup> to review and either grant or deny approval of new drugs and therapies.<sup>24</sup> When a priority

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18. Ridley et al., *supra* note 16, at 313.

19. Andrew Witty, *New Strategies for Innovation in Global Health: A Pharmaceutical Industry Perspective*, 30 HEALTH AFFS. 118, 124 (2011). The Ridley et al. paper suggested the adoption of a similar mechanism for Europe and, in 2011, David Ridley & Afonso Calles Sánchez specifically described and proposed a European priority review voucher system. David B. Ridley & Alfonso Calles Sánchez, *Introduction of European Priority Review Vouchers to Encourage Development of New Medicines for Neglected Diseases*, 376 THE LANCET 922, 922 (2010).

20. See Ridley et al., *supra* note 16, at 315 (describing the proposal’s goal to create a market for financially “unattractive” diseases).

21. See *infra* Part II.B.2 (discussing drug affordability).

22. Gaffney et al., *infra* note 34.

23. See U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY EXPEDITED PROGRAMS FOR SERIOUS CONDITIONS – DRUGS AND BIOLOGICS 25 (2014), <http://www.fda.gov/downloads/Drugs/Guidances/UCM358301.pdf> (comparing the FDA’s expedited goal to action within six months of receiving the application with its standard ten-month framework) [hereinafter GUIDANCE FOR INDUSTRY]; see also U.S. FOOD & DRUG ADMIN., TROPICAL DISEASE PRIORITY REVIEW VOUCHERS GUIDANCE FOR INDUSTRY 6 (2016), <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080599.pdf> (stating, “FDA commits to a goal to review and act on 90 percent of standard applications for N[ew] M[olecular] E[ntity] and original B[iologics] L[icense] A[pplications] submissions within 10 months of the 60-day filing date.”) [hereinafter TROPICAL DISEASE PRIORITY REVIEW VOUCHERS].

24. Average review times also vary depending on type of drug and drug complexity. A 2014 study examined review times at FDA’s Center for Drug Evaluation and Research (“CDER”) and found “wide variance” among divisions, with Oncology and Antivirals approving new drugs approximately three times quicker than the agency’s least efficient divisions. Oncology and Antivirals took on average under 200 days to approve a new drug, whereas the slowest division, Neurology, took close to 600 days. JOSEPH A. DIMASI ET AL., AN FDA REPORT CARD: WIDE VARIANCE IN PERFORMANCE FOUND AMONG AGENCY’S DRUG REVIEW DIVISIONS 6, 8 (2014).

review voucher is redeemed, the agency must attempt to bring that period down to six months.<sup>25</sup> Pharmaceutical companies benefiting from a voucher are therefore able to enter the market four months earlier, reaping the corresponding financial gains.<sup>26</sup> The incentive to engage in R&D for neglected diseases thus materializes in the form of sales of a second (potentially blockbuster) drug.<sup>27</sup> Short as this window of time may seem, for the pharmaceutical industry, “four months of earlier market access could translate into hundreds of millions of dollars.”<sup>28</sup>

In addition to the possibility of direct use, Ridley et alia suggested that the vouchers should be transferable.<sup>29</sup> As an alternative to entering the market ahead of time, a voucher holder would be allowed to transfer or sell it to another company.<sup>30</sup> In the first iteration of the program, Congress chose to restrict the number of times a voucher could be transferred, but the law was amended to remove that limitation in 2014.<sup>31</sup> To date there have been five confirmed sales, ranging from \$67 to \$350 million.<sup>32</sup>

The combined transfers and sales of vouchers that have occurred since the program was implemented in the United States provide an idea of the de facto economic value of the vouchers. By extension, they should also help delineate the profile of the incentive for companies to engage in R&D in voucher-qualifying areas. For instance, Praluent, an injectable cholesterol-lowering treatment, and Odefsey, used to treat HIV-1 infections, have entered the market with a voucher.<sup>33</sup> In both cases, the voucher had been acquired

25. See U.S. FOOD & DRUG ADMIN., FAST TRACK, BREAKTHROUGH THERAPY, ACCELERATED APPROVAL, PRIORITY REVIEW, <http://www.fda.gov/forpatients/approvals/fast/ucm20041766.htm> (last updated Sept. 14, 2015) [hereinafter FAST TRACK] (“A Priority Review designation means FDA’s goal is to take action on an application within 6 months.”).

26. U.S. FOOD & DRUG ADMIN., FDA’S EFFORTS ON RARE AND NEGLECTED DISEASES: HEARING BEFORE THE SUBCOMM. ON AGRIC., RURAL DEV., FOOD & DRUG ADMIN., AND RELATED AGENCIES, COMM. ON APPROPRIATIONS, UNITED STATES SENATE 6 (2010), <http://docs.house.gov/meetings/FA/FA16/20130627/101069/HHRG-113-FA16-Wstate-GoodmanJ-20130627.pdf> [hereinafter HEARING] (recording the statement of Jessie L. Goodman, Chief Scientist and Deputy Commissioner for Science and Public Health, Food and Drug Administration).

27. *Id.*

28. *FDA’s Efforts on Rare and Neglected Diseases*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/NewsEvents/Testimony/ucm216991.htm> (last updated June 23, 2010).

29. Ridley et al., *supra* note 16, at 322.

30. *Id.* at 317.

31. See *infra* Part III.B.

32. *Infra* Table 1.

33. *FDA Approves Praluent to Treat Certain Patients with High Cholesterol*, U.S. FOOD & DRUG ADMIN. (July 24, 2015), <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm455883.htm>; *Gilead Sciences Says U.S. FDA Approves Odefsey*, REUTERS (Mar 1, 2016, 2:16 PM), <http://www.reuters.com/article/idUSASC08EH3>.

from another company.<sup>34</sup> In order to expedite review of Praluent, Sanofi acquired the voucher from BioMarin at a price tag of \$67 million, which indicates that Sanofi expected returns in excess of that amount.<sup>35</sup> In the case of Odefsey, Gilead obtained the voucher from Knight Therapeutics for \$125 million, which puts the estimated return over \$130 million.<sup>36</sup> Likewise, the record-setting transaction in which United sold a (so-far unused) voucher to AbbVie for \$350 million indicates that, in the future, AbbVie expects to gain approval for a drug that is likely to generate more than that amount after entering the market four months ahead of standard review.<sup>37</sup>

| Year | Seller                | Purchaser            | Amount        |
|------|-----------------------|----------------------|---------------|
| 2014 | BioMarin              | Sanofi and Regeneron | \$67 million  |
| 2014 | Knight                | Gilead               | \$125 million |
| 2015 | United                | AbbVie               | \$350 million |
| 2015 | Retrophin             | Sanofi               | \$245 million |
| 2016 | Unknown <sup>38</sup> | Gilead               | undisclosed   |

Table 1: Priority Review Voucher Sales

FDA's mission of ensuring the safety and efficacy of drugs<sup>39</sup> is unlikely to be compromised by the redemption of a voucher per se, as the agency routinely engages in processes to expedite review of drugs deemed promising outside the voucher context.<sup>40</sup> The agency has different pathways to speed up review of drugs that treat "serious medical conditions," particularly in cases where such drugs "are the first available treatment or if the drug has

34. Alexander Gaffney et al., *Regulatory Explainer: Everything You Need to Know About FDA's Priority Review Vouchers*, REG. AFF. PROF'L SOC'Y (Nov. 3, 2016), <http://www.raps.org/Regulatory-Focus/News/2015/07/02/21722/Regulatory-Explainer-Everything-You-Need-to-Know-About-FDA%E2%80%99s-Priority-Review-Vouchers/>.

35. *Id.* (explaining that Sanofi expects returns in addition to the voucher user fee).

36. *Id.*

37. *Id.*

38. In July of 2016, Gilead indicated that it had purchased a voucher, but did not make public any information about the sale or plans for its use. *See* GILEAD SCIENCES, INC., CURRENT REPORT (FORM 8-K) (July 25, 2016), <http://investors.gilead.com/phoenix.zhtml?c=69964&p=irol-SECText&TEXT=aHR0cDovL2FwaS50ZW5rd2l6YXJkLmNvbS9maWxpbmcueG1sP2lwYWdlPTExMDUwOTAzJkRTRVE9MCZTRVE9MCZTUURFU0M9U0VDVEIPTI9FTIRJUKUmc3Vic2lkPTU3>. Some commentators have raised the possibility that this might be the voucher awarded earlier in 2016 to vaccine company PaxVax Bermuda for Vaxchora, a single-dose oral cholera vaccine. *See* Gaffney et al, *supra* note 34.

39. *See What We Do: FDA Mission*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/AboutFDA/WhatWeDo/> (last updated Apr. 4, 2017).

40. *See* GUIDANCE FOR INDUSTRY, *supra* note 23, at 1; *see also infra* note 41 and accompanying text.

advantages over existing treatments.”<sup>41</sup> One of these pathways is known as “priority review” and was created in 1992 by the Prescription Drug User Fee Act.<sup>42</sup> When a drug is granted priority review status, the FDA directs its “overall attention and resources” to reviewing the application.<sup>43</sup> In practice, this translates into a shortening of the average review period from ten to six months.<sup>44</sup> The voucher program inscribes certain drug applications into an existing category—priority review—for which these drugs might not have otherwise qualified.

Although engaging in priority review is by now a routine process for the FDA,<sup>45</sup> shifting to priority review upon redemption of a voucher does have an impact on the agency, which has been plagued by funding and staff shortcomings since well before the voucher system was devised.<sup>46</sup> In the 2006 paper introducing the concept of priority review vouchers, Ridley et alia estimated that the “cost to the FDA of changing a drug’s status from standard to priority is approximately \$1 million” and proposed a voucher user

41. See FAST TRACK, *supra* note 25; *For Patients: Breakthrough Therapy*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/forpatients/approvals/fast/ucm405397.htm> (last updated September 15, 2014) (Sponsors of drugs that “treat serious conditions and fill an unmet medical need” may request *fast track* designation. Sponsors of drugs treating serious conditions may request *breakthrough therapy* designation “when preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s).” *Accelerated approval* is available “for drugs for serious conditions that fill an unmet medical need on whether the drug has an effect on a surrogate or an intermediate clinical endpoint.”). As indicated above, *priority review* sets “a goal date for taking action on an application within 6 months of receipt.” U.S. FOOD & DRUG ADMIN., REVIEW DESIGNATION POLICY: PRIORITY (P) AND STANDARD (S), MANUAL OF POLICIES AND PROCEDURES 2 (2013), <https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm082000.pdf> [hereinafter P AND S POLICY MANUAL].

42. *Id.*; See also Ernst R. Berndt et al., *Industry Funding of the FDA: Effects of PDUFA on Approval Times and Withdrawal Rates*, 4 NATURE REV. DRUG DISCOVERY 545, 546 (July 2005).

43. U.S. FOOD & DRUG ADMIN., PRIORITY REVIEW, <http://www.fda.gov/ForPatients/Approvals/Fast/ucm405405.htm> (last updated Sep. 15, 2014).

44. P AND S POLICY MANUAL, *supra* note 41, at 2.

45. See Joseph A. DiMasi & Henry G. Grabowski, *Economics of New Oncology Drug Development*, 25 J. CLINICAL ONCOLOGY 210, 216 (Jan. 2007) (discussing a 2007 study that found that 71% of approved oncology drugs had received priority review, whereas for other drugs the rate was 40%); John K. Jenkins, *Regulatory Flexibility and Lessons Learned: Drugs for Rare Diseases*, U.S. FOOD & DRUG ADMIN., 12 (Oct. 18, 2016), <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM525805.pdf> (showing that during the 2008-2016 period (up to September 7, 2016) the number of NMEs approved under priority review was 75% for rare diseases and 30% for non-rare diseases).

46. See, e.g., Charles Marwick, *FDA Funding Problems Imperil Safety of Biological Products in the United States*, 279 JAMA 899, 901 (1998) (discussing the disparity between the increase between the number of areas FDA has been called to regulate over time and the amount of funding available to the agency).



fee that would match or surpass that amount.<sup>47</sup> For fiscal year 2017 the fee has been set at \$2,706,000 for all types of vouchers.<sup>48</sup>

Even if the user fee can compensate for the economic cost associated with granting priority review in cases where the FDA might otherwise have denied that status, it is still not enough to dispel all concerns about the impact the program might have on the agency. These concerns are especially salient with regard to autonomy in its agenda-setting, as described in Part IV.<sup>49</sup>

In spite of potential direct and indirect costs, the voucher program quickly gathered political support.<sup>50</sup> Senator Sam Brownback spearheaded the incorporation of the program into the Food and Drug Administration Amendments Act (FDAAA), which was signed into law on September 27, 2007, a mere year and a half after the concept of the vouchers was first introduced in a scientific publication.<sup>51</sup> A second voucher program was created in 2012, covering rare pediatric diseases, and the recently approved 21<sup>st</sup> Century Cures Act introduced a third voucher program, covering drugs used to respond to bioterrorism or natural disasters (commonly known as medical countermeasures).<sup>52</sup>

## 2. Development of the Voucher Program

The priority review voucher program was created in 2007 “to stimulate new drug development” in neglected tropical diseases.<sup>53</sup> Eligible tropical diseases are defined by a closed list, which originally encompassed 16 diseases, including tuberculosis, malaria, cholera and Human African

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47. See Ridley et al., *supra* note 16, at 315, 318.

48. But see Zachary Brennan, *Priority Review Voucher Fees to Decline in FY 2017*, REG. AFFS. PROF’LS SOC’Y (Sept. 29, 2016), <http://www.raps.org/Regulatory-Focus/News/2016/09/29/25926/Priority-Review-Voucher-Fees-to-Decline-in-FY-2017/> (providing a comparison of 2016 to 2017 noting the decrease in fees for priority vouchers). This is actually a decrease from FY 2016, in which the fee was set at \$2,727,000. In 2011, the fee for vouchers for tropical diseases was set at \$4,582,000, rising to \$5,280,000 in 2012 and then declining to \$3,559,000 in 2013. When pediatric disease vouchers were introduced (*see infra* note 66) the fee was set to match the tropical disease fee at \$2,325,000 in 2014, and there has been fee parity for both programs ever since.

49. See *infra* Part IV.

50. See Sam Brownback, *Eliminating Neglected Diseases: Impact of Published Paper*, 26 HEALTH AFFS. 1505, 1509 (2007) (offering Senator Brownback’s support of a priority review voucher program in Congress).

51. Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 1102, 121 Stat. 823 (2007).

52. *What are Medical Countermeasures?*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/AboutMCMi/ucm431268.htm> (last visited Feb. 20, 2017); see also *infra* Part III.B.

53. Gaffney et al., *supra* note 34 (noting that section 1102 of the FDAAA created the Neglected Tropical Disease Voucher System).

trypanosomiasis (commonly known as sleeping sickness).<sup>54</sup> As detailed in Part III, Ebola and Zika were not part of the initial list. The FDA has the authority to add “[a]ny other infectious disease for which there is no significant market in developed nations and that disproportionately affects poor and marginalized populations,”<sup>55</sup> a prerogative that the agency first used in August 2015 to add Chagas and neurocysticercosis to the neglected tropical disease voucher program.<sup>56</sup> At the time, the FDA also created a docket for public recommendations for further additions to the list.<sup>57</sup>

Additionally, the statute gives the FDA the authority to enforce requirements and limitations on the use of vouchers. During the first seven years of the program, the statute required drug sponsors to notify the FDA at least 365 days before redeeming a priority voucher, a period that was shortened in 2014 to a minimum of 90 days.<sup>58</sup> Initially, transfers of vouchers were also limited and could only take place once. In 2008, the FDA clarified that “contractual arrangements such as the use of an option or transfer of the right to designate the voucher’s recipient” were within the terms of the statute.<sup>59</sup> Since 2014, there have been no limits to the number of times a voucher may be transferred,<sup>60</sup> but a letter of transfer is required.<sup>61</sup>

The tropical disease vouchers may be used in combination with other incentives initiatives or programs. For instance, a drug might qualify simultaneously for the voucher and for orphan drug designation,<sup>62</sup> which would make it eligible for “marketing exclusivity and tax credits for qualified clinical testing,” as well certain fee exemptions.<sup>63</sup>

54. 21 U.S.C. § 360n(a)(3).

55. TROPICAL DISEASE PRIORITY REVIEW VOUCHERS GUIDANCE, *supra* note 23, at 4.

56. Designating Additions to the Current List of Tropical Diseases in Section 1102 of the Food and Drug Administration Amendments Act, 80 Fed. Reg. 50559, 50559–65 (Aug. 25, 2015) (to be codified at 21 C.F.R. p. 317), <https://www.gpo.gov/fdsys/pkg/FR-2015-08-20/pdf/2015-20554.pdf> [hereinafter Additions to Tropical Diseases].

57. DEP’T OF HEALTH & HUMAN SERVS., U.S. FOOD & DRUG ADMIN., FDA-2008-N-0567 (Nov. 5, 2008), <http://www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-N-0567-nhc.pdf>.

58. 21 U.S.C. § 360n(b)(4).

59. TROPICAL DISEASE PRIORITY REVIEW VOUCHERS GUIDANCE, *supra* note 23, at 5.

60. 21 U.S.C. § 360n(b)(2); *see also* TROPICAL DISEASE PRIORITY REVIEW VOUCHERS GUIDANCE, *supra* note 23, at 8 (explaining the FD&C Act and modifications).

61. TROPICAL DISEASE PRIORITY REVIEW VOUCHERS GUIDANCE, *supra* note 23, at 8.

62. Aarti Sharma et al., *Orphan Drug: Development Trends and Strategies*, 2 J. PHARMACY & BIOALLIED SCI. 290, 291 (2010), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2996062/>

(An orphan drug can be defined as “is one that has been developed specifically to treat a rare medical condition, the condition itself being referred to as ‘orphan disease.’”); *see also* 21 U.S.C. § 360bb (explaining voucher designation for rare diseases by the Secretary of Health and Human Services).

63. TROPICAL DISEASE PRIORITY REVIEW VOUCHERS GUIDANCE, *supra* note 23, at 10; 21 U.S.C. § 335a(o)(2)(a).

So far, the FDA has awarded four vouchers for neglected tropical diseases. The 2012 voucher awarded to Janssen (Johnson & Johnson) for Sirturo,<sup>64</sup> a bedaquiline-based drug used to treat multidrug-resistant pulmonary tuberculosis, was the first tuberculosis drug to receive FDA approval in 40 years.<sup>65</sup>

| Year | Company                | Qualifying disease |
|------|------------------------|--------------------|
| 2009 | Novartis               | malaria            |
| 2012 | Janssen (J&)           | tuberculosis       |
| 2014 | Knight<br>Therapeutics | leishmaniasis      |
| 2016 | PaxVax Bermuda         | cholera            |

Table 2: Priority review vouchers awarded for neglected tropical diseases, 2007-2016

Five years after the neglected tropical disease program was created, Section 529 of the FDCA introduced a similar voucher-based incentives program for rare pediatric diseases.<sup>66</sup> FDCA defines rare pediatric disease as one that “primarily affects individuals aged from birth to 18 years,”<sup>67</sup> and an FDA guidance on the pediatric voucher program further clarifies that a drug qualifies for a pediatric voucher “if the entire prevalence of the disease or condition in the U.S. is below 200,000 and if more than 50% of patients with the disease are 0 through 18 years of age.”<sup>68</sup>

From the start, sponsors of qualifying pediatric drugs were required to notify the FDA 90 days before using the voucher, and the transfer of pediatric vouchers was never subject to limitations, as was initially the case with tropical diseases.<sup>69</sup> Pediatric vouchers may be used in conjunction with other

64. Press Release, Johnson & Johnson, FDA Grants Accelerated Approval for SIRTURO™ (Bedaquiline) as Part of Combination Therapy to Treat Adults with Pulmonary Multi-Drug Resistant Tuberculosis (Dec. 31, 2012), <https://www.jnj.com/media-center/press-releases/fda-grants-accelerated-approval-for-sirturo-bedaquiline-as-part-of-combination-therapy-to-treat-adults-with-pulmonary-multi-drug-resistant-tuberculosis>.

65. See Katie Thomas, *F.D.A. Approves Drug for Resistant Tuberculosis*, N.Y. TIMES (Dec. 31, 2012), <http://www.nytimes.com/2013/01/01/business/fda-approves-new-tuberculosis-drug.html> (discussing the FDA’s approval for Sirturo as a new treatment for multi-drug resistance tuberculosis).

66. 21 U.S.C. § 360ff.

67. 21 U.S.C. § 360ff(a)(3).

68. U.S. FOOD & DRUG ADMIN., RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHERS, GUIDANCE FOR INDUSTRY, 3 (2014), <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM423325.pdf> [hereinafter PEDIATRIC VOUCHER GUIDANCE].

69. 21 U.S.C. § 360ff.

incentives programs.<sup>70</sup>

A distinctive feature of the pediatric voucher program was that it gave the Government Accountability Office (GAO) a year counting from the awarding of the third rare pediatric disease priority voucher to “conduct a study of the effectiveness” of the program.<sup>71</sup> Specifically, GAO was to report on:

- (i) The indications for which each rare disease product for which a priority review voucher was awarded (...);
- (ii) Whether, and to what extent, an unmet need related to the treatment or prevention of a rare pediatric disease was met through the approval of such a rare disease product;
- (iii) The value of the priority review voucher if transferred;
- (iv) Identification of each drug for which a priority review voucher was used;
- (v) The length of the period of time between the date on which a priority review voucher was awarded and the date on which it was used.<sup>72</sup>

So far, seven vouchers have been awarded for rare pediatric diseases, at a rate that is five times higher than the one for neglected tropical diseases.

| Year | Company                 | Qualifying disease               |
|------|-------------------------|----------------------------------|
| 2014 | BioMarin                | Morquio A syndrome               |
| 2015 | United Therapeutics     | High-risk neuroblastoma          |
| 2015 | Asklepiion Pharma       | Bile acid synthesis disorder     |
| 2015 | Wellstat Therapeutics   | Hereditary orotic aciduria       |
| 2015 | Alexion Pharmaceuticals | Hypophosphatasia                 |
| 2015 | Alexion Pharmaceuticals | Lysosomal acid lipase deficiency |
| 2016 | Sarepta                 | Duchenne muscular dystrophy      |

Table 3: Priority review vouchers awarded for rare pediatric diseases, 2012-2016

70. 21 U.S.C. § 360ff(g); *see also* PEDIATRIC VOUCHER GUIDANCE, *supra* note 68, at 1–2 (discussing how as with the tropical disease vouchers, diseases qualifying for pediatric vouchers may cumulatively qualify for orphan drug designation and corresponding benefits).

71. 21 U.S.C. § 360ff(i)(A); *see also infra* Part II.B.

72. 21 U.S.C. § 360ff(i)(B).

The original sunset provision established that the pediatric voucher program would come to an end one year after the FDA issued the third voucher for a rare pediatric disease.<sup>73</sup> That third voucher was granted to Asklepiion on March 17, 2015 for Cholbam, a drug that treats patients lacking enzymes to synthesize bile acid.<sup>74</sup> In January 2016, Congress reauthorized the program through September 2016<sup>75</sup> and a second short-term reauthorization prolonged it until December 31, 2016.<sup>76</sup> The 21<sup>st</sup> Century Cures Act now extends the program until 2020.<sup>77</sup> Drugs receiving rare pediatric designation before October 1, 2020, will be eligible for a voucher if approved before October 1, 2022.<sup>78</sup>

### B. Criticism of the Voucher Program

In theory, the revenue generated, either by direct redemption or sale of a priority review voucher, functions as a reward in areas where traditional incentives—such as patents—have failed to generate substantial innovation. The prize-like benefit is justified as a mechanism to incentivize costly R&D in areas with small disease populations, rendering them attractive to pharmaceutical companies who would otherwise avoid markets that offer few prospects of covering their investment. The particular appeal of the voucher system is that, unlike other types of incentives,<sup>79</sup> vouchers do not require any direct financial support from the government or tax-based contributions. As seen in the previous section, this feature renders them politically attractive and has helped extend the life of the program.

To accomplish its goals,<sup>80</sup> the voucher program must however produce two interlinked yet distinct outcomes: 1) pharmaceutical companies should invest in R&D for neglected and/or rare diseases as a direct result of the voucher

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73. 21 U.S.C. § 360ff(b)(5) (“TERMINATION OF AUTHORITY.— 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.”).

74. See Press Release, U.S. Food & Drug Admin., FDA Approves Cholbam to Treat Rare Bile Acid Synthesis Disorders (Mar. 17, 2015), <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm438572.htm> (explaining rare bile acid synthesis disorders and the hoped effect Cholbam will have on them).

75. Advancing Hope Act of 2016, Pub. L. No. 114-229, § 1878, 130 Stat. 943, 946 (2016).

76. Press Release, Kids V Cancer, President Obama Signs the Advancing Hope Act to Extend the Creating Hope Act to December 31, 2016 (Sept. 30, 2016), <http://www.kidsvcancer.org/president-obama-signs-the-advancing-hope-act-to-extend-the-creating-hope-act-to-december-31-2016/>.

77. 21st Century Cures Act, § 2152.

78. *Id.*

79. Ouellette & Hemel, *supra* note 9, at 1008.

80. See TROPICAL DISEASE PRIORITY REVIEW VOUCHERS, *supra* note 23; see also Ridley et al., *supra* note 16.

incentive; and 2) if approved by the FDA, drugs and therapies for the diseases targeted by the program should be made available to patients at prices they can afford. Early evidence from the two existing types of vouchers suggests that the current design of the program might not be conducive to achieving either of these outcomes.

So far, there is a single formal evaluation of the vouchers—focusing only on rare pediatric diseases—and that evaluation has contributed little to a comprehensive assessment of the vouchers as incentives. Pursuant to 21 U.S.C. § 360ff(i)(A),<sup>81</sup> in March 2016 the GAO issued a report that bears the most self-explanatory of titles: *Rare Diseases – Too Early to Gauge Effectiveness of FDA’s Pediatric Voucher Program*.<sup>82</sup> The report raises important questions, especially with regard to the effect of the program on the FDA.<sup>83</sup> The Agency expressed the view that the program:

adversely affects the agency’s ability to set its public health priorities by requiring FDA to provide priority reviews of new drug applications that would not otherwise qualify if they do not treat a serious condition or provide a significant improvement in safety or effectiveness. Additionally, FDA officials said that the additional workload from the program strains the agency’s resources.<sup>84</sup>

However, the main conclusion of the report is that, given the extended life cycle of drug R&D, the then 3-year-old pediatric voucher program had yet to generate enough evidence to accurately assess whether the vouchers were “encouraging the development of drugs for rare pediatric diseases.”<sup>85</sup>

In contrast with the findings of the report, commentators have been more overt in criticizing the voucher program, in both of its current iterations.<sup>86</sup> By now, sufficient empirical evidence has emerged that it is possible to identify and analyze trends shared by the pediatric and the tropical disease programs. These trends suggest that it is unlikely that the vouchers are accomplishing the goals for which they were designed. The following sections examine the two-fold criticism of the program, starting with the problem of incentives to increased R&D in voucher-eligible areas, and then turning to the question of

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81. 21 U.S.C. 360ff(i)(1)(A).

82. See generally U.S. GOV’T ACCOUNTABILITY OFF., GAO-16-319, RARE DISEASES: TOO EARLY TO GAUGE EFFECTIVENESS OF FDA PEDIATRIC VOUCHER PROGRAM (Mar. 2, 2016), <http://www.gao.gov/products/GAO-16-319> [hereinafter GAO REPORT].

83. *Id.*

84. U.S. GOV’T ACCOUNTABILITY OFF., HIGHLIGHTS OF GAO-16-319, A REPORT TO CONGRESSIONAL COMMITTEES (Mar. 2, 2016), <http://www.gao.gov/products/GAO-16-319> [hereinafter HIGHLIGHTS OF GAO-16-319].

85. GAO REPORT, *supra* note 82, at 9.

86. See, e.g., Aaron S. Kesselheim, *Drug Development for Neglected Diseases — The Trouble with FDA Review Vouchers*, 359 NEW ENG. J. MED. 1981, 1981 (2008).

availability of affordable drugs approved under the existing voucher programs.

### 1. Lack of R&D in Voucher-eligible Diseases

In April 2009, the FDA granted Novartis a tropical disease voucher (and the first-ever priority voucher) for Coartem, an artemisinin-based combination therapy for malaria.<sup>87</sup> Artemisinin combination therapies are consensually regarded as “generally highly effective and well tolerated” and are the standard treatment recommend by the World Health Organization (WHO) for uncomplicated malaria.<sup>88</sup> When Novartis sought regulatory approval for Coartem in the U.S., the drug had been in use for close to a decade and was already registered in 85 other countries.<sup>89</sup> Novartis stated that it had been considering registering the drug in the U.S. before the creation of the vouchers, citing “pressure from the U.S. Government and army to supply traveling American citizens” as the main reason for registering the drug.<sup>90</sup> Similarly, in March 2014, Knight Therapeutics was awarded a neglected tropical disease voucher after obtaining regulatory approval for Impavido, a miltefosine-based drug used in the treatment of leishmaniasis.<sup>91</sup> The bulk of miltefosine R&D took place during the 1990s with funding from the WHO and other institutions.<sup>92</sup> Knight Therapeutics, while never involved in the R&D process, went on to sell the voucher to Gilead for \$125 million.<sup>93</sup> These two examples illustrate the disjointed dynamics of the program, with the incentive-benefit being appropriated by players that do not engage in drug-related R&D.<sup>94</sup>

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87. Tatum Anderson, *Novartis Under Fire for Accepting New Reward for Old Drug*, 373 THE LANCET 1414, 1414 (2009).

88. See WORLD HEALTH ORG., GUIDELINES FOR THE TREATMENT OF MALARIA THIRD EDITION 16 (2015), [http://apps.who.int/iris/bitstream/10665/162441/1/9789241549127\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/162441/1/9789241549127_eng.pdf).

89. See Anderson, *supra* note 87, at 1414.

90. See *id.*

91. Press Release, Knight Therapeutics, Inc., Knight Therapeutics, Inc., Announces FDA Approval for Impavido (Miltefosine) for the Treatment of Visceral, Mucosal and Cutaneous Leishmaniasis – Awarded Priority Review Voucher (Mar. 19, 2014), <http://www.gud-knight.com/en/knight-therapeutics-inc-announces-fda-approval-for-impavido-miltefosine-for-the-treatment-of-visceral-mucosal-and-cutaneous-leishmaniasis-awarded-priority-review-voucher>.

92. Bernard Pécoul & Manica Balasegaram, *FDA Voucher for Leishmaniasis Treatment: Can Both Patients and Companies Win?*, PLOS BLOGS (Jan. 20, 2015), <http://blogs.plos.org/speakingofmedicine/2015/01/20/fda-voucher-leishmaniasis-treatment-can-patients-companies-win/>.

93. Press Release, Knight Therapeutics, Inc., Knight Sells Priority Review Voucher to Gilead (Nov. 19, 2014), <http://www.gud-knight.com/en/knight-sells-priority-review-voucher-to-gilead>.

94. Focusing exclusively on the pediatric vouchers, GAO has found that “each of the

Signs that the industry is planning to reinvest voucher-money on R&D for tropical or rare pediatric diseases are tentative at best. When interviewed during the course of the pediatric program evaluation, representatives of pharmaceutical companies that made money from the sale of a voucher told GAO that they planned “to reinvest portions of the proceeds they received into additional research on rare pediatric diseases.”<sup>95</sup> However, all available evidence indicates that drug sponsors are not investing in innovative R&D for voucher-eligible diseases, but rather acquiring fully developed drugs and bringing them to the FDA for review.<sup>96</sup> To be sure, these companies still bear the non-negligible costs of acquiring the drugs and of regulatory review, but these are not the types of costs that the voucher program was designed to cover. As per current practice, the program is subsidizing the non-negligible, yet modest costs (by pharmaceutical industry standards) of bringing existing drugs into the United States market. And, since there is no requirement that voucher-money be used to fund R&D on voucher-eligible diseases, the drugs so far approved through voucher priority review do not target niche or underfunded areas.<sup>97</sup>

## 2. Drug Affordability

Even if we were to settle for a system of vouchers that merely brings existing drugs into the United States market, the no-strings-attached design

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drugs awarded pediatric vouchers were in development prior to the voucher program’s implementation. Any sponsors motivated by this relatively new program to attempt to develop drugs for such diseases would likely be years away from submitting their new drug applications to FDA.” GAO REPORT, *supra* note 82, at 9–10.

95. GAO REPORT, *supra* note 82.

96. *Id.*

97. In 2011, Novartis unsuccessfully redeemed the voucher it was awarded for its combination therapy for malaria. The company used the voucher to speed up review of a biologics license application for Ilaris, a canakinumab-based treatment for gouty arthritis. The Arthritis Drugs Advisory Committee at the FDA voted 11-1 against approving the drug. Following voucher redemptions fared better; in 2015, Sanofi used a voucher and obtained approval of Praluent, which is used to treat high cholesterol levels; in 2016, Gilead used a voucher and obtained approval for Odefsey, used in HIV-1 infections; and also in 2016, Sanofi again used a voucher and obtained approval for Soliqua, a combination therapy used in adults with type 2 diabetes. All three drugs approved through a priority review voucher thus target chronic and mainstream diseases. See Kurt R. Karst, *Priority Review Vouchers – Not Much Bang for The Buck*, FDA LAW BLOG (July 11, 2011), [http://www.fdalawblog.net/fda\\_blog\\_hyman\\_phelps/2011/07/priority-review-vouchers-not-much-bang-for-the-buck.html](http://www.fdalawblog.net/fda_blog_hyman_phelps/2011/07/priority-review-vouchers-not-much-bang-for-the-buck.html); Press Release, U.S. Food & Drug Admin., FDA Approves Praluent to Treat Certain Patients with High Cholesterol (July 24, 2015), <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm455883.htm>; and Press Release, Sanofi, Sanofi Receives FDA Approval of Soliqua 100/33 for the Treatment of Adults with Type 2 Diabetes (Nov. 21, 2016), <http://www.news.sanofi.us/2016-11-21-Sanofi-Receives-FDA-Approval-of-Soliqua-100-33-for-the-Treatment-of-Adults-with-Type-2-Diabetes>.



of the voucher program produces yet another undesirable result; there is no law that ensures that voucher-redeemed drugs will become available to patients at affordable prices.<sup>98</sup> In the 2006 paper, Ridley et alia submitted that “the incentive mechanism has little value if treatments are developed that do not reach patients. The developer should work with global and local stakeholders prior to FDA approval to ensure that the product will be used.”<sup>99</sup>

The caveat has two components: on the one hand, it is necessary to ensure that the drug will be manufactured and distributed in the first place; on the other, even when commercialized, voucher-spiced drugs and therapies might be priced at levels that generate substantial deadweight loss, and therefore, it is also crucial to guarantee affordability of these drugs. Currently, however, there is no legal mechanism to prevent pharmaceutical companies from setting monopolistic prices for drugs for which they have successfully redeemed a voucher. A case in point is Vimizim, the drug for which BioMarin received the inaugural pediatric voucher—the same voucher the company later transferred to Sanofi and Regeneron for \$67 million.<sup>100</sup> Vimizim costs \$380,000 a year per patient, an amount that puts it in the top five of the world’s most expensive drugs.<sup>101</sup> These numbers do not constitute an isolated example. The two drugs for which Alexion was granted tropical disease vouchers in 2015, Strensiq (for hypophosphatasia) and Kanuma (for lysosomal acid lipase deficiency), have an annual cost of \$285,000 and \$310,000 respectively.<sup>102</sup>

There have been proposals to require that pharmaceutical companies guarantee affordable access to a drug before a voucher is awarded,<sup>103</sup> but the recently approved 21<sup>st</sup> Century Cures Act, which creates a new voucher program, is silent on this topic.<sup>104</sup>

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98. See Ridley et al., *supra* note 16, at 321.

99. *Id.*

100. GAO REPORT, *supra* note 82, at 12.

101. See Alex Philippidis, *The High Cost of Rare Disease Drugs*, GENETIC ENG’G & BIOTECH. NEWS (Mar. 4, 2014), <http://www.genengnews.com/gen-exclusives/the-high-cost-of-rare-disease-drugs/77900055>. Vizimim is expected to generate \$400 million to \$500 million in yearly revenue for the BioMarin; see Marvin M. Goldenberg, *Pharmaceutical Approval Update*, 39 PHARMACY & THERAPEUTICS 337, 337–38 (2014).

102. Amy Nordrum, *Drug Prices: World’s Most Expensive Medicine Costs \$440,000 a Year, But is it Worth the Expense?*, INT’L. BUS. TIMES, (Feb. 13, 2016), <http://www.ibtimes.com/drug-prices-worlds-most-expensive-medicine-costs-440000-year-it-worth-expense-2302609>.

103. See Pécoul & Balasegaram, *supra* note 92; see Cameron Arnold & Thomas Pogge, *Improving the Incentives of the FDA Voucher Program for Neglected Tropical Diseases* (Spring/Summer 2015), <https://www.brown.edu/initiatives/journal-world-affairs/sites/brown.edu/initiatives/journal-world-affairs/files/private/articles/Arnold%20and%20Pogge.pdf>.

104. See Arnold & Pogge, *supra* note 103.

### III. RECENT EXPANSION OF THE VOUCHER PROGRAM

#### A. *Expansion of Eligible Tropical Diseases in the Wake of the Ebola and Zika Outbreaks*

As described in Part II, the FDA has the authority to expand the list of tropical diseases that qualify for priority review vouchers by administrative order.<sup>105</sup> On two separate occasions, though sharing the same motivation, Congress also added Ebola and Zika to the list. First, in December 2014, all strains of filoviruses—the family that includes the Ebola virus—were made voucher-eligible.<sup>106</sup> This was accomplished a short four months after the WHO declared the 2014 West Africa Ebola outbreak a public health emergency. In April 2016, Congress again expanded the list to include the Zika virus, only two months after the WHO declaration of public health emergency.<sup>107</sup>

The addition of Ebola and Zika to the list of voucher-eligible neglected tropical diseases is noteworthy for two reasons. First, it showcases the goodwill associated with the voucher program. While Congress disagreed on many aspects of the response to Ebola and Zika, delaying funding to address both public health emergencies,<sup>108</sup> it made each disease eligible for a priority review voucher within months of the beginning of each outbreak.<sup>109</sup> Second, the inclusion of Ebola and Zika in the voucher program offers new evidence of the misalignment between the incentives offered by the voucher program and their impact on R&D in neglected diseases.<sup>110</sup>

For the purposes of the voucher program, Ebola and Zika are treated similarly; both are tropical diseases lacking a vaccine<sup>111</sup> and endemic to areas

105. See *supra* Part II. FDA added Chagas and neurocysticercosis to the list in 2015. See Additions to Tropical Diseases, *supra* note 56, at 50, 559.

106. 21 U.S.C. § 360n(a)(2).

107. Press Release, Kaiser Family Found., House Approves Bipartisan Bill Adding Zika To FDA's Priority Review Voucher Qualifying Diseases List; President Obama Expected To Sign (Apr. 13, 2016), <http://kff.org/news-summary/house-approves-bipartisan-bill-adding-zika-to-fdas-priority-review-voucher-qualifying-diseases-list-president-obama-expected-to-sign/>; see also Sarah Ferris, *House Approves Bill to Speed Up Zika Drugs*, THE HILL (Apr. 12, 2016), <http://thehill.com/policy/healthcare/276045-house-approves-bill-to-speed-up-drugs-for-zika-virus>.

108. See Alison Kodjak, *Congress Ends Spat, Agrees to Fund \$1.1 Billion to Combat Zika*, NPR (Sept. 28, 2016), <http://www.npr.org/sections/health-shots/2016/09/28/495806979/congress-ends-spat-over-zika-funding-approves-1-1-billion>.

109. See S.2917 - *Adding Ebola to the FDA Priority Review Voucher Program Act*, *infra* note 124; see Kaiser Family Foundation, *supra* note 107.

110. Kesselheim, *supra* note 86.

111. See WORLD HEALTH ORG., *Ebola Virus Disease*, <http://www.who.int/mediacentre/factsheets/fs103/en/> (last updated Jan. 2016); see also WORLD HEALTH ORG., *Zika Virus*, <http://www.who.int/mediacentre/factsheets/zika/en/> (last updated Sept. 6, 2016).

of the world with unattractive markets for mainstream biopharmaceutical R&D.<sup>112</sup> However, the viruses' R&D histories are considerably different. In the case of Ebola, as early as 2006, the Department of Homeland Security assessed the virus as a "material threat to the U.S. population sufficient to affect national security" and the Department of Health and Human Services listed Ebola as a high-priority threat.<sup>113</sup> Furthermore, the linkage between Ebola and bioterrorism has shaped the institutional makeup of players involved in Ebola and filoviruses R&D, and by extension the amount of funding. To give but a few examples, ZMapp, a "monoclonal antibody cocktail," was developed through a partnership between the Biomedical Advanced Research and Development Authority (BARDA), the National Institute of Allergy and Infectious Diseases (NIAID), the Department of Defense, and California-based Mapp Biopharmaceutical.<sup>114</sup> Several of these entities, like BARDA or NIAID, entered multiple partnerships for different products. For instance, BARDA also started funding the development and manufacture of a recombinant vesicular stomatitis virus vaccine (rVSV) against Ebola in late 2014.<sup>115</sup> NIAID partnered with GlaxoSmithKline and the National Institutes of Health (NIH) and funded vaccines targeting the Zaire and Sudan strains of Ebola.<sup>116</sup>

The FDA was involved in the response to the Ebola outbreak and its aftermath at different levels,<sup>117</sup> from guidance drafting to clinical trials.<sup>118</sup> Notably, the agency issued eleven emergency use authorizations for

112. *See supra* Part I.

113. *See* U.S. DEP'T OF HEALTH & HUMAN SERVS., 2015 PUBLIC HEALTH EMERGENCY MEDICAL COUNTERMEASURES ENTERPRISE (PHEMCE) STRATEGY AND IMPLEMENTATION PLAN 8, 15, <https://www.phe.gov/Preparedness/mcm/phemce/Pages/2015-factsheet.aspx> (last updated Dec. 22, 2015) [hereinafter PHEMCE] (listing Ebola on the high priority threat list of the Department of Health and Human Service's "Public Health Emergency Medical Countermeasures Enterprise Strategy and Implementation Plan").

114. *Id.*

115. *Id.* at 16–17.

116. Specifically, the partnership funded a monovalent vaccine (cAd3-EBOZ) targeting the Zaire strain of Ebola and a bivalent vaccine (cAd3-EBO) targeting the Zaire and Sudan strains of Ebola. NAT'L INST. OF ALLERGY AND INFECTIOUS DISEASES, EBOLA: NIAID/GSK INVESTIGATIONAL EBOLA VACCINE (cAd3-EBOZ) (Feb. 26, 2016), <https://www.niaid.nih.gov/diseases-conditions/ebola-vaccines>.

117. U.S. FOOD & DRUG ADMIN., EMERGENCY PREPAREDNESS AND RESPONSE: EBOLA RESPONSE UPDATES FROM FDA, <http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/ucm410308.htm> (last updated Jan. 30, 2017).

118. U.S. FOOD & DRUG ADMIN., VACCINES AND RELATED BIOLOGICAL PRODUCTS, BRIEFING DOCUMENT OF THE ADVISORY COMMITTEE MEETING, LICENSURE OF EBOLA VACCINES: DEMONSTRATION OF EFFECTIVENESS (May 12, 2015), <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM445819.pdf>.

unapproved medical products or unapproved uses of approved medical products to be used in Ebola R&D between 2014 and 2016.<sup>119</sup> The FDA is also co-sponsoring post-outbreak Ebola R&D. In May 2016, the agency issued a \$3.6 million contract to Stanford University to conduct studies on survivors of the outbreak.<sup>120</sup> But even with added institutional support arising from biosecurity concerns—which Zika lacked—by the time Ebola vaccine trials began, the number of reported cases had already begun declining<sup>121</sup> and, as of early 2017, there is no approved vaccine.<sup>122</sup>

While the real question is whether the voucher program will be able to incentivize future innovation on Ebola, Zika, and similar diseases, it bears noting that the partnerships to speed up R&D on Ebola and Zika formed before the inclusion of these viruses on the voucher-eligible list. A simple look at the chronology of the response to Ebola puts the significance of expanding the program to cover Ebola into perspective. The West Africa outbreak began in March 2014, but the WHO did not declare it an emergency until mid-August.<sup>123</sup> Congress added Ebola to the voucher program in December 2014.<sup>124</sup> Meanwhile, the aforementioned recombinant vaccine (rVSV) was licensed to an American pharmaceutical company in 2010, received funding by BARDA in 2014-2015, and underwent phase I clinical trials from late 2014 to early 2015.<sup>125</sup> A bivalent vaccine (cAd3-EBO-Z) was developed with partial funding from NIH and the NIAID and entered clinical trials in 2014.<sup>126</sup> Several other vaccine candidates followed similar

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119. U.S. FOOD & DRUG ADMIN., EMERGENCY USE AUTHORIZATIONS: 2014 EBOLA VIRUS EMERGENCY USE AUTHORIZATION, <http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm#ebola> (last updated Mar. 7, 2017).

120. U.S. FOOD & DRUG ADMIN., SURVIVOR STUDIES: BETTER UNDERSTANDING EBOLA'S AFTER-EFFECTS TO HELP FIND NEW TREATMENTS, <http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/CMRegulatoryScience/ucm500274.htm> (last updated Jan. 31, 2017).

121. See Kai Kupferschmidt, *Second Ebola Vaccine Trial May Be Too Little, Too Late*, SCI. MAG. (Apr. 14, 2015), <http://www.sciencemag.org/news/2015/04/second-ebola-vaccine-trial-may-be-too-little-too-late>.

122. There is however hope that a vaccine might soon reach the market. See *Final Trial Results Confirm Ebola Vaccine Provides High Protection Against Disease*, WORLD HEALTH ORG., (Dec. 23, 2016), <http://www.who.int/mediacentre/news/releases/2016/ebola-vaccine-results/en/>.

123. Media Centre Statement, World Health Org., Statement on the 1st meeting of the IHR Emergency Committee on the 2014 Ebola Outbreak in West Africa (Aug. 8, 2014), <http://www.who.int/mediacentre/news/statements/2014/ebola-20140808/en/>.

124. See S.2917 - *Adding Ebola to the FDA Priority Review Voucher Program Act*; X see also Public Law No: 113-233, Dec.16, 2014.

125. J.A. Regules et al., *A Recombinant Vesicular Stomatitis Virus Ebola Vaccine*, NEW ENG. J. MED. 330, 331 (Jan. 26, 2017), <http://www.nejm.org/doi/full/10.1056/NEJMoa1414216#t=article>.

126. NAT'L INST. OF ALLERGY AND INFECTIOUS DISEASES, *supra* note 116.

timelines.<sup>127</sup> In all cases, partnerships formed before the tropical disease vouchers expanded to cover Ebola and other filoviruses, and economic resources mobilized before the voucher incentive. In the future, the sponsor who obtains regulatory approval from the FDA to market an Ebola vaccine in the United States will be able to collect the voucher reward—either by using it to speed up review of another drug or by selling it.

The impact of the voucher program on Zika is identical, although the R&D background is different. Even though the virus was identified in 1947, science on Zika is significantly less developed than on Ebola.<sup>128</sup> Before 2015, Zika “was not considered to be a major pathogen,” but since the outbreak, nearly 1,000 scientific publications on the virus have emerged.<sup>129</sup> Disease complexity is not the only factor that has slowed down R&D in this area. While linked to devastating problems like microcephaly, the virus is not lethal like Ebola, is not associated with bioterrorism, and before popularization of air travel was unlikely to spread in a meaningful way outside endemic areas in the developing world.<sup>130</sup>

As of early 2017, there are at least 40 entities involved in the development of a Zika vaccine.<sup>131</sup> Some of these companies were or still are also involved in Ebola R&D.<sup>132</sup> Additionally, there is federal funding from the NIH/NIAID<sup>133</sup> and the Walter Reed Army Institute of Research (Department

127. The remaining cases are VesiculoVax, MVA-BN Filo and AdVAdVac, DPX-Ebola, Novavaxglycoprotein recombinant vaccine, VXA ZEBOV GP, the Rabies Vector vaccine, Inovio’s Ebola vaccine, the Baculovirus Expression Vector System-derived Ebola vaccine, GOVX-E301 and GOVX-E302. See William W. Fisher & Katrine Geddes, *Learning From Ebola: How Drug-Development Policy Could Help Stop Outbreaks of Infectious Diseases* 17–26 BERKMAN CTR. FOR INTERNET & SOC’Y, GLOBAL ACCESS IN ACTION (GAiA) (Oct. 14, 2015), [https://cyber.harvard.edu/people/tfisher/Learning\\_from\\_Ebola.pdf](https://cyber.harvard.edu/people/tfisher/Learning_from_Ebola.pdf). All of these vaccines received support from U.S. government agencies, with NIAID funding several candidates.

128. See Jeff Lyon, *Zika: Worse Than Thalidomide?*, 319 JAMA 1246, 1248 (2016) (discussing the areas on which long-term Zika research is still needed).

129. See Alan D. T. Barrett, *Zika Vaccine Candidates Progress through Nonclinical Development and Enter Clinical Trials*, NPJ VACCINES (2016), <http://www.nature.com/articles/npjvaccines201623>.

130. See Daniel R. Lucey & Lawrence O. Gostin, *The Emerging Zika Pandemic – Enhancing Preparedness*, 315 JAMA 865, 866 (2016) (contrasting the transregional magnitude of the 2015 Zika outbreak with previous outbreaks).

131. *Id.*

132. See, e.g., Matthew Patane, *NewLink Genetics gets \$8.1 million for Ebola vaccine*, DES MOINES REG. (Sept. 25, 2015), <http://www.desmoinesregister.com/story/tech/2015/09/25/newlink-genetics-ebola-vaccine-dtra-money/72793540/>; See Katie Thomas, *The Race for a Zika Vaccine*, N.Y. TIMES (Nov. 19, 2016), [https://www.nytimes.com/2016/11/20/business/testing-the-limits-of-biotech-in-the-race-for-a-zika-vaccine.html?\\_r=0](https://www.nytimes.com/2016/11/20/business/testing-the-limits-of-biotech-in-the-race-for-a-zika-vaccine.html?_r=0).

133. See NAT’L INST. OF ALLERGY & INFECTIOUS DISEASES, HOW NIAID IS ADDRESSING ZIKA VIRUS, <https://www.niaid.nih.gov/diseases-conditions/addressing-zika> (last updated Jul. 27, 2016).

of Defense).<sup>134</sup> At the time of writing, clinical trials are underway.<sup>135</sup>

Congress added Zika to the list of voucher-eligible diseases in April 2016.<sup>136</sup> As with Ebola, there was no window of time for the voucher program to possibly have any bearing on the R&D landscape that generated the current vaccine candidates. Yet the program will reward sponsors of Zika vaccines for gaining FDA approval. Even so, Congress rushed to approve the inclusion of Zika on the tropical disease list—the same Congress that shortly thereafter could not agree on funding for the domestic response to Zika, stalling the reallocation of Ebola response funds, at a time when the Centers for Disease Control (CDC) were running out of money to combat the spread of Zika.<sup>137</sup>

The expansion of the list of tropical diseases to include Ebola and Zika is aligned with the architecture of the voucher program: it opens an additional stream of incentives to two traditionally neglected diseases that are endemic to markets of limited purchasing power. However, the condensed period of time in which funders and innovators came together to enhance R&D on Ebola and Zika sheds light on the fact that all resulting biopharmaceutical innovation was completely detached from this type of incentives program. Instead, that innovation was both hampered by pre-existing market failures (like the pre-2015 concentration of Zika cases in neglected markets) and driven by pre-existing incentives (like the role of bioterrorism in Ebola R&D or the fear factor introduced by the high number of fatalities during the West Africa Ebola outbreak and the congenital defects linked with Zika).

The issue therefore becomes one of assessing whether adding Ebola and Zika to the voucher program is likely to encourage future R&D on these pathogens. Whereas Ebola will likely maintain the status of high priority threat,<sup>138</sup> Zika ceased to be considered a public health emergency in November 2016.<sup>139</sup> Typically, post-emergency funding for outbreak diseases decreases quickly.<sup>140</sup> While the magnitude of the Zika outbreak will probably

134. See Gary Sheftick, *Army Researchers Testing Zika Vaccine*, U.S. ARMY (Jul. 6, 2016), [https://www.army.mil/article/170960/army\\_researchers\\_testing\\_zika\\_vaccine](https://www.army.mil/article/170960/army_researchers_testing_zika_vaccine).

135. Barrett, *supra* note 129.

136. See Clarke, *supra* note 107.

137. See Kelsey Snell, *Another Failed Zika Vote Could be the Start of a Resolution*, WASH. POST (Sept. 6, 2016), [https://www.washingtonpost.com/news/powerpost/wp/2016/09/06/another-failed-zika-vote-could-be-the-start-of-a-resolution/?utm\\_term=.4da19293bdc9](https://www.washingtonpost.com/news/powerpost/wp/2016/09/06/another-failed-zika-vote-could-be-the-start-of-a-resolution/?utm_term=.4da19293bdc9).

138. PHEMCE, *supra* note 113; see also Orlando Cenciarelli et al., *Viral Bioterrorism: Learning the Lesson of Ebola Virus in West Africa 2013-2015*, 210 VIRUS RES., 318, 319 (2015) (noting that, even though the West Africa outbreak is over, Ebola remains one the major pathogens associated with potential bioterrorism threats).

139. See Lena H. Sun, *WHO No Longer Considers Zika a Global Health Emergency*, WASH. POST (Nov. 18, 2016), [https://www.washingtonpost.com/news/to-your-health/wp/2016/11/18/who-no-longer-considers-zika-a-global-health-emergency-2/?utm\\_term=.96d5c724f0f2](https://www.washingtonpost.com/news/to-your-health/wp/2016/11/18/who-no-longer-considers-zika-a-global-health-emergency-2/?utm_term=.96d5c724f0f2).

140. The WHO started reallocating Ebola funds to Zika even before the response to Ebola

sustain interest and moderate funding for R&D for a while, domestic and international focus will shift towards the next infectious disease.<sup>141</sup> That leaves the question of whether the vouchers are sufficiently powerful to stimulate additional innovation around Zika and Ebola. As discussed in Part IV, the economic footprint of the program appears to be too small to achieve that goal.<sup>142</sup>

*B. The 21<sup>st</sup> Century Cures Act and Vouchers for Medical Countermeasures*

The FDA defines medical countermeasures as “products (biologics, drugs, devices) that may be used in the event of a potential public health emergency stemming from a terrorist attack with a biological, chemical, or radiological/nuclear material, a naturally occurring emerging disease, or a natural disaster.”<sup>143</sup> The 21<sup>st</sup> Century Cures Act (“the Act”) creates a third type of voucher program covering these products.<sup>144</sup> The Act defines a “material threat medical countermeasure application” as an application for a drug that is intended “to prevent, or treat harm from a biological, chemical, radiological, or nuclear agent identified as a material threat;”<sup>145</sup> or “to mitigate, prevent, or treat harm from a condition that may result in adverse health consequences or death and may be caused by administering a drug, or biological product against such agent.”<sup>146</sup> Similar to the pre-existing programs, vouchers for medical countermeasures are transferable, and there is no limitation on the number of times they may be sold or otherwise transferred.<sup>147</sup> Drugs qualifying for the new voucher program may cumulatively benefit from “any other incentive programs.”<sup>148</sup> A temporal limitation applies, however, as the program is scheduled to sunset on October 1, 2023.<sup>149</sup>

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was completed, for instance.

141. Before Ebola and Zika, the WHO had issued two emergency declarations, one for H1N1 (swine flu) in 2009 and another for polio in 2014. Other infectious disease outbreaks never achieved that status, such as Chikungunya.

142. See *infra* note 153.

143. *What are Medical Countermeasures?*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/AboutMCMi/ucm431268.htm> (last updated Oct. 12, 2016).

144. 21st Century Cures Act, § 3086.

145. 21st Century Cures Act, § 3086 (a)(4)(A)(i).

146. 21st Century Cures Act, § 3086 (a)(4)(A)(ii).

147. 21st Century Cures Act, § 3086 (b)(2).

148. 21st Century Cures Act, § 3086 (e).

149. 21st Century Cures Act, § 3086 (g).

#### IV. THE FUTURE OF THE PROGRAM

##### A. Possible Fixes and Alternatives

###### 1. Existing Proposals

Most proposals to reform the voucher program focus on the two problems described in Part III. The first is the lack of innovative R&D for diseases that qualify for vouchers. In both the nearly decade-long tropical disease program and the more recent pediatric program, the preferred *modus operandi* of pharmaceutical companies seeking a voucher has been to avoid engaging in costly R&D—the market failure that the vouchers were supposed to attenuate—and instead bear the substantially lower costs of bringing existing drugs (or versions that do not appear to be more effective) to regulatory review. To counter this trend, there have been several calls for the recipient of a voucher to be required to reuse part of the voucher money for R&D in voucher-eligible diseases, or to “show some level of investment” in R&D related to the voucher-qualifying drug.<sup>150</sup> The way in which investment would be determined—by what metrics and at what stage—remains to be described in the literature. Other proposals try to address the question of affordability in the context of the voucher program by suggesting that would-be voucher recipients should be required to agree *ex ante* to sell the drug at affordable prices.<sup>151</sup>

A more radical approach would be to recognize that the voucher program is indeed failing as an incentives mechanism for R&D in underfunded diseases. As currently designed, the program is more likely to result in cross-subsidization of mainstream diseases than in innovative R&D for pathogens like Ebola, Zika or rare pediatric diseases, as illustrated by the analysis of the relationship between the addition of Ebola and Zika in the priority review voucher program and the formation of Ebola and Zika R&D partnerships during the recent outbreaks.<sup>152</sup>

Even when considering the prices fetched by the sales of vouchers in recent years, and even if the program did not trigger any R&D or affordability concerns, it might be that the program will always be too small to truly impact allocation of R&D resources within the pharmaceutical industry. As Aaron Kesselheim points out:

The prospect of a payment of as much as \$350 million a decade or so in the future may nevertheless be insufficient for large pharmaceutical manufacturers accustomed to substantially higher revenues to change their

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150. See Kesselheim et al., *supra* note 86, at 1982.

151. See Pécoul & Balasegaram, *supra* note 92.

152. See *supra* Part III.A.



investments to tropical or rare pediatric diseases. For instance, Sanofi, which was involved in the purchase of 2 vouchers, reported revenues of more than \$43 billion in 2014.<sup>153</sup>

Against this backdrop, prolonging the life of the voucher program not only reinforces the market failures that are left unsolved by the patent system,<sup>154</sup> it also perpetuates a system that is nominally cost-neutral to the FDA but that in practice entails resource displacement and affects the agency's priority-setting agenda.<sup>155</sup>

Nevertheless, political support for the voucher system—rooted in a misconception of the vouchers as cost-neutral drivers of increased R&D in neglected diseases—does not appear to wane. Calls for the program to sunset or be cancelled are likely to be futile, as they have been in the past.<sup>156</sup> The 21<sup>st</sup> Century Cures Act supports this view, as described in the following section. Given this scenario, if and when Congress revisits the voucher program, it would be critical to at least mitigate the R&D and affordability problems triggered by current practices. In particular, a requirement establishing that a modicum of the revenue generated by the sale of a voucher be redirected towards a voucher-eligible disease would be a first step, and potentially not impossible to negotiate from a political standpoint. Restrictions on the ability of sponsors to obtain a voucher by gaining FDA approval for drugs already commercialized abroad should also be put in place, although it might be harder to compromise on these restrictions. Finally, making the vouchers conditional on price negotiations guaranteeing affordability of drugs would also be desirable, although probably another hard sell.

## 2. Impact of the 21st Century Cures Act

The 21st Century Cures Act has been a controversial piece of legislation throughout its drafting history, having been dubbed “one of the most-lobbied health care bills in recent history, with nearly three lobbyists working for its passage or defeat for every lawmaker on Capitol Hill.”<sup>157</sup> The Act allocates

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153. See Aaron S. Kesselheim, *Experience With the Priority Review Voucher Program for Drug Development*, 314 JAMA 1687, 1688 (2015).

154. Trouiller et al., *supra* note 17.

155. See Witty, *supra* note 19.

156. In the past, some of these calls have come from the FDA itself. See John Carroll, *That Priority Review Voucher Program? The FDA Hates It*, FIERCEBIOTECH (Mar. 3, 2016), <http://www.fiercebiotech.com/r-d/priority-review-voucher-program-fda-hates-it>.

157. Sydney Lupkin, *Legislation That Would Shape FDA and NIH Triggers Lobbying Frenzy*, NPR (Nov. 25, 2016), <http://www.npr.org/sections/health-shots/2016/11/25/503176370/legislation-that-would-shape-fda-and-nih-triggers-lobbying-frenzy>; see also Michael Hiltzik, *The 21st Century Cures Act: A Huge Handout to the Drug Industry Disguised as a Pro-Research Bounty*, L.A. TIMES (Dec. 5, 2015),

over \$6 billion to fund medical research, but has drawn extensive criticism over provisions that codify long-standing demands of the pharmaceutical industry.<sup>158</sup> Extensive portions of the Act affect the FDA,<sup>159</sup> including the process(es) through which the Agency reviews drug applications.<sup>160</sup>

As noted above, the Act also has a direct impact on the priority review voucher program, namely by creating a new stream for medical countermeasures.<sup>161</sup> Moreover, the new legislation also makes some strides in incorporating mandatory assessment mechanisms for all types of vouchers (and not just for pediatric vouchers, as until now), as well as reinforcing the idea that the vouchers are supposed to enhance innovation for neglected or rare diseases. Section 3014 of the 21st Century Cures Act mandates that GAO conduct a study of the multiple priority review voucher programs.<sup>162</sup> The resulting reports must be submitted to the Committee on Health, Education, Labor, and Pensions of the Senate and to the Committee on Energy and Commerce of the House by January 31, 2020.<sup>163</sup> Section 3014(c) provides an exhaustive list of issues to be addressed by GAO. Among these, it is worth highlighting the provision that mandates a determination of “whether, and to what extent, the voucher impacted the sponsor’s decision to develop the drug.”<sup>164</sup> For drugs approved under the neglected tropical disease program, the proposed legislation mandates a determination of whether the approval or licensure of the drug addresses “global unmet needs” in the prevention or treatment of tropical diseases.<sup>165</sup> And, similarly for the rare pediatric diseases voucher program, the report must present a determination of whether the

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<http://www.latimes.com/business/hiltzik/la-fi-hiltzik-21st-century-20161205-story.html>; Sydney Lupkin & Steven Findlay, *Winners and Losers with the 21st Century Cures Bill*, NPR (Dec. 2, 2016), <http://www.npr.org/sections/health-shots/2016/12/02/504139105/winners-and-losers-if-21st-century-cures-bill-becomes-law>.

158. See Russell Berman, *Congress Nears a Breakthrough on Medical Research Funding*, THE ATLANTIC (Dec. 1, 2016), <https://www.theatlantic.com/politics/archive/2016/12/cures-act-compromise-elizabeth-warren/509228/> (describing criticism of the Act); see also Sam Stein, Matt Fuller & Ryan Grim, *Congress Is About to Pass A Bill That Shows D.C. at its Worst — It May Also Turn Around the Opioid Crisis and Cure Cancer*, HUFF. POST (Nov. 29, 2016), [http://www.huffingtonpost.com/entry/congress-21st-century-cures\\_us\\_583e3d98e4b0ae0e7cdaca32](http://www.huffingtonpost.com/entry/congress-21st-century-cures_us_583e3d98e4b0ae0e7cdaca32); Ameet Sarpatwari & Michael Sinha, *The Current 21st Century Cures Legislation Is Still A Bad Deal For Patients*, HEALTH AFFS. BLOG (Nov. 30, 2016), <http://healthaffairs.org/blog/2016/11/30/the-current-21st-century-cures-legislation-is-still-a-bad-deal-for-patients/>.

159. 21st Century Cures Act, Title II.

160. For an overview of the FDA-specific provisions in the proposed Act, see Brennan, *supra* note 48.

161. See Brennan, *supra* note 48.

162. See 21st Century Cures Act, § 3014 (a).

163. 21st Century Cures Act, § 3014 (b).

164. 21st Century Cures Act, § 3014 (c)(1)(B).

165. 21st Century Cures Act, § 3014 (c)(1)(C)(i).

approval or licensure of the drug addressed an “unmet need.”<sup>166</sup> If a priority review voucher for medical countermeasures is approved, a similar determination needs to be made, assessing whether approval or licensure of a drug “affected the Nation’s preparedness against a chemical, biological, radiological, or nuclear threat, including naturally occurring threats.”<sup>167</sup> The Act further emphasizes the need by establishing a separate requirement that the GAO report assess “whether any improvements to such programs are necessary to appropriately target incentives for the development of drugs that would likely not otherwise be developed, or developed in as timely a manner.”<sup>168</sup> Collectively, these requirements are more stringent than the ones that were in place after the GAO’s study of the pediatric voucher program.<sup>169</sup>

Catering to the concerns periodically voiced by the FDA about the impact of the voucher programs on its resources, the Act also mandates an evaluation of “the resources used by the Food and Drug Administration in reviewing drugs for which vouchers were used, including the effect of the programs on the Food and Drug Administration’s review of drugs for which priority review vouchers were not awarded or used.”<sup>170</sup>

While the 21st Century Cures Act does nothing to directly address the two main problems associated with the vouchers—lack of R&D on neglected diseases and affordability—it does provide a better normative framework for evaluating the successes and failures of the program as an incentives mechanism. This modest improvement should facilitate informed debate about the merits of the program in years to come.

#### *B. Revisiting the role of FDA as a locus for incentives policy*

In addition to issues that are intrinsic to the awarding and use of the vouchers, Congress’ use of an agency like the FDA as tool for innovation policy raises further questions. The FDA has a storied role in pharmaceutical innovation, but one that is primarily associated with its mission as a gatekeeper: the main focus of the agency is to ensure that drugs are safe and effective, a role that is undeniably shaped by underlying policy choices. As Peter Barton Hutt has written, it “is difficult to find any significant issue faced by FDA that is not ultimately a matter of policy, informed by both scientific and legal considerations.”<sup>171</sup>

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166. 21st Century Cures Act, § 3014 (c)(1)(C)(ii).

167. 21st Century Cures Act, § 3014 (c)(1)(C)(iii).

168. 21st Century Cures Act, § 3014 (c)(3)(B).

169. *See* 21 U.S.C. § 360ff(i)(1)(B).

170. 21st Century Cures Act, § 3014 (c)(3)(A).

171. Peter Barton Hutt, *Historical Themes and Developments at FDA Over the Past Fifty Years*, FDA IN THE TWENTY-FIRST CENTURY: THE CHALLENGES OF REGULATING DRUGS AND NEW TECHNOLOGIES 28 (2015).

In addition to its gatekeeping function, the FDA also has explicit and implicit roles in innovation policy, as demonstrated by Rebecca Eisenberg.<sup>172</sup> For example, FDA regulation has become “an important adjunct to the patent system in protecting innovating firms from competition in product markets.”<sup>173</sup> The types of market exclusivity that FDA regulation layers on top (or, in some cases, in lieu of) patent rights directly impacts decision-making processes in the pharmaceutical industry, particularly at the level of funding and R&D strategies.

But while the combined roles played by the FDA may and do effectively shape the types of pharmaceutical innovation that we get,<sup>174</sup> never has the agency been called to partake in an incentives scheme as it does under the voucher program. It is one thing to acknowledge that FDA regulation and rulemaking is informed by policy and will, which in turn affect industry behavior; it is another to use agency review as an integral component of the economic incentive.

As described in Ridley’s 2006 paper and subsequently implemented, the program purports to have no impact on the Agency because it is cost-neutral—that is, the economic cost of resource displacement is absorbed by the fee paid by drug sponsors wishing to redeem the voucher. Moreover, the 90-day notification requirement ensures that the agency will have the time necessary to adjust to an expedited timeline.<sup>175</sup> Yet a simple budgetary balancing act does not truly depict the extent of the impact of the voucher program on the agency, which has been vocal about not endorsing the vouchers.<sup>176</sup> The GAO Report, albeit focused solely on pediatric vouchers, made the agency’s position abundantly clear:

FDA officials stated that, while they strongly support the goal of incentivizing drug development for rare pediatric diseases, they have seen no evidence that the program is effective. The program’s authorization, as amended, is set to terminate October 1, 2016, and FDA officials said they do not support the program’s continuation. They expressed concern that the program adversely affects the agency’s ability to set its public health priorities by requiring FDA to provide priority reviews of new drug applications that would not otherwise qualify if they do not treat a serious condition or provide a significant improvement in safety or effectiveness. Additionally, FDA officials said that the additional workload from the program strains the agency’s resources.<sup>177</sup>

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172. See Eisenberg, *supra* note 5, at 346.

173. *Id.* at 347.

174. *Id.* at 346.

175. 21 U.S.C. § 360n(b)(4).

176. See Carroll, *supra* note 156.

177. HIGHLIGHTS OF GAO-16-319, *supra* note 84.

As the 21<sup>st</sup> Century Cures Act is implemented, the FDA will continue to be part of an incentives scheme that the Agency finds contrary to its mission. The impact and consequences of allowing private parties to influence Agency goal setting has yet to be fully addressed in the literature and raises questions that exceed the scope of the Article. Nevertheless, as new vouchers are granted and redeemed, this is an area that deserves close monitoring.

## V. CONCLUSION

Although Congress acted with good intentions, the efficacy of the program is questionable. GAO's evaluation of the pediatric voucher program was inconclusive, but evidence seems to suggest that most, if not all, drugs that have received a voucher were already in development before each of the voucher categories was implemented. In this sense, the incentive provided by the vouchers is perversely diverted towards areas where there are fewer, if any, shortages of R&D incentives. The current design of the program also fails to ensure that drugs for which a voucher is redeemed are available to patients at affordable prices.

Despite these shortcomings, the recent additions of filoviruses and Zika to the list of voucher-eligible diseases, as well of the expansion of the program to cover medical countermeasures, indicate that Congressional support for the vouchers will likely endure. The 21<sup>st</sup> Century Cures Act is poised to improve the parameters for evaluation of the program in future GAO reports, but does little to solve the incentives problem at the core of the voucher mechanism, or to address its affordability issues.

Finally, while it has been widely documented that current incentives for R&D in low-burden diseases are subpar, co-involving the FDA in experiments with alternative incentives models is not without its risks. The program displaces Agency resources, arguably impacting the Agency's overall implicit and explicit innovation policies. It also brings into question whether the FDA is the best locus for anchoring prize-type incentives, even in indirect forms such as the voucher program.

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