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COMMENTARY

Priority Review Vouchers: GAO Report Provides Scant Evidence of Success

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Priority Review Voucher (PRV) programs are in place to provide incentives for drug development in areas of unmet need where traditional incentives are felt to be insufficient. PRV incentives were first passed into law in 2007 for neglected tropical diseases and subsequently expanded to rare pediatric diseases and medical countermeasures. In 2016, Congress tasked the Government Accounting Office (GAO) to conduct a "study addressing the effectiveness and overall impact of the…priority review voucher programs." That report was published recently and as it provides weak evidence of "overall impact," it deserves scrutiny by policy makers and legislators as they consider the value of PRV incentives in driving targeted therapeutic innovation.[1]

COMMENTARY

In 2006, faculty from Duke University published an article proposing that the US government adopt a novel program to incentivize therapeutic development in neglected tropical infectious diseases. The article posited that existing incentives were insufficient to attract drug development in these disease due to inadequate US market size resulting in insufficient projected revenues to offset the substantial costs of clinical development.[2] Existing incentives at that time included government cost-sharing in development ("push" incentives; e.g., orphan drug grants) and extending periods of data exclusivity ("pull" incentives; e.g., orphan drug exclusivity). Importantly, these incentives impart economic cost to the government and taxpayers, either directly, such as with grants, or indirectly by delaying generic competition given longer market exclusivity.

The 2006 paper proposed a new incentive where drugs that treated certain designated tropical diseases, upon US Food and Drug Administration (FDA) approval, would be granted a transferable voucher for a "Priority Review." These vouchers would allow the holder to submit a subsequent application to the FDA for a non-priority drug (i.e., either not treating a serious condition and/or not an important therapeutic advance) and yet receive a 6-month "priority" review period rather than the standard 10-month review. The authors posited that getting to market 4 months earlier could be worth US $300 million or more, providing a large potential economic value to the grantee that could be realized by exercising it for another of their own drug programs or through sale of the voucher. The paper also stated that unlike traditional push and pull incentives, PRVs would provide a public good without costs to the government, beyond those needed for the FDA to do an expedient review. Following this publication, Congress passed a PRV program for neglected tropical diseases in 2007. Congress later expanded PRVs to rare pediatric diseases and to medical countermeasures. The first PRV was granted by the FDA in 2009; 31 total PRVs were awarded through 2019, yet only 16 have been redeemed (**Figure 1**). Of note, the majority of these PRV grants and redemptions have been in the last 5 years.

As a part of the 2016 law called the 21st Century Cures Act, Congress required the GAO to evaluate the PRV programs; the GAO published its report in January 2020. The report is intended to inform future congressional actions regarding any renewal of existing PRV programs (the pediatric PRV program begins sunsetting at the end of fiscal year (FY)2020, medical countermeasures PRVs in 2023) or expanding PRVs to other areas. The report provides a mixed picture of the value of these incentive programs, with little evidence PRVs truly drive new drug development. Further, the report offers no clear conclusions on the actual "costs" to the FDA and its overall mission. As Congress considers future legislation on PRVs, there are several points related to the assumptions of the 2006 paper, the subsequent changes in the drug development and the regulatory environment, and the findings by the GAO that are important to consider. Some of these are discussed below.

The 2006 paper proposed that the value of obtaining market approval 4 months early upon redeeming a voucher could be worth US $322 million, importantly offsetting the costs of clinical development for a designated product. Although the paper expressed uncertainties on what that actual value might prove to be, it stated the figure could be considerably higher. The GAO report found that whereas one early PRV sold for US $350 million, the publicly available data on the 9 PRVs sold since 2017 showed prices paid between $80 and $130 million, a far lower number. Although the prices paid may not be a perfect measure of overall value, particularly as many PRVs have not been sold or redeemed, the prices support that the original paper's assumptions were significant overestimates and therefore the financial incentives are not as robust as assumed when the PRVs were first legislated.

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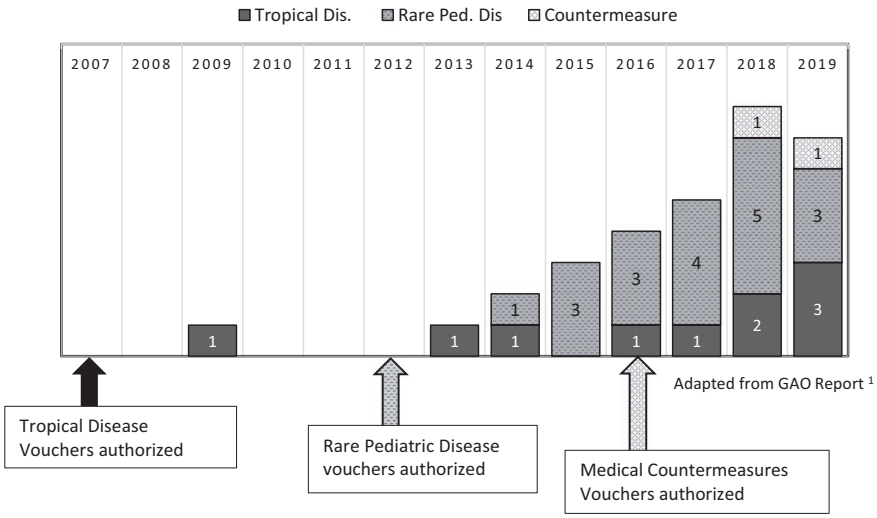

Figure 1 Number and types of priority review vouchers granted fiscal year (FY)2009–2019. GAO, Government Accounting Office.

A measure of success of these incentives is the robustness of PRVs granted and clinical development in the relevant disease areas (see **Figure 1**). In the 13 years PRVs have been in place for neglected tropical diseases, the report states that only 10 vouchers have been awarded. One analysis cited in the report states that in years since the first PRV legislation, the proportion of drugs in development for the designated tropical diseases has marginally decreased relative to the general development pipeline.[3] The lack of a proportional increase in development and the paucity of vouchers granted for tropical diseases suggest the PRVs have not had a significant impact. For medical countermeasures against biological threats, only two PRVs have been granted to date. On the other hand, the recent efforts by Biomedical Advanced Research and Development Authority (BARDA) and the administration on "Project Warp Speed" to rapidly develop coronavirus disease 2019 (COVID-19) vaccines provides a striking example of how aggressive and directed application of more traditional push incentives may produce timely and robust results.[4]

The most successful PRV program in terms of PRVs awarded has been in rare pediatric diseases, with 19 PRVs awarded since that program was instituted in 2012. One important point is that 7 of these 19 were granted by 2016. With fewer than 4 years from legislation to the FDA approvals for which these 7 vouchers were granted, the relevant drugs were likely well into development when the program started, as clinical development commonly lasts 6–7 years.[5] For at least these seven drugs, the incentives were likely not a factor in initiating development. Indeed, another study cited by the report found no effect of the rare pediatric disease program on drugs entering or successfully completing development for relevant diseases.[6]

It is important to understand that rare diseases already had existing incentives, notably orphan drug incentives, which include both broader and longer exclusivity periods than standard drugs (pull incentives), as well as tax breaks and clinical development grants (push incentives). Given the GAO's findings, it seems likely that providing stronger traditional incentives for pediatric drug development could be more successful than PRVs. Further, unlike assumed in the 2006 paper, recent market trends show that products approved for rare pediatric diseases may be able to garner significant United States revenue For instance, the average annual pricing of drugs approved under the Orphan Drug programs was reported to be over US $180,000 in 2018.[7] Many of the drugs granted rare pediatric disease PRVs are reportedly priced considerably higher than that, with the highest price reported for a drug granted a PRV of ~ $2.1 million (a gene therapy for spinal muscular atrophy, albeit this is a one-time administration).[8] Although the GAO report does not delve into ultimate pricing of products granted PRVs, it is important to consider if PRVs are still needed in driving development, particularly in rare pediatric diseases. Notably, the report cites discussions with seven sponsors granted PRVs. These sponsors reported that whereas PRVs were a factor in development decisions, only one sponsor reported that the prospect of a PRV was a primary factor in moving a drug into pediatric development.

Besides assumptions on value and effectiveness, another important consideration are the costs of the programs to the FDA. The GAO report considers the US $44 million of additional User Fees collected for the 16 redeemed PRVs as a potential balance to any associated resources needed to conduct these expedient reviews. However, the report further notes that the FDA does not track resources in a way that allowed for an analysis of the sufficiency of this offset. Regardless, one must understand that the FDA is not rife with spare capacity. First, the FDA is chronically under-resourced in its professional staff, due to issues with both hiring and retention.[9] Further, the agency cannot hire flexibly to meet surges in workload. This reality is further compounded by the FDA not being able to predict when or in what therapeutic area a PRV may be redeemed. To meet the demands when a voucher is redeemed, the FDA has to shift resources away from other important activities, such as authoring new product guidances or providing additional interaction sponsors. Although not having data on

the "costs" of a redeemed voucher to the drug review program, the report states that the administration of the PRV programs imposes its own demands on the FDA, including drafting PRV-related guidance, writing regulations to modify the eligible diseases, and responding to requests for rare pediatric disease designations. Whereas not explicitly considered in the report, the fundamental basis of the program is tantamount to putting the FDA service up for sale to the highest bidder. Any perception of such is particularly problematic, as critics have implied that user fees themselves have made the FDA more beholden to sponsors, leading to an increase in drug safety issues.[10] Although this author disagrees with this implication, trust in the FDA's independence is critical to the public trust in the safety and efficacy of US therapeutics.

In summary, the GAO report provides little evidence that the PRV programs have significantly incentivized development in the three areas where PRVs are currently in place. In considering renewal of the Rare Pediatric and/or the Medical Countermeasure PRV programs and/or any potential expansion of the PRV programs to other disease areas, it is critical for Congress to assess the true burden and costs of the program for the FDA in a way the GAO could not and the impact of PRVs on the FDA's mission, particularly since the GAO report shows weak evidence of PRVs truly incentivizing development. Further, critical appraisals of PRV incentives must include assumptions that reflect contemporary evidence development drivers, how drug development and regulatory review have changed since 2007, as well as experience with drug pricing of products granted PRVs, rather than continuing to rely on assumptions from an analysis authored in 2006 that appear to no longer fully hold.

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1. US Food and Drug Administration. Drug Development: FDA's priority review voucher programs: Published: January 31, 2020. <https://www.gao.gov/products/GAO-20-251>. Accessed May 30, 2020.
2. Ridley, D.B., Grabowski, H.G. & Moe, J.L. Developing drugs for developing countries. *Health Aff.* **25**, 313–324 (2006).
3. Jain, N., Hwang, T., Franklin, J.M. & Kesselheim, A.S. Association of the priority review voucher with neglected tropical disease drug and vaccine development. *JAMA* **318**, 388–389 (2017).
4. <https://www.hhs.gov/about/news/2020/06/16/fact-sheet-explaining-operation-warp-speed.html>. Accessed July 25, 2020.
5. <http://phrma-docs.phrma.org/sites/default/files/pdf/rd_brochure_022307.pdf>. Accessed May 30, 2020.
6. Hwang, T.J., Bourgeois, F.T., Franklin, J.M. & Kesselheim, A.S. Impact of the priority review voucher program on drug development for rare pediatric diseases. *Health Aff.* **38**, 313–319 (2019).
7. <https://hbr.org/2017/04/the-cost-of-drugs-for-rare-diseases-is-threatening-the-u-s-health-care-system>. Accessed May 30, 2020.
8. <https://www.forbes.com/sites/joshuacohen/2019/06/05/at-over-2-million-zolgensma-is-the-worlds-most-expensive-therapy-yet-relatively-cost-effective/#21643e8a45f5>. Accessed May 30, 2020.
9. <https://endpts.com/after-closing-the-gap-on-new-hires-fda-could-face-an-exodus-of-top-regulators/>. Accessed May 30, 2020.
10. Gabay, M. The prescription drug user fee act: cause for concern? *Hosp. Pharm.* **53**, 88–89 (2018).