



# Priority review vouchers for tropical diseases

Impact, distribution, effectiveness,  
and potential improvements

Global Health and  
Development Department

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## Editorial note

This report was produced by Rethink Priorities during August and September 2023. The project was supported by Open Philanthropy (“OP”), which does not necessarily endorse our conclusions.

The report evaluates the value and effectiveness of the United States’ Tropical Disease Priority Review Voucher Program, which was initiated in 2007 to incentivize research and development for medical products targeting neglected tropical diseases. (While PRVs have since been legislated for purposes, we focus our attention on this application.) Specifically, we describe some of the program's history to date (e.g., past issuances, voucher sales/use dynamics, and evidence of gaming), the usage extent of PRV-awarded medical products, academic and anecdotal evidence of the program's incentive effect, and ways in which we think the program could be improved.

We have tried to flag major sources of uncertainty in the report and are open to revising our views as more information becomes available. While preparing this report for publication, we learned that Valneva was awarded a PRV for developing the first Chikungunya vaccine in November 2023 ([Dunleavy, 2023](#)), but we did not incorporate this information in the report or associated spreadsheets.

We are grateful for the invaluable input of our interviewees. Please note that our interviewees spoke with us in a personal capacity and not on behalf of their respective organizations.

## Executive summary

We catalog [information about the 13 issuances of Priority Review Vouchers](#) (PRV) under the United States' Tropical Disease PRV Program and, for the seven cases with sufficient data, attempt to estimate the number of treatment courses per 1,000 relevant disease cases, or “use rate.” Among the seven products with use rate estimates, we find three with high use rates (>100 courses per 1,000 cases), two have medium use rates (10-100), and two have low use rates (<10). We also find that while all high-use-rate products have been on the market for >10 years, not all products marketed for that long achieve high use rates, and find diverse outcomes in use-rate trajectories, including sharp discontinuities and both upward and downward trends.

Given that PRV recipients can either use or sell their voucher, we also explore [the dynamics of how the PRVs' value is distributed](#) among different types of players in the industry. We find that PRV sales proceeds go toward repayment for shareholders of small pharmaceutical companies or toward (promises of) further drug development for neglected tropical diseases. Large pharmaceutical companies that receive PRV awards tend to retain or use the voucher for faster FDA review of a profitable drug in their pipelines.

Additionally, we review four academic studies that attempt to quantify the [effectiveness of PRVs](#) at inducing medical innovations for neglected tropical diseases. Based on their findings and our assessment of study quality, we think it is unlikely that the TD PRV Program had a large, consistent effect on R&D for tropical diseases, but that the results are potentially consistent with a small marginal effect. Additionally, there is historic anecdotal evidence of “gaming the system” — seeking a voucher for a drug that has already been developed and marketed outside of the US — though we think it is unlikely to continue to be an issue going forward given that the opportunities to do so have likely been exhausted.

We then formulate a [rough estimate of the value of the TD PRV Program](#) to Open Philanthropy, focusing on a case study of willingness to pay (WTP) for the development of a single drug (pretomanid). While the estimate suggests a value in the tens of millions of US dollars for one drug (implying a WTP in the tens of thousands of dollars), we caution against excessively anchoring on these results given significant uncertainty regarding model structure and inputs.

Finally, several [possible improvements](#) to the PRV program emerged from the literature and conversations with experts. These include advocacy to limit the growing supply of PRVs, to require access plans (and proof of follow-through) to earn a PRV, to increase administrative transparency and clarity, and to tie the value of the PRV to the social value of the medical innovation (rather than the voucher). We discuss experts' critiques of the voucher program as well as opportunities beyond the PRV to incentivize research and development in the field of neglected tropical diseases.



## Introduction

Priority review vouchers (PRVs) are a policy tool that the US government legislated in 2007 as an incentive for drug sponsors to engage in research and development (R&D) targeting neglected tropical diseases. From a global health perspective, such incentives may act as a solution to the low profitability of drugs for neglected tropical diseases, for which there is high need but low ability to pay. [Aerts et al. \(2022\)](#) point out that “[while] neglected diseases account for 12% of the global health burden, their share of R&D activity barely reaches 1%” (p. 190).

The US Food and Drug Administration (FDA) may award a PRV to a drug sponsor upon FDA approval of a product (drug, vaccine, or device) that demonstrates progress toward alleviating the health burden from neglected tropical diseases. The recipient of the PRV may either use the voucher — which can be submitted with a product approval application for “priority review,” reducing the FDA review process from 10 months to six months — or they can sell the voucher to another drug sponsor with profitable drugs in their pipelines. The value of the voucher rests in the potential for it to bring forward FDA approval for a drug that is likely to be highly profitable, and for which four months of earlier exclusivity and product marketing is worth significant value to the FDA approval applicant.

Given Open Philanthropy’s interest in R&D targeting tropical diseases, we devote our attention only to PRVs awarded for addressing a need related to tropical diseases, which represent about a third of all vouchers distributed through September 2019 ([Government Accountability Office \[GAO\], 2020](#), p. 12, Figure 2).<sup>1</sup> Most of the remaining vouchers were granted for rare pediatric diseases (RPDs), which have very different market dynamics: tropical disease treatments have large potential markets with limited ability to pay, while RPD treatments have small markets but may be able to command very high per-unit prices. [Bialas et al. \(2016\)](#) estimate the earning potential of a drug treating a tropical disease versus a drug treating an RPD and find that the RPD drug is expected to be more profitable. Among other dynamics, the authors note that tropical disease drug courses are often short, and may also reduce the transmission of contagious tropical diseases, reducing the patient population over time; on the other hand, drugs treating RPDs are often prescribed indefinitely, and may also improve patient lifespan, increasing the patient population over time.

For this project, we spoke with [Matt Clancy](#) (innovation economist and Research Fellow at Open Philanthropy), [David Ridley](#) (Professor of the Practice and Research Fellow at Duke’s Fuqua School of Business), and [Murray Lumpkin](#) (Deputy Director of Regulatory Affairs, Bill & Melinda Gates Foundation). While Ridley is part of the team that first proposed the PRV mechanism and remains an advocate, he mentioned that [Aaron Kesselheim](#) — Professor of Medicine at Harvard University’s Center for Bioethics — is a lead critic of PRVs, so we occasionally reference Kesselheim’s views based on our reading of the literature he has published (though we have not spoken with him directly).

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<sup>1</sup> As of September 2019, most vouchers had been distributed for medical developments related to rare pediatric conditions (61.3%) and a minority for medical countermeasures (6.5%; [GAO, 2020](#), Figure 2, p. 12).

## PRV issuances and extent of use

To date, the FDA has issued 13 vouchers under the TD PRV program

In [this spreadsheet](#), we catalog all known issuances of PRVs under the TD PRV program. As of 2023, our research indicates **13 products (10 medicines and three vaccines) for tropical diseases have been awarded PRVs upon FDA approval.**

We found no reliable, comprehensive, and up-to-date databases of PRV approvals. Two proprietary resources that initially seemed promising proved to be out of date<sup>2</sup> and unreliable.<sup>3</sup> To compile our list, we therefore sourced an initial list of issuances from 2007 to ~2020 from Knowledge Ecology International ([Drug Database, 2020](#)). We then supplemented the list with four additional TD PRVs from David Ridley's [interactive resource](#) (last updated in 2022). Finally, we determined through several online searches<sup>4</sup> that it is highly unlikely any further TD PRVs have been issued since fexinidazole in 2021. David Ridley also confirmed that he believes our list is up to date as of August 2023.

Most qualifying diseases are associated with zero voucher issuances, and there is high variation in whether products also obtain WHO Prequalification or are listed on the WHO Essential Medicines List

We present different views of the data in two sheets. [First](#) (“PRV issuances by disease”), we show TD PRV issuances for each qualifying tropical disease. As of 2023, 27 tropical diseases qualify for PRV issuance.<sup>5</sup> We find the following:

- Only 10 (37%) diseases have at least one PRV issuance for any class of product.
- The maximum number of issuances any disease has is two, and three (11%) diseases have two PRV issuances.
- Seven (26%) diseases have at least one PRV issuance for a medicine, and three (11%) diseases have at least one PRV issuance for a vaccine.
- No disease has received both a medicinal PRV issuance and a vaccine PRV issuance.

[Second](#) (“Approvals by drug awarded PRVs”), we compare each product’s FDA submission and approval times with whether (and if so, when) it obtains WHO Prequalification (PQ) and is listed on the WHO Essential Medicines List (EML). We find the following:

- Products that have received TD PRV issuances upon FDA approval also obtain WHO PQ in a minority (5/13; 38%) of cases.
- However, they are listed on the WHO EML in a majority (8/13; 62%) of cases.

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<sup>2</sup> Thomson Reuters publishes a “continually monitored and revised” tracker for priority review vouchers ([Practical Law Life Science & FDA Regulatory, 2023](#)). However, the last TD PRV issuance Thomson Reuters documents is from 2019, and the resource is therefore out of date.

<sup>3</sup> An August 2023 infographic from Citeline’s *Pink Sheet* ([Ellis-Tait, 2023](#)) claims that four drugs received PRV issuances in 2023. Our request for more information regarding the analysis returned two spreadsheets, which we found to contain one erroneous issuance and which do not name the drugs that supposedly received issuances in 2023. We therefore put lower weight on Citeline’s information.

<sup>4</sup> During this exercise, we also learned that several products in the late stages of development are slated for potential TD PRV issuances: a Chikungunya vaccine from either Valneva or Bavarian Nordic, which appear to be in a tight race with each other ([Grogan, 2023](#); [Taylor, 2023](#)), as well as a human African trypanosomiasis treatment from PaxMedica ([PaxMedica, 2023](#)).

<sup>5</sup> The current list was sequentially established by legislation and secretarial authority. Of the 27 tropical diseases, 16 were initially specified under §524(a)(3) of the FD&C Act, two were added by subsequent legislation, and nine were added by secretarial order ([FDA, 2020](#)).



- Only a few (3/13; 23%) products have both obtained WHO PQ and been listed on the WHO EML.
- Among the products that have also obtained WHO PQ, the majority (3/5; 60%) had already received the distinction prior to FDA approval — e.g., Coartem obtained WHO PQ in 2004 and FDA approval/PRV issuance in 2009.
- From the limited data available, medicines and vaccines do not notably differ in their rates of obtaining WHO PQ or being listed on the WHO EML.

Not all product classes are eligible for WHO PQ (i.e., not all tropical diseases are eligible), and some jurisdictions directly authorize products without their passing through the procedure. Therefore, it may not be surprising, or a sign of poor global access, that a product does not obtain WHO PQ. We did not have time to look into which products may have been eligible.

### Among seven PRV-awarded products with sufficient data, three have high use rates, two have medium use rates, and two have low use rates

In [this sheet](#) of the spreadsheet (“Drug extents of use and use rates”), we describe the extent of use of each PRV recipient. Specifically, we estimate treatment courses per 1,000 cases (henceforth “use rate”), which we present as a measure of how well the product has penetrated its potential user pool. We only have moderate confidence in these outputs given poor overall data availability, and found it feasible to estimate use rates for seven of the 13 voucher recipients. In [Table 1](#), we categorize them as high, medium, or low use.<sup>6</sup>

**Table 1:** Estimated use rates of PRV-awarded drugs and vaccines

| Category   | PRV-awarded drug/vaccine               | Use rate (courses per 1,000 cases) | Year first approved anywhere | Relevant annual DALY burden |
|--|--|------------------------------------|------------------------------|-----------------------------|
| <b>High use rate</b><br>>100 courses per 1,000 cases     | Lampit (nifurtimox)                    | ~260                               | 2007                         | ~86,000                     |
|  | Sirturo (bedaquiline)                  | ~150                               | 2012                         | ~816,000                    |
|  | Coartem (artemether/lumefantrine)      | ~136                               | 1999                         | ~37,000,000                 |
| <b>Medium use rate</b><br>10-100 courses per 1,000 cases | Impavido (miltefosine)                 | ~56                                | 2002                         | ~360,000                    |
|  | Pretomanid                             | ~23                                | 2019                         | ~477,000                    |
| <b>Low use rate</b><br><10 courses per 1,000             | Dengvaxia (dengue tetravalent vaccine) | ~0.7                               | 2015                         | - (vaccine)                 |
|  | Moxidectin                             | 0 (not yet shipped)                | 2018                         | - (irregular)               |

<sup>6</sup> This categorization is motivated by (1) the simplicity of powers of 10 and (2) contextual knowledge. In particular, we understand that ACTs, including Coartem (~136 courses/1,000 cases), are among the best-distributed treatments, while Impavido (~56 courses/1,000 cases) distribution has been criticized for being subpar ([Sunyoto et al., 2018](#)). We thus draw a boundary at 100 courses/1,000 cases. Furthermore, we understand that Dengvaxia’s sales are disastrously low compared to initial expectations of 20 million-27 million treatment courses/year ([Aguiar et al., 2016](#)). As ~23 million would entail ~143 courses/1,000 cases (high use rate), while the current figure, ~119,000, is less than 0.5% of 23 million and yields ~0.7 courses/1,000 cases (a rate that seems very low), we draw a second boundary at 10 courses/1,000 cases.

| <i>cases</i>       |                            |                                  |       | <i>incidence</i>                 |
|--------------------|----------------------------|----------------------------------|-------|----------------------------------|
| <b>No estimate</b> | Vaxchora (cholera vaccine) | - ( <i>not for LMICs</i> )       | 2016  | - ( <i>vaccine</i> )             |
|                    | Benznidazole               | - ( <i>no shipment data</i> )    | 1990s | ~57,000                          |
|                    | Krintafel (tafenoquine)    | - ( <i>no shipment data</i> )    | 2018  | ~623,000                         |
|                    | Fexinidazole               | - ( <i>no shipment data</i> )    | 2021  | ~37,000                          |
|                    | Egaten (triclabendazole)   | - ( <i>irregular incidence</i> ) | 2018  | - ( <i>irregular incidence</i> ) |
|                    | Ervebo (Ebola vaccine)     | - ( <i>irregular incidence</i> ) | 2019  | - ( <i>vaccine</i> )             |

*Note.* To describe use rates, we first separately estimate two quantities: annual treatment courses delivered<sup>7</sup> and age-adjusted, specific annual incidence of disease.<sup>8</sup> We then divide treatment courses by 1,000 incidence to obtain estimates of use rate. We also report year of approval in any country (which may predate FDA approval) to give some indication of how much use rate could depend on the duration over which a product has been marketed. For drugs but not vaccines (given complexities in determining DALYs for those at risk but who do not contract a disease), we also report our estimate of the relevant annual DALY burden for a drug’s specific indication to give some indication of the size of disease burden that could be alleviated. For our full calculations, see [here](#).

We find that all high-use-rate products have been marketed for >10 years, but not all products marketed that long achieve high use rates; and while use-rate trajectories are unclear for most products, we observe diverse outcomes

**First, although all products with high use rates have been marketed for >10 years, products that have been marketed for >10 years do not uniformly have high use rates.** Given that we expect use rates to reach a peak some years after a product’s initial approval, we observe, as expected, that earlier initial approval is somewhat associated with higher use rates. Specifically, we find that all three products classified as “high use rate” were first marketed in any country

<sup>7</sup> As data were sparse and not centrally reported, these numbers only represent our very rough estimates. We rely on sources of varying quality (see columns D and E in the [sheet](#)). Specifically, we used company reports of shipments in three cases, peer-reviewed articles in three cases, global health organizations in two cases, a company report of revenues in one case, an industry news article in one case, and a disease burden estimate in one case. For one product, we found no information and could not use disease burden, as it was too high to meaningfully bound our result.

<sup>8</sup> This is the annual number of new cases of the specific indication treated by each product, i.e., the particular form(s) of a disease and age groups for which each product is indicated. For vaccines, we use an estimate of the number of people at risk of infection instead of incidence. For products that treat diseases with irregular incidence, we do not calculate use rate.

before 2013,<sup>9</sup> and among the five products approved since 2018, we find that the only two that have use rate estimates are classified as “medium” or “low use rate.”<sup>10</sup> However, three earlier-approved products do not hold a “high use rate” classification or have no use rate estimates,<sup>11</sup> which plausibly reflects the longstanding challenge of poor access to tropical disease products long after they are successfully developed and approved.

**Second, while there is little information on general use-rate trajectories for all PRV-awarded products, there is evidence of sharp discontinuities in use rate.** For example, successful price reductions negotiated by Stop TB’s Global Drug Facility for bedaquiline (including Sirturo) mean that shipments will increase from ~4,600<sup>12</sup> to ~22,000 shipments per year,<sup>13</sup> or from ~31 to ~150 courses per 1,000 cases (see also [Stop TB, 2023a](#)). From 2023 to 2024, its classification would therefore have changed from “medium use rate” to “high use rate.” It seems plausible to us that similar access initiatives — whose arrangement can be fully independent of the TD PRV program but could also be funded by voucher sale proceeds, as is promised for moxidectin ([Olliario et al., 2018](#)) — could generally cause similarly rapid changes in use rate in the future.

**Third, in addition to possible upward trends with time as noted in our first point, we find that certain products may see downward trends in use rate and use over time.** For instance, Dengvaxia — which was initially expected to reach 60 million-80 million doses, or 20 million-27 million treatment courses, per year ([Aguilar et al., 2016](#)) — has encountered safety-related controversies ([Fatima & Syed, 2018](#)). Given that [Aguilar et al. \(2016\)](#) report that 1 million doses (~333,000 courses) were shipped to the Philippines alone in 2016, and only ~3 million doses (~1 million courses) were sold from 2015 to 2023 ([Sanofi, 2023](#), p. 8), there has been a significant decline in use rate over time. The example of fexinidazole is also illustrative but concerns raw use figures rather than use rates. As human African trypanosomiasis eradication efforts continue apace, with incidence down 95% from 2001 ([WHO, 2022](#)), we expect annual shipments of fexinidazole to decline as well — although use rates may in fact increase.

**Fourth, anecdotal evidence suggests PRV approval likely has no effect on use-rate trajectory for products that have already been marketed.** We spotlight the case of Impavido (miltefosine)

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<sup>9</sup> (1) Coartem’s (artemether/lumefantrine; ~136 courses/1,000 cases) first international approval came in 1999 ([Premji, 2009](#)), while its FDA approval came in 2009 ([FDA, 2009](#)). (2) Sirturo’s (bedaquiline; ~150 courses/1,000 cases) FDA approval — also its first international approval — came in 2012 ([FDA, 2012](#)). (3) Lampit (nifurtimox) has been donated by BayerHealthcare to the WHO since 2007 ([Jannin & Villa, 2007](#)) and was FDA-approved in 2020 ([FDA, 2020](#)).

<sup>10</sup> (1) For Krintafel (tafenoquine; no estimate), approved since 2018, we have no information about use rates but presume that it is very low given it had only been distributed in Brazil as of 2022 ([PATH, 2022](#)). (2) For fexinidazole (no estimate), approved since 2018, we have no information about use rates, but fexinidazole might be expected to have higher use rates given the low burden of disease ([WHO, 2023](#)). (3) Moxidectin (0 courses/1,000 cases), approved since 2018, has likely not been distributed as of 2023 ([MDGH, 2023](#)). (4) For Ervebo (Ebola vaccine), approved since 2019, a use rate is challenging to estimate given the sporadic incidence of Ebola, but vaccination efforts in the recent DRC epidemic were praised by [Woolsey and Geisbert \(2021\)](#). (5) Pretomanid (~23.2 courses/1,000 cases), approved since 2019, is classified as medium use.

<sup>11</sup> (1) Impavido (miltefosine; ~56 courses/1,000 cases) has been approved since 2002, but is described as challenging to access ([Sunyoto et al., 2018](#); see also [Box](#)). (2) Benznidazole (no estimate) has been supplied since at least the 1990s; it faced a global shortage in 2011 and was only produced by one company from the 1990s to 2012 ([Potet, 2012](#)). (3) Egaten (triclabendazole; no estimate) has been supplied since at least 2005, and we found no signs indicating whether it is well-accessed.

<sup>12</sup> Only 37,000 treatment courses from 2012 to 2019 ([Médecins Sans Frontières, 2020](#)).

<sup>13</sup> Cost savings are estimated to enable an additional 51,000 treatment courses to be procured from July 2023 to December 2024; we assume half of those will be Sirturo and half will be the other brand of bedaquiline from Lupin, and add that figure to the ~4,600 baseline ([Stop TB, 2023b](#)).

in the box below, which readers may find useful to contrast with the cases of benznidazole and moxidectin, as described [later](#).

### Box: No sign of improvement to Impavido access despite PRV approval

Among the four TD PRV recipients that first gained approval in any country before 2013, Impavido (miltefosine) has the lowest use rate, estimated at ~56 treatment courses per 1,000 cases. As [Sunyoto et al. \(2018\)](#) detail, the access barriers to miltefosine are complex and longstanding, and have seen scant relief since Paladin Labs was granted a PRV (since inherited by Knight) for registering Impavido in the US in 2014.

The drug was initially developed through a public-private partnership between the WHO's Special Programme for Research and Training in Tropical Diseases (WHO/TDR) and Asta Medica that was widely considered to be successful, as evidenced by the short time it took to bring miltefosine to market (p. 2). Clinical trials began in 1996 and the drug was approved in India in 2002 (p. 3). Access agreements were signed at the beginning of the partnership but saw unsuccessful, uneven, and slow implementation, culminating in prices at more than two times the price at which the drug has been estimated to be cost-effective for public health systems (p. 4). Additional challenges have included frequent stock-outs, inadequate logistical systems, long lead times for manufacturers, onerous requirements to qualify for preferential prices, and the lack of a collective bargaining entity (p. 5). The 2014 award of a PRV to Knight Therapeutics — which played no role in the drug's development, but acquired rights to the drug via a drug ownership transfer and multiple corporate acquisitions/restructurings (p. 3, Figure 1) — was associated with “no improvements in miltefosine pricing or access in global markets” (p. 6). The authors argue, “In the case of miltefosine, as a drug co-developed with public money and already licensed in key countries, the lucrative incentive seems misplaced” (p. 6).

In 2014, the Drugs for Neglected Diseases initiative (DNDi) and Médecins Sans Frontières (MSF) also [jointly urged](#) Impavido's license holders and manufacturers to “ensure broad, sustainable access.” In their letter, the organizations criticized “blatant hindrances to patient access” and highlighted that the “PRV mechanism, which aims to stimulate or at least reward drug development for neglected diseases, currently contains no access provisions and fails to ensure that only entities that invested in R&D are awarded the voucher.”

## Distribution of PRV “winnings”

Once the FDA awards a drug sponsor with a PRV, the drug sponsor may choose to redeem or sell the voucher. PRVs are inherently valuable; voucher holders initially sold them for between \$65 million and over \$350 million, and ultimately the price stabilized around \$100 million in the late 2010s ([GAO, 2020](#), Figure 4, p. 15). According to our research, five of the 13 TD PRVs have been sold. Additionally, eight of them have been redeemed, four of which were secured directly through medical innovations related to tropical diseases (i.e., they were originally awarded to the company that redeemed them), and four of which were purchased.<sup>14</sup>

<sup>14</sup> Note that we treat the development of Ervebo (Ebola vaccine) by Lumos Pharma and Merck here as having been purchased, even though Merck was part of the development partnership. One PRV purchased by Novo Nordisk has not yet been redeemed to our knowledge, which explains why five have been sold while only four of those have been redeemed.

Of five tropical disease PRV sales to date, proceeds from two (40%) transactions benefited organizations committed to reducing the global burden from tropical diseases, while proceeds from the other three (60%) transactions benefited small pharmaceutical companies

Of the 13 TD PRVs we have identified, we are aware that five have been sold. In the following, we summarize our current knowledge and understanding of these transactions, including transaction details (buyer, seller, and price) as well as the distribution of the proceeds of the sale.

**Knight Therapeutics sold its PRV (from the approval of Impavido) in 2014 for \$125 million, with 100% of proceeds going to shareholders (moderate-high confidence):** Following the PRV awarded to Paladin Labs — a relatively small Canadian pharmaceutical company with \$2.3 billion in revenue in 2022<sup>15</sup> — for registering a drug to treat leishmaniasis, the CEO of Paladin Labs sold the company and founded Knight Therapeutics (“Knight” hereafter). Knight inherited Paladin Labs’ PRV and sold it in March of 2014 for \$125 million to Gilead Sciences, Inc. (“Gilead” hereafter). At the time it sold, it was the only PRV on the market.<sup>16</sup> From our reading of the media regarding the sale,<sup>17</sup> it seems likely that 100% of the proceeds from the sale were distributed to Knight’s shareholders, given that “Knight Therapeutics’ shares began trading on the TSX-V on March 3, 2014 and graduated to the TSX<sup>18</sup> on April 29, 2014 under the symbol GUD” ([Knight, 2014](#)). In other words, Knight graduated from an “early-stage” company to the status of a more established stock issuer the month it received the PRV.

**PaxVax Bermuda Ltd. sold its PRV (from the approval of Vaxchora) in 2016 for \$290 million, with 100% of proceeds going to shareholders (high confidence):** The second TD PRV sale took place in June 2016, when Gilead again purchased a PRV. The seller was a small (\$1.1 billion in revenue in 2022) pharmaceutical company called PaxVax Bermuda Ltd. (“PaxVax” hereafter), whose focus was on creating and selling vaccines for Western travelers and which received a PRV for development of an oral cholera vaccine. Gilead paid \$290 million for the PRV, 100% of which was distributed to the shareholders of PaxVax ([Securities and Exchange Commission, 2017](#)). In 2018, Emergent BioTech acquired PaxVax, with the goal to develop “even more vaccines in areas of significant unmet need, with a commitment to addressing emerging and recalcitrant global health threats” ([PR Newswire, 2018](#)). Gilead used its two PRVs to fast-track approval of HIV-1 drugs, Odefsey and Biktarvy, respectively. Odefsey sales revenue in 2022 was \$1.5 billion, and Biktarvy sales revenue in 2022 was \$10.4 billion ([Gilead, 2023](#)), so that four months of sales revenue equated to \$500 million and \$3.5 billion in revenue for the two drugs, respectively.

**Chemo Research, S.L., sold its PRV (awarded for approval of benznidazole in 2017) for an undisclosed price on an undisclosed date, with a “substantial part” of the proceeds going toward continued TD drug development (moderate-high confidence):** Chemo Research, S.L.

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<sup>15</sup> When ranked by pharmaceutical sales revenue in 2022, the top 10 largest pharmaceutical companies each generated \$36.1 billion to \$52.6 billion in revenue.

<sup>16</sup> While Knight’s PRV was the only one on the market, it was not the first to sell; BioMarin had sold a PRV (that it received for a medical innovation related to rare pediatric diseases) two weeks prior to Knight’s auctioning of its PRV for \$67.5 million ([Hains, 2014](#)).

<sup>17</sup> “Gilead has agreed to pay Knight \$125 million in cash for the PRV. Other terms of the transaction were not disclosed, except that global investment banking firm Jefferies LLC advised Knight on the deal” ([Root, 2014](#)).

<sup>18</sup> The TSX is the Toronto Stock Exchange: “The difference between TSX and TSX-V is in the listing requirements: TSX focuses on senior issuers, and TSX-V focuses on early-stage companies looking to access growth capital” ([Day Trade the World, 2020](#)).



received a TD PRV in August 2017, and our best guess is that their subsequent PRV sale to Novo Nordisk, Inc. (“Novo” hereafter) occurred in late 2018 or early 2019, as the latter redeemed the PRV in March 2019. The sale value is undisclosed, but a “substantial part” of the proceeds from the sale was agreed to be “directed toward enhancing treatment for Chagas patients and improving patient health in other disease areas,” according to the “terms of collaboration between Chemo, Mundo Sano, and [DNDi]” ([DNDi, 2017](#)). Novo redeemed the PRV for expedited FDA approval of Rybelsus, an “adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes” ([Novomedlink, n.d.](#)), which generated about \$1.7 billion in revenue in 2022 ([Novo Nordisk, 2022](#), p. 37).

**Medicines Development for Global Health sold its PRV (awarded for approval of moxidectin) in 2019 for an undisclosed sale value, with 100% of the proceeds distributed to organizations pursuing TD drug development (high confidence):** In May 2019, [Medicines Development for Global Health \(MDGH\)](#) sold to Novo — once again, for an undisclosed amount — the PRV it had been awarded 11 months earlier for developing a drug that treats onchocerciasis. The proceeds were shared (with an unclear apportioning) between MDGH and its drug development partner, the [World Health Organization’s Special Programme for Research and Training in Tropical Diseases \(WHO TDR\)](#), to be used in pursuit of medical solutions for neglected tropical diseases ([Olliaro et al., 2018](#)). Novo has not redeemed this PRV, to our knowledge.

**Lumos Pharma’s 60% share of the PRV it shared with Merck (awarded for approval of Ervebo, a vaccine for Ebola) sold in 2020 for \$60 million, with 100% invested into Lumos Pharmas’ rare disease-related pursuits (high confidence):** Finally, in July 2020, Merck purchased Lumos Pharma’s portion of its jointly earned PRV for the development of an Ebola vaccine. The PRV was valued at \$100 million and Lumos Pharma held 60% of the value, so Merck paid \$60 million to Lumos to take full ownership of the PRV. The funds will “support the expansion of [Lumos Pharma’s] pipeline through the in-licensing or acquisition of another novel therapeutic candidate for those suffering from rare diseases,” which is Lumos Pharma’s focus, with its subsequent sights set on an oral growth hormone to treat Pediatric Growth Hormone Deficiency (PGHD). Merck redeemed the PRV for approval of an anti-cancer medication called belzutifan ([Merck, 2021](#)), which brought in \$40 million in revenue in 2022 ([Merck, 2023](#)).

In general, large pharmaceutical companies aim to acquire and redeem PRVs (and do not sell them) to secure revenue from potential high-revenue drugs more quickly, while small pharmaceutical companies and mission-driven organizations aim to sell them

Our spreadsheet includes a [sheet](#) (“PRV sales and value distribution by sponsor”) that aims to shed light on the question of how the value of these PRVs has so far been distributed among drug sponsors along various dimensions, including annual revenue generation (in 2022). From this exercise, we observe the following patterns.

**Almost all of the PRV recipients whose total annual revenue in 2022 was less than \$2.5 billion have sold their PRVs, while high-revenue pharmaceutical companies have either retained or redeemed their PRVs.** Six TD PRVs were awarded to large pharmaceutical companies (making for five unique recipients, as Sanofi received two PRVs) that generated total annual revenue of \$26 billion or more in 2022 (and were in the top 20 pharmaceutical companies by revenue generation that year), while the remaining seven PRVs were awarded to



either mission-driven organizations with zero profit or small pharmaceutical companies that generated a total annual revenue in 2022 of \$2.5 billion or less. Only one PRV in the latter group, awarded to the TB Alliance (a not-for-profit), has not been sold (nor redeemed). Among the five unique recipients with high annual revenue, all have been redeemed apart from the two granted to Sanofi in May 2019 and July 2021.

For three cases in our spreadsheet where the dates of the PRV award, sale, and redemption are known (i.e., PRVs awarded for development of Impavido [miltefosine], Vaxchora [cholera vaccine], and Ervebo [Ebola vaccine]), we observe that the lapse between PRV award to sale is at most eight months (and sale to redemption is at most one year).<sup>19</sup> It therefore seems as though the low- or no-revenue organizations seek out the PRV for the purpose of generating revenue from the relatively quick sale of the PRV, once awarded. The lack of PRV sales from the high-revenue companies suggest that the four-month acceleration of their review process is more valuable than the potential revenue from the PRV sale.<sup>20</sup>

**In all cases, purchasers of PRVs are large pharmaceutical companies that generate significantly more revenue than the PRVs' sellers, which are generally small pharmaceutical companies or not-for-profits.** Gilead Sciences, Inc. — which generated \$27.3 billion in revenue in 2022 — purchased PRVs from PaxVax Bermuda Ltd. (purchased by Emergent BioSolutions, which generated \$1.1 billion in revenue in 2022) and Paladin Labs Inc., which generated \$2.3 billion in revenue in 2022. Similarly, Novo Nordisk, Inc. — which generated \$25 billion in revenue in 2022 — purchased PRVs from Chemo Research, S.L., which generated \$1.9 billion in revenue in 2022, and Medicines Development for Global Health (MDGH), a not-for-profit. Both Gilead Sciences, Inc. and Novo Nordisk, Inc. have purchased two tropical disease PRVs without having received any for their own drug developments for tropical diseases. One partnership between Merck (\$59.3 billion in revenue in 2022) and Lumos Pharma (\$1.5 million in 2022) led to a PRV buyout by Merck for 60% of the PRV's \$100 million value, allowing Lumos to pursue expansion of its pipeline of treatments for rare diseases.

[Ridley et al. \(2021\)](#) provide information about a few cases in which the **proceeds from sales of PRVs were used to support global health projects**:

- PaxVax, which developed Vaxchora, used the funds from the voucher sale to support other vaccine development, including work on a chikungunya vaccine.
- Medicines for Malaria Venture, which partnered with GlaxoSmithKline to develop tafenoquine, reinvested its share of the value of the voucher<sup>21</sup> into malaria product development.
- Benznidazole was already developed and in use as a treatment for Chagas disease when the disease was added to the list of PRV-eligible tropical diseases. A race to register

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<sup>19</sup> Additionally, for the seven cases where redemption and approval dates are known, redemption to approval is at most eight months, which is slightly longer than the six-month approval period allotted by the PRV.

<sup>20</sup> [Aerts et al. \(2022\)](#) suggest that the value of the PRV would not incentivize large pharmaceutical companies: “[I]t seems reasonable to believe that large pharmaceutical companies, some with yearly revenues exceeding \$50 billion, are unlikely to shift or expand their portfolio towards risky projects for tropical diseases based solely on a voucher that can be sold for as low as \$68 million. Furthermore, even if sold at its highest price (\$338 million), it would not be sufficient to cover the total cost of developing and launching a new product.” (p. 196).

<sup>21</sup> The voucher was issued solely to GlaxoSmithKline, which gave an undisclosed portion of the voucher value to Medicines for Malaria Venture “so that it could recoup some of its development costs” ([Ridley et al. 2021](#), p. 1248). This appears to be qualitatively distinct from the nature of Sanofi and DNDi's sharing of the PRV awarded for benznidazole, where the two partners “equally share rights to the voucher” ([Liu, 2021](#)). Thus, while it undoubtedly was a development partner for tafenoquine, our [spreadsheet](#) does not include Medicines for Malaria Venture as a PRV recipient.

benznidazole with the FDA ensued, and a partnership between the Drugs for Neglected Diseases Initiative (DNDi), Insud Pharma, and the Mundo Sano Foundation ultimately received a PRV for the drug's approval. DNDi and Insud Pharma agreed to commit half of their profits from the voucher sale to charitable efforts, including patient access to benznidazole. Proceeds from the voucher sale are supporting three Mundo Sano Chagas disease programs: outreach to pregnant women with Chagas disease, investment in diagnostics, and offering benznidazole at affordable prices.

- Medicines Development for Global Health, which developed moxidectin with investment from the Global Health Investment Fund, intended to use proceeds from the voucher sale to fund access programs, similarly to the benznidazole partnership. However, the WHO PQ process for moxidectin unexpectedly required extensive additional trials. Proceeds from the voucher sale, after paying back investors, have helped to pay for these trials, but were not able to subsidize broad access.

## Incentive effect of PRVs

Quantitative evidence for PRVs inducing R&D spending for tropical diseases is inconclusive, but is suggestive of either no effect or, at best, a weak (and perhaps negligible) positive effect

We have found four studies that attempt to assess the effect of the PRV program by analyzing data from the drug development and approval pipeline. Based on the overall results of these studies, we think it is unlikely that the PRV program had a large, consistent effect on R&D for tropical diseases. However, the results are potentially consistent with a small marginal effect.

[Aerts et al. \(2022\)](#) investigate the question of whether the incentive boosted R&D for tropical diseases using a difference-in-difference-in-differences (DDD) approach. Specifically, they compare differences in the start of Phase II or III clinical trials for drugs and vaccines<sup>22</sup> that become PRV-eligible versus those that are reliably PRV-ineligible,<sup>23</sup> and look at the differences in numbers of trials across registries where the policy applies (i.e., [ClinicalTrials.gov](#)) versus registries where it does not (i.e., all WHO International Clinical Trials Registry Platform [ICTRP]<sup>24</sup> trials not registered on ClinicalTrials.gov) for the years 2005-2019. If the ratio of eligible to ineligible drugs and vaccines is larger in ClinicalTrials.gov relative to other registries after the policy, one could interpret a positive causal effect of the PRV policy on R&D activities. We spent 30-60 minutes assessing the internal validity of the DDD estimation, and the causal interpretation appears sound to us so long as any contemporaneous changes indeed apply globally, though the authors do not explore related robustness tests.<sup>25</sup>

<sup>22</sup> For data quality purposes, the authors exclude devices.

<sup>23</sup> For PRV-ineligible drugs and vaccines, the authors include non-communicable diseases with large markets in high-income countries, and which are responsible for the highest number of DALYs in HICs, to assure ineligibility for the PRV policy over time. (p. 192)

<sup>24</sup> The WHO ICTRP collates information on ongoing, completed, and terminated trials from 18 [registries](#) globally.

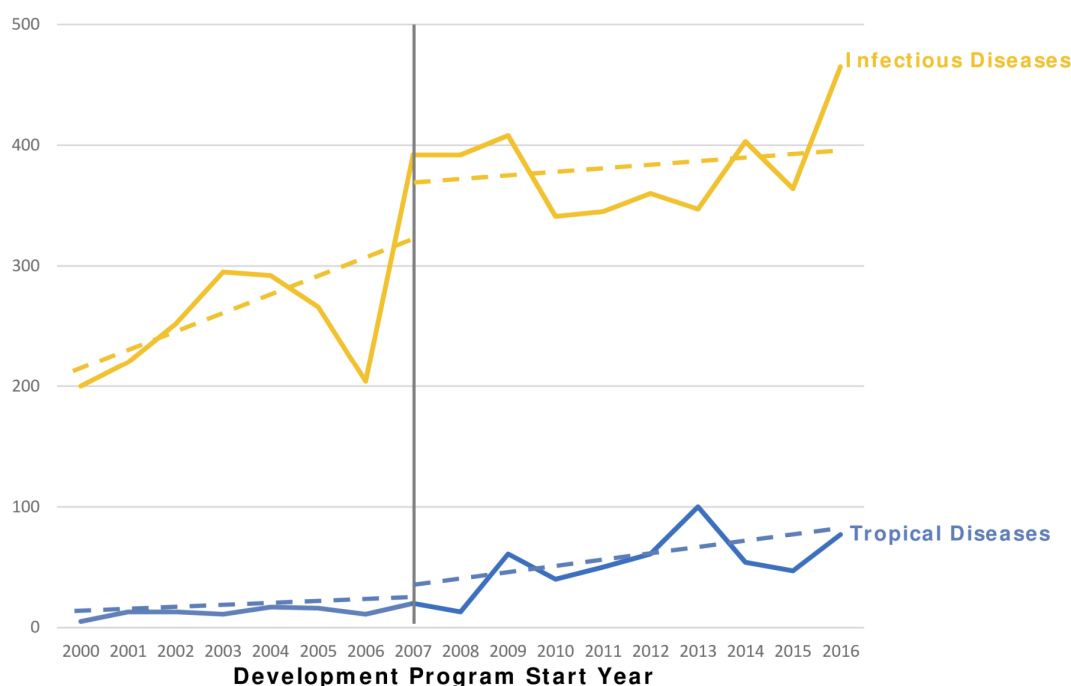
<sup>25</sup> The DDD estimator only requires one parallel trends assumption to result in an unbiased estimator “so long as the bias is the same in both [difference-in-difference (DD)] estimators” from the previous estimation stage ([Olden & Møen, 2022](#), p. 532), and the decision to use the DD estimator “to a large extent rests on intuition” (p. 531). The third differencing serves the purpose of differencing out bias in the DD estimators. In this case, we may assume some bias in the DD estimator that simply looks at the difference in clinical trial registry across PRV-eligible and PRV-ineligible diseases in the US alone since, for example, we may be overlooking another variable omitted from the analysis, such as large contemporaneous injections of funding for neglected tropical diseases from another organization (e.g., see discussion [below](#)). The DD estimator could then be picking up the effect of the contemporaneous funding injection and attributing it to PRVs, whereas if we assume the contemporaneous change applies globally (and not

The authors do not find an effect of PRVs on clinical trials in their main model nor in any of their robustness tests.<sup>26</sup> While the marginal effect (of a Poisson regression) is positive, the test is not statistically significant ( $p=0.31$  in their main model specification,  $N=2941$ ; Table 2, p. 195). Unfortunately, data limitations preclude investigation across sponsor types (for-profit versus not-for-profit) and other outcome variables like “time to market launch, probability of market launch, or probability to move successfully across the clinical phases” (p. 196).

[Kerr et al. \(2018\)](#) use data from Citeline’s [Pharmaprojects](#) database, which “tracks drug development from the preclinical stage to worldwide market launch, and identifies programs that have been discontinued at any stage” ([Kerr et al., 2018](#), p. 3). The authors compare the number of tropical disease drug development programs that are started before and after the PRV program launch. For comparison, they also look at the number of drug development programs for infectious diseases more generally.

They find that new tropical disease drug development programs have increased since the PRV program began. Development programs for the “control” group of all infectious disease development programs have also increased over the study period, but do not show the same pattern of steeper increase after 2007 than before 2007 ([Figure 1](#)).

*Figure 1: Number of infectious and tropical disease drugs under development before and after the TD PRV program begins in 2007 (vertical line)*



Source: Pharmaprojects

Note. From [Kerr et al. \(2018\)](#), p. 7.

The authors describe the trends as follows: “The number of new infectious disease drug development programs increased in 2007 and continued at this approximate level. The trend in the number of new tropical disease drug development programs begun each year was

just in the US), the DDD estimator would difference out this effect and leave us with just the PRV effect, since non-US countries are not eligible for this funding.

<sup>26</sup> Their robustness tests involve inclusion of Phase I trials, varying lagged effects of user fees, and controlling for extensions to rare pediatric conditions (pp. 195-196).

increasing slightly over time before the PRV program was enacted. After the PRV program was enacted, the trend for new tropical disease programs increased, approaching overall trend for infectious disease programs” (p. 5). The authors’ differences-in-differences regression analysis “found a positive, statistically significant result that indicates that the PRV program might have increased tropical disease drug development” (p. 5).

We spent about two hours looking into funding injections from the Bill and Melinda Gates Foundation (BMGF) — the start of which also took place in the early 2000s, somewhat coinciding<sup>27</sup> with the beginning of the PRV program (i.e., in 2007) — to assess the extent to which BMGF funding (i.e., not the PRV program) may be driving any increase in tropical disease drug development. [Reviewing data for 13 PRV-eligible drugs](#) that were relatively quick to identify in [G-Finder](#),<sup>28</sup> we find that BMGF spending accounted for about 5% of all R&D spending for these 13 drugs from 2007-2021, and about 7% of spending on Phase I, II, and III trials. It seems plausible that this funding injection partially accounts for the small and statistically insignificant marginal effect found in [Aerts et al. \(2022\)](#), as well as the positive statistically significant effect in [Kerr et al. \(2018\)](#), neither of which attempt to explicitly control for this funding injection nor consider related robustness tests. We discuss how we might spend more time exploring the robustness of these studies’ results [here](#).

[Jain et al. \(2017\)](#) compare the number of new drugs and vaccines for neglected tropical diseases that entered Phase I clinical trials before and after the PRV program launch. They find that between 2000 and 2007, 32 “novel products intended to prevent or treat neglected tropical diseases” started Phase I trials, while between 2008 and 2014, 34 such products started Phase I trials (p. 388). However, they emphasize the proportion of neglected tropical disease drugs among all products in development; since the total number of Phase I trials increased from 1,704 to 2,302, they find that the proportion of Phase I trials for neglected tropical disease drugs fell, from 1.9% pre-launch to 1.5% post-launch.

The fourth study we are aware of is [Bialas et al. \(2016\)](#), an early quantitative take on the effect of the PRV program which simply compares the number of drugs approved for treatment of tropical diseases (and rare pediatric diseases) before and after the program launch. By their count, three TD drugs were approved in the 3.5 years post-launch, compared to none in the 3.5 years before program launch.<sup>29</sup> Indeed, they note that no new TD treatments were approved in the 10 years before program launch.

### Interviewees acknowledged the potential effectiveness of the PRV incentive but expressed reservations about incentive strength and non-guaranteed benefits from voucher redemption

We interviewed two experts regarding the effectiveness of PRVs as an incentive: David Ridley, who is part of the team that originally proposed the use of PRVs for encouraging innovation in the neglected tropical disease space, and Murray Lumpkin, who previously worked as an FDA administrator for 25 years.

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<sup>27</sup> For example, BMGF committed ~\$70 million during the same period that PRV legislation was considered and passed ([BMGF, 2006](#)).

<sup>28</sup> Note that G-Finder data dates back to 2007, so we do not have information on any relevant funding injections prior to the PRV program.

<sup>29</sup> There were three rare pediatric disease drug approvals in the 3.5 years before program launch, compared to six in the 3.5 years after.

**Ridley expressed certainty that PRVs have indeed incentivized research and development, but indicated that the strength of the incentive has notably declined as the resale value of the vouchers has dropped to \$100 million.** When asked why very few TD PRVs have been issued in recent years, Ridley stated that the lack of profitability in the tropical disease space places a limit on pharmaceutical R&D in the space, and that the decline in voucher value has exacerbated this problem. However, he expects that the creation of a European voucher program would cause R&D to pick up.

The development of Sirturo (bedaquiline) within Janssen Pharmaceuticals, which is part of Johnson & Johnson, illustrates how the TD PRV program can encourage the development of global health priority drugs within large for-profit pharmaceutical companies. [Ridley et al. \(2021\)](#), relying on an unnamed source within Janssen, write that after Phase II trials of bedaquiline there was pressure within the company to end the program and invest in more lucrative drugs instead. The bedaquiline program continued in part because those who supported the program were able to point to the expected monetary value of a PRV. After the voucher was awarded, the global public health business unit sold the voucher internally to another Janssen business unit, and the funds from the internal sale helped to scale the global public health business unit.

Ridley also cited a paper ([Hwang et al., 2019](#)) on PRVs and innovation for rare pediatric diseases (RPD), which is supportive of PRVs despite some of its authors having been openly critical of the policy tool. The article shows evidence of a statistically significant effect of the voucher program on rare pediatric drugs moving from phase 1 to 2. The article also gives evidence (though only significant with about 90% confidence) of drugs moving from phase 2 to 3.

In our conversation, **Lumpkin also acknowledged that PRVs carry some incentive value, but emphasized that pharmaceutical companies are wary about the non-guaranteed nature of PRVs' benefits.** He noted that a major contributor to the non-guaranteed nature of the benefit is that a potential blockbuster product (whose priority review is bought with a voucher) must obtain approval on the first cycle of review after the voucher has been redeemed. If such a product were required to undergo multiple cycles of review after redemption, he explained, the PRV's supposed benefits would be diminished or even nullified.

In terms of the range of incentives that could potentially be offered to companies, **both interviewees said that a more powerful incentive than a PRV would be guaranteed-benefit programs such as patent term extensions and exclusivity extensions**, although they come with greater costs to purchasers (including the US government) and patients, who have to wait longer to access cheaper generic versions of the product. Ridley pointed to transferrable exclusivity vouchers (TEVs; see also [Boyer et al., 2022](#)), as an example of a guaranteed-benefit incentive that companies would favor. Lumpkin concurred that TEVs would offer a greater incentive, adding that "they could be of varied time lengths depending on the societal/public health value of the product which led to the voucher being issued to a company)." Lumpkin also gave the example of six-month market exclusivity extensions that the FDA offers for pediatric drugs (see also [FDA, 2022](#)).

Different jurisdictions seem to have approached the trade-offs between incentives to companies and costs to patients differently. While Ridley noted that the PRV programs in the US were adopted after failed attempts to authorize TEV initiatives, Lumpkin said that the European Union has not adopted PRVs partly out of concern about the non-guaranteed nature of the benefit, and partly due to the EU's ability to mandate pediatric trials rather than create



an incentive. As Ridley also noted, a TEV program is under active consideration in the EU ([Allen & Overy, 2023](#)), but he does not expect the proposal to pass.

## While PRVs can lead to positive impacts on R&D, the design of the policy tool is critical to avoid drug sponsors’ “gaming the system”

[Olliario et al. \(2018\)](#) provide an ideal example of PRVs at work. Around 185 million people are at risk of onchocerciasis (or river blindness)<sup>30</sup> — a tropical disease eligible for PRV. In the 1970s, WHO TDR established moxidectin as a potential treatment and entered into an agreement with a pharmaceutical company that owned moxidectin, who eventually withdrew from the partnership in 2011. TDR then partnered with a not-for-profit organization, MDGH, which “leveraged the PRV for a US\$13 million investment by the Global Health Investment Fund (GHIF), making this the first social impact investment raised specifically on the potential value of a PRV” ([Olliario et al., 2018](#), p. 2). Each partner also contributed \$15 million (and the previous partner likely around \$20 million) to repurpose the historically veterinary drug for human use, and the GHIF funding helped to achieve regulatory compliance and prepare the submission for FDA approval. Moxidectin had not been registered outside of the US previously, and PRV sale proceeds would remain targeted toward solutions for neglected tropical diseases.

However, PRVs have not always had such a purely positive impact. Two (of several) stakeholder interviewees from the [GAO \(2020\)](#) investigation made claims<sup>31</sup> that “PRV programs are an incentive to obtain FDA approval for a drug that has already been developed and marketed outside of the United States but are not an incentive for developing new drugs” (p. 26).<sup>32</sup> In fact, several PRVs (e.g., Coartem, Egaten, and Impavido) have been awarded for products that had been previously licensed or registered outside the US ([Aerts et al., 2022](#), Table 1, p. 192).

The Drugs for Neglected Diseases Initiative (DNDi) and Medecins Sans Frontieres (MSF) claim to have been testing miltefosine (a leishmaniasis drug) when Paladin Labs submitted Impavido for approval to the FDA in March 2014. DNDi and MSF claim that Paladin Labs<sup>33</sup> actually invested very little in R&D for the drug,<sup>34</sup> instead piggybacking off of R&D “largely conducted in the mid-1990s by the WHO/TDR ... and partners, with private and public funding” ([DNDi, 2014](#)). Meanwhile, Knight (founded by Paladin Labs’ CEO) would ultimately receive \$125

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<sup>30</sup> Onchocerciasis is caused by a parasitic worm transmitted via blackflies, with 99% of infected individuals living in Africa.

<sup>31</sup> “One of these stakeholders and an additional stakeholder also noted that PRVs are often a source of additional revenue to drug sponsors that would have developed their PRV drug anyway and did not need the PRV to finance drug development” (p. 26).

<sup>32</sup> A footnote from the report states that “To qualify for the tropical disease PRV program, applications must contain reports of one or more new clinical investigations (other than bioavailability studies) that are essential to the approval of the application and conducted or sponsored by the sponsor, and an attestation from the sponsor that such reports were not submitted as part of an application for marketing approval or licensure by a regulatory authority in India, Brazil, Thailand, or any country that is a member of the Pharmaceutical Inspection Convention or the Pharmaceutical Inspection Cooperation Scheme prior to September 27, 2007. This may preclude certain drugs that were developed and marketed outside of the United States prior to 2007 from tropical disease PRV program eligibility” (p. 26).

<sup>33</sup> The CEO of Paladin Labs sold the company to Endo Health in 2014 and founded Knight, which inherited and sold the PRV ([Hains, 2014](#)).

<sup>34</sup> “Miltefosine was discovered in the 1980s and the R&D for its use against leishmaniasis was conducted in the 1990s by the WHO and partners. Miltefosine then changed hands numerous times: from Zentaris to Paladin to Endo. Knight Therapeutics was created from Endo in early 2014 with a sole product registered: Impavido® (miltefosine). By the time Knight sold its PRV, most R&D costs had been borne by other public and private actors. Knight’s CFO recently said that FDA approval cost about \$10 million, which seems to be the only significant investment that Knight has made for this drug” ([PLOS Guest Blogger, 2015](#)).



million from the PRV's sale to Gilead Sciences, Inc. DNDi and MSF called for Knight to “disclose the actual cost of production,” “price the drug at-cost,” “maintain the registration ... in all disease-endemic countries,” and “support additional clinical studies,” and asserted that “[t]he blatant hindrances to patient access to miltefosine for this neglected disease should be examined to the same extent as, and in conjunction with, the important economic benefit that Knight Therapeutics has received for selling the PRV for R&D that the company did not carry out” ([DNDi, 2014](#)). Access issues ensued — both abroad and in the US.

We are currently unclear regarding the reasoning behind the sale of Paladin Labs and formation of a new company (Knight Therapeutics) for the sale of the PRV, and we would be curious to understand whether this move gives further indication of “gaming the system.” In our interview with David Ridley, he said that this particular case was the only one he could think of where most of the value of the PRV went to the “innovator” rather than to patients, and he consistently referenced this particular case study as an example of a wasted voucher.

Aaron Kesselheim also references a case that ultimately did not come to fruition, though is indicative of the intentions of pharma companies to game the PRV system. Specifically, Martin Skhrelidze of KaloBios had intended to buy the rights to benznidazole to revive his failing biotech company without having invested in any of the drug's development ([Fierce Biotech, 2015](#)). The drug did ultimately receive a PRV, which the FDA granted to Chemo Research, S.L.<sup>35</sup>

The executive directors of DNDi and MSF also point out “gaming” by Novartis in gaining a PRV for FDA approval of Coartem, which had “been in use for some time in Africa,” as well as unaffordability from PRV-awarded drugs such as Janssen's Sirturo (bedaquiline) in developing countries ([Pécoul & Balasegaram, 2015](#)).

## Rough estimate of PRV program value

We apply a speed-up model to a PRV-awarded tuberculosis drug — pretomanid, developed by the TB Alliance — as a starting point for Open Philanthropy to assess the value of the TD PRV program

We [formulated a rough estimate](#) of the value in OP\$<sup>36</sup> of the program's possible PRV-induced speed-up of a drug for a neglected tropical disease, doing our best to align our approach with Open Philanthropy's own approach to estimating the value of speeding up drug developments.

We apply the model to pretomanid, a treatment for adults with severe drug-resistant forms of tuberculosis, which the TB Alliance developed and for which it received a PRV. We selected

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<sup>35</sup> “Chemo Group played a central role in registering benznidazole with the FDA, in close collaboration with its US-based pharmaceutical division Exeltis, corporate social responsibility partner Mundo Sano, with the support of the Drugs for Neglected Diseases initiative (DNDi), a non-profit drug development organization. DNDi supported U.S. registration through provision of technical expertise and sharing of data from DNDi-led clinical trials. The approval of benznidazole will facilitate the delivery of life-saving medical treatment to people with Chagas disease.” (DNDi, 2017)

<sup>36</sup> “OP\$” is a unit of value used by Open Philanthropy (this project's client) to measure social return on investment (SROI). As of the writing of this report, Open Philanthropy used a funding bar of 1,500x SROI for grantmaking within its Global Health and Wellbeing portfolio, meaning that each dollar disbursed was expected to yield at least the equivalent of \$1,500 in social value.

pretomanid (our reasons were threefold and are explained in the following footnote).<sup>37</sup> Nonetheless, we emphasize that we were unable to identify a PRV-awarded drug for which we can argue broad representativeness of PRV-awarded drugs, and we therefore do not attempt to extrapolate the estimation outputs for pretomanid to assess broader program value.

To determine the value of the TD PRV program using pretomanid as our case study of choice, we first estimate the annual burden of the relevant extensively drug-resistant (XDR) and multidrug-resistant (MDR) forms<sup>38</sup> of pulmonary tuberculosis (TB) for which pretomanid is indicated. We do so by adjusting the annual DALYs attributed to TB in 2019 by a ratio of the XDR-/MDR-TB incidence to overall TB incidence. We then estimate the disease burden in the year of peak drug use/distribution (“scale-up”) by estimating the annual trend in TB cases from 2000 to 2019 (leading up to the drug’s development), assuming a seven-year delay between FDA approval and reaching peak scaling potential. We multiply these by the DALY burden to estimate the DALY burden in the year that the drug meets its scaling potential, then apply a 50% DALY “haircut” in line with OP’s internal parameter selection. The burden we estimate is ~402,000 DALYs/year.

We obtain a “use rate” of pretomanid from our [main spreadsheet](#) (“Drug extents of use and use rates”), as described [earlier](#), which shows ~23 pretomanid treatment courses are delivered for every 1,000 relevant cases of disease during the period 2020-2022 (~2021). To match the seven-year scale-up time frame assumed in the burden portion, we attempt to estimate the pretomanid use rate at peak scale-up using a logistic function with  $k = 0.3$  and assuming an inflection point at the midpoint from approval to peak scale-up (3.5 years after approval). The use rate we obtain is ~60 treatment courses per 1,000 incident cases of relevant TB. (Note that this model design is arbitrary and only intended as illustrative.)

We then attempt to identify the extent to which the TD PRV program has led to DALYs averted through the potential advancement in pretomanid’s development. To do so, we assume that the impact of these treatments on DALYs is 18%, our best guess (based on low-quality evidence) of the reduction in the DALY burden with pretomanid versus previously available treatments.<sup>39</sup> Multiplying the extent of the drug’s use by this treatment discount factor provides an estimate of the reduction in burden for the MDR-TB. Finally, given our fairly low confidence that the TD PRV program led to a major speed-up in drug development — given TB Alliance’s lack of a

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<sup>37</sup> First, we excluded the six products for which we could not calculate a use rate (treatment courses per 1,000 new cases; see [Table 1](#)). Second, we assumed that a product with a somewhat middling use rate within our sample would be more likely to be representative of PRV-awarded products more generally. A since-revised estimate showed pretomanid as having the median number of estimated treatment courses per 1,000 cases among the seven drugs/vaccines for which we have estimates; our current estimate still places it near the median, at fifth out of seven in use rate. Third, pretomanid was approved relatively recently, in contrast to Coartem (third) and Impavido (fourth/median), all of which were in use before the TD PRV program existed, such that the PRV incentive likely had zero contribution to their development.

<sup>38</sup> “Pretomanid is an antimycobacterial indicated, as part of a combination regimen with bedaquiline and linezolid, for the treatment of adults with pulmonary extensively drug resistant (XDR) treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis (TB)” ([RxList, 2023](#)).

<sup>39</sup> Low-quality evidence suggests that on a pretomanid-containing regimen, ~90% of drug-resistant TB patients have favorable outcomes ([Conradie et al., 2020](#)). With earlier regimens, ~66% of drug-resistant TB patients have favorable outcomes ([Kwon et al., 2008](#)). Arbitrarily assuming that a favorable outcome reduces the DALY burden of TB by half compared to an unfavorable outcome, a patient on the new regimen can expect 80% of the DALY burden compared to the previous regimen.

profitable drug pipeline and its retention of the voucher since 2019<sup>40</sup> — we estimate that the PRV accelerated pretomanid development by three months.<sup>41</sup>

Our calculations suggest that a grantmaker could be willing to pay tens of thousands of dollars for a PRV program that accelerates the development of a single drug (pretomanid), but our result is highly sensitive to uncertain parameters and only applied to one non-representative drug, leading us to put low confidence in model outputs

Based on our inputs — some of which we acknowledge are highly uncertain and should be stress tested to align with OP’s beliefs — and the OP-specific parameters shared with us during the calculation process, we find that the PRV averted 536 DALYs per year, worth about \$54 million in OP\$ assuming three months of speed-up of the drug development.

Beyond built-in uncertainty in some of the model inputs (in particular the haircuts and the speed-up attributable to the program<sup>42</sup>), perhaps our primary concern with the speed-up model is that speed-ups of arbitrarily small amounts of time can still indicate quite a large program value. The authors of the report mutually agree that the sensitivity of the model’s output to highly uncertain inputs leaves us with low confidence in the estimated value. One author suggested that the process of deciding which drug/vaccine to use as a case study led them to believe there may not be a real success story of PRVs leading to a *high-quality* and *widely used* product that was *truly incentivized* by the TD PRV program. Another author believes that it is possible that MDGH’s development of moxidectin could represent such a case (with potential additional benefits from voucher sale), though, as we believe it has not yet commenced use ([Table 1](#)), we do not attempt to work out the value of this product.

Thus, it seems possible that there could be big wins if we trust the model structure and account for post-award R&D benefits from voucher sales, but we lack evidence to support the realization of this possibility to date. Still, we hope that interaction with the model can provide some insight into the value of the TD PRV program and potential program improvements from Open Philanthropy’s perspective. Using our current parameters and the assessment based on the pretomanid case study alone, our model suggests that the value in OP\$ for a program that leads to the sped-up development of a single product may be in the tens of millions of USD, with OP’s willingness-to-pay in the tens of thousands of USD (using a bar of 1,500x). However, for drugs targeting diseases with higher burdens (as opposed to particular indications with relatively small burdens, as in the case of pretomanid; see also the “Relevant annual DALY

<sup>40</sup> All other PRVs awarded between 2014-2019 to small pharmaceutical companies (2022 revenue <\$2.5 million) and not-for-profits for which we have data sold their PRVs within a year of receiving them. To our knowledge, the TB Alliance has retained its PRV, suggesting it is in a comfortable financial position regardless of the voucher in part due to endowments from BMGF and USAID.

<sup>41</sup> We do not believe the PRV was integral to the development of pretomanid, but rather served as an “added bonus” for its development. The TB Alliance has endowments from USAID (with a pledge of up to \$40 million starting in 2008; [TB Alliance, 2008](#)) and the Bill and Melinda Gates Foundation (starting with a five-year commitment of >\$100m as early as 2006; [TB Alliance, 2006](#)), with contributions additionally coming from several other [donors](#). As a subtle indication of importance, a PBS announcement of pretomanid mentions the above donors and does not mention the voucher incentive ([Rohrich, 2019](#)), and the embedded quotes from the TB Alliance also do not mention the voucher. We note that the time from PRV award to PRV sale has been under one year for other PRV-awarded drugs, and TB Alliance has not yet sold their PRV to our knowledge, perhaps indicating that the award was not a primary driver behind the development of pretomanid.

<sup>42</sup> The output scales linearly with the speed-up parameter input. Changing the speed-up parameter from 0.25 to 0.1 changes the WTP from \$54 million to \$21 million, while increasing it to one year increases it to \$214 million.

burden” column in [Table 1](#)), this valuation exercise may imply a much higher willingness-to-pay. The value of the program will also heavily depend on the expectation of how many drugs or vaccines are brought forward by the program.

## Room for program improvement

Potential improvements include limiting the supply of PRVs, requiring access plans to earn a PRV, increasing administrative transparency and clarity, and tying the value of the PRV to the social value of the medical innovation

Potential improvements to the program aim to address several critiques that we have identified in the literature — primarily from reading the work of Aaron Kesselheim (lead PRV critic and a professor of medicine) — which include:

- Problems with relying on the profit motive of pharmaceutical companies, including lack of sustained commitment to solutions for resource-poor settings and vulnerability to changes in vouchers’ value<sup>43</sup>
- Neglected issue of affordable access following FDA approval<sup>44</sup>
- Economic inefficiency due to the temporal disconnect between the innovation and the reward (and uncertainty around the existence/size of the future reward),<sup>45</sup> and the disconnect between the size of the incentive and the social benefits of the innovation<sup>46</sup>

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<sup>43</sup> “It is especially problematic to rely on pharmaceutical companies’ profit motive as the key to developing drugs for resource-poor settings. Effectively conducting research into treatments for neglected diseases involves a more sustained commitment than can be achieved simply by rationalizing the revenue that arises from it. If any changes in the drug-development marketplace, such as initiation of federal drug-reimbursement guidelines in the United States, diminish the perceived value of these vouchers, then any research started solely in anticipation of voucher revenue will again cease, to the detriment of public health” ([Kesselheim, 2008](#)).

<sup>44</sup> “Whether the voucher is successful at improving drug innovation, it clearly does not ensure affordable access to the products either in the United States (elosulfase costs \$380,000 per year) or overseas” ([Kesselheim, 2015](#), p. E1).

<sup>45</sup> “It is inefficient because the program does not directly connect the incentive with the innovation. Large pharmaceutical companies traditionally have not conducted effective research programs on tropical diseases. These manufacturers will be unlikely to start such a program merely because of the prospect of earning a voucher some years in the future, since the voucher’s value depends on the success of potential “blockbuster” drugs that are currently in their pipelines, which is far from assured” ([Kesselheim, 2008](#)).

<sup>46</sup> “Another source of inefficiency is that a voucher’s value will bear no relation to the usefulness of the drug whose development it is intended to reward. For example, the law stipulates that no voucher will be earned for a product whose “active ingredient” was previously approved. As a result, an effective novel antimalarial drug that degrades in the heat and must be taken six times a day would earn its sponsor a voucher, but no voucher would be granted for a follow-on formulation that might be more useful in resource-poor settings. Even more problematically, a sponsor rewarded with a voucher for FDA approval of a product for a neglected disease will have no incentive to follow through with implementation of the therapy. After an innovative product is approved in the United States, there can be significant delays before it reaches patients in developing countries, and drug-company ownership of its intellectual property may make it unaffordable. The human papillomavirus vaccine, for example, could be useful in combating cervical cancer in developing countries, but while it remains under patent protection, intellectual property rights and logistic problems have hindered its dissemination in resource-poor settings” ([Kesselheim, 2008](#)).



- Lack of transparency, both from the FDA<sup>47</sup> and in the transactions between voucher sellers and buyers<sup>48</sup>
- Lack of a requirement for the voucher recipient to have actually invested in product innovation and development (i.e., the recipient could submit for a voucher for a product that was developed and marketed previously outside of the US; see [here](#))<sup>49</sup>
- Existence of few organizations with motives that are purely or even highly aligned with global public health objectives, which can take advantage of the voucher for the purpose of identifying solutions for neglected tropical diseases<sup>50</sup>
- Adverse impacts on achieving socially optimal health outcomes<sup>51</sup>

With these critiques in mind, there are a number of ways that the incentive mechanisms behind PRVs could be updated to better align with global health objectives, which we describe in rough order of our take on their importance thus far.

**Be considerate about the supply of vouchers:** In our interview with David Ridley, he said that it is critical to “be thoughtful about the supply of vouchers,” since increasing the number of vouchers reduces their value. According to Ridley, the “investors that funded the river blindness drug [moxidectin] said they wouldn’t do it again, since they funded it based on the expectation that a voucher would sell for \$200 million.” The increase in PRVs following the expansion of the program (in particular to rare pediatric diseases) has led to a stabilization of PRV sale value around \$100 million in recent years, and academic experts claim that values below that threshold provide limited incentive for tropical disease-related drug development ([Ridley & Regnier, 2016](#); [Olliaro et al., 2018](#)), perhaps particularly for nonprofits that do not

<sup>47</sup> “One drug sponsor told us FDA’s process for determining the list of tropical diseases eligible for a PRV was not transparent and wanted clarification on FDA’s timeline for editing this list.<sup>43</sup> Another drug sponsor told us it wanted clarification on whether a drug would merit priority review on its own, so the sponsor could determine whether to redeem a PRV for that drug.” ([GAO, 2020](#), p. 28)

<sup>48</sup> “Relying on these sorts of transactions to spur innovation is speculative as well, and the deals between small and large pharmaceutical companies affecting agents of great importance to global health will lack transparency. Such deals may include other payments or exchanges of intellectual property that raise the cost or restrict the future availability of the products” ([Kesselheim, 2008](#)).

<sup>49</sup> For example: (i) “To earn the voucher, Novartis submitted to the FDA 8 of the 20 studies it had sponsored from 1993 to 2007 to support approval of the drug abroad,” and (ii) “Miltefosine was originally developed as an anticancer agent in the 1980s but was found to cure visceral leishmaniasis in the late 1990s. Paladin Laboratories acquired rights to the drug in 2008 for \$8.5 million and submitted an application to the FDA for miltefosine in 2013 based on trials it had not conducted dating back to 1999. The drug was approved in 2014.” ([Kesselheim, 2015](#), p. E1)

<sup>50</sup> “Medicines Development recently announced plans to earn a voucher by seeking FDA approval of moxidectin, an antiparasitic product long used to treat onchocerciasis (river blindness) outside the United States. However, few such drug companies exist to take advantage of this pathway.” ([Kesselheim, 2015](#), p. E1)

<sup>51</sup> “The Food and Drug Administration (FDA) has been publicly critical of the PRV mechanism. In a recent governmental performance audit, FDA officials contended that the PRV program fundamentally interferes with the agency’s ability to set priorities based on public health needs and warned about the adverse effects of voucher implementation. When describing the kind of drugs that are likely to have a PRV applied, FDA’s Director of the Office of New Drugs stated that imposing a 6-month review is very challenging and has the adverse impact of requiring managers and reviewers to refocus time and resources away from other important public health work, such as reviewing other applications for potentially much more serious conditions or drafting of guidance documents on issues related to drug development” ([Mostaghim & Kesselheim, 2016](#), pp. 1001-1002). “In addition, too-speedy FDA review may lead to bad regulatory decision making.” ([Kesselheim, 2008](#))

intend to redeem the PRV.<sup>52</sup> David Ridley mentioned in our interview that the target value should be around \$200 million to provide adequate incentive. However, since prices have stabilized around \$100 million, he said, “you need the voucher plus something else, like funding from Gates, BARDA, or potentially even a voucher from Europe if they start a program; it’s not free to expand the program, there’s a real opportunity cost.”

**Require access plans:** [GAO \(2020\)](#) — as well as several other voices in the literature — suggest a number of additional improvements to the policy tool (pp. 27-28). They suggest that the policy could require submission by the company trying to obtain from the FDA a PRV for its PRV-eligible application of an access plan to reach those most in need with the tropical disease product, supplying it at cost, especially in low-income settings. Ridley emphasized the need for this improvement to the policy tool, citing the benefits of requiring companies to consider in advance where they plan to register the product, the specifics of their business plan, and who their partners will be. Then, he said, the “do-gooders” in the company (of which he is convinced there are many in global health units) and the public can hold them accountable. Lumpkin similarly emphasized the importance of pressuring companies to affordably market tropical disease drugs (in addition to developing them).

**Link the incentive more directly to global health benefits and objectives:** In our interview with Matt Clancy, innovation economist and Research Fellow at Open Philanthropy, he recalled that during his tenure with the US Department of Agriculture years ago, the department investigated PRVs as a potential incentive mechanism in veterinary medicine. One counterargument raised by another economist in government, he recalls, was primarily that PRVs are an inefficient tool from an economic perspective. In other words, the policy tool does not incentivize innovation according to its social value, but rather according to the value of a voucher (either its use or its sale) at a given point in time. Its “only merit” was that it “obfuscated the cost” of the policy intervention, making it more politically feasible to initiate and maintain than would, say, subsidies equivalent to the social value of the R&D that the policy tool aims to encourage. He is not an expert on PRVs per se, but he did wonder aloud whether the PRV award could be contingent on a certain number of people being treated for the tropical disease for which the PRV is awarded (instead of simply getting a drug approved).

**Increase administrative transparency and clarity:** A couple of stakeholders GAO interviewed suggested administrative changes, such as further transparency in determining which diseases are eligible and clarity on whether FDA approval submissions were assessed on their merits to receive priority review on their own (i.e., without the PRV). Ridley agreed that clarity for drugmakers is valuable, though he recognizes that the FDA can never promise approval in advance based on a set list of criteria. He provided an example of an antiparasitic that would increase compliance by reducing the number of pills necessary, though the drug sponsors could not get sufficient evidence since compliance is always high in high-quality clinical trials. Due to lack of evidence, the FDA did not reward the drug sponsor a PRV. The drug sponsor would have preferred to know the evidence requirements upfront, and lack of clarity on these criteria has led to a “fail fast” mantra, which he said can have adverse effects if it leads to low

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<sup>52</sup> “This is particularly the case for nonprofit organizations that depend on public or philanthropic funding and/or need to raise money from “investment” funds. [Moxidectin](#) is a case in point: even though repurposing is comparatively cheap, the estimated total cost to bring moxidectin to FDA registration may well have exceeded \$50 million. In contrast to public and/or philanthropic funders, investment funds inevitably require reimbursement and significant return on investment. This substantially reduces the proceeds from the PRV sale available for additional work required to bring the drug to the target countries, including registration, additional studies to inform guidelines and policy, and finally, to make it available and affordable to those who need it.”



development of innovations that have potential but do not appear promising at first (e.g., mRNA vaccines).

**Remove eligibility for pandemics (or where innovation is otherwise already highly incentivized):** Ridley also suggested that the PRV legislation should have been written to remove eligibility for PRVs in cases like COVID-19 vaccines, which got medical countermeasure PRVs. “The idea of the program was to incentivize solutions for diseases that are not currently major problems in the US, since those will receive significant government incentives anyway.”

### Two further suggested improvements — restricting eligibility to drugs not yet marketed or developed outside of the US, as well as to organizations with financial need — feature in the literature but seem less promising

**Restrict PRVs to new drugs:** GAO additionally suggests that PRV awards could be restricted to drugs that are truly innovative in the sense that they have not been “developed and marketed” outside of the United States previously (p. 26). Ridley admitted that this shortcoming was “something they got wrong initially,” but that the “low-hanging fruit has now been plucked.”<sup>53</sup> In other words, all opportunities for gaming the system in this way have been exhausted and, he said, “If we do it in Europe, we’ll do it right. If a drug has been approved by another stringent regulatory authority more than two years ago, it would not be eligible.” Thus, this improvement appears to lack relevance going forward.

**Grant awards only to organizations with financial need:** Finally, GAO recommends that awards could be granted only to drug developers with financial need, who otherwise would not be able to develop the drug without financial support. It is unclear to us the extent to which PRVs currently incentivize big pharma companies to innovate with respect to tropical diseases, so we would want to gain a deeper understanding of the downsides of this potential improvement before endorsing it. Ridley supported this intuition by disagreeing with this suggested improvement, since “it’s good that players like J&J, GSK, and Sanofi are in the game, given they have a lot of advantages, scale, and expertise, and that they are vulnerable to being publicly shamed.”

### Potential “red lines” in improvement efforts include those that infringe on the program’s budget neutrality and that further compress FDA review time

**Non-budget-neutral options could be unpalatable to US lawmakers:** In our conversation, Lumpkin emphasized that a major advantage of the PRV programs is their direct cost neutrality for the US government, which experts agree facilitated the passage of legislation that created the programs.<sup>54</sup> Lumpkin further indicated that alternatives — such as exclusivity extension vouchers and TEVs that could prevent a generic version of the product from coming to market sooner — would present costs that many US lawmakers would find unacceptable. According to Lumpkin, “It would be surprising if Congress bought into [non-cost-neutral changes to the PRV program] due to the budget implications.” Ridley has also indicated that the

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<sup>53</sup> Another “mistake” Ridley mentioned was the long notice period for redeeming a PRV at the outset of the program, which led to Novartis’s failed priority review application for FDA approval of the second indication of its arthritis drug, Ilaris. In brief, the long notice period meant that drug developers had too much uncertainty about potential drugs they could submit for approval (e.g., they may not have advanced sufficiently in their clinical trial research). In the mid-2010s, the notice period was changed to 90 days.

<sup>54</sup> See also [Hamming \(2013\)](#), which attributes the “strong bipartisan support” enjoyed by the 2007 bill introducing PRVs to the provision’s “budget-neutral promise” (p. 400).

provision was considered “free” by several US senators, and that this factored into their initial support for the provision.

**Compression of FDA priority review time could be technically infeasible:** In our conversation, Lumpkin opined that the current six-month time frame for FDA priority review would be difficult to compress further without significantly compromising the quality of review — potentially weakening assurances of safety, efficacy, and manufacturing quality — given the extensive items and procedures involved in a typical review. He further emphasized that scaling up the FDA workforce would be unlikely to sufficiently increase the pace of review. Over the years, Lumpkin said, the idea of decreasing the six-month time frame for a priority review has been discussed and is always discarded as infeasible and incompatible with the FDA’s public health mission.

### Potential learnings from European tropical disease review procedures include inviting LMIC regulators to attend advisory committees and reforming commercial confidentiality to improve FDA-WHO links

While the immediate financial incentive of the TD PRV program (a voucher worth ~\$100 million) has no direct non-US counterpart, several initiatives also promise to extend high-income countries’ regulatory capacity to serve global health interests. Two examples from Europe are the [EU-Medicines for all \(EU-M4all\)](#) procedure, previously known as the Article 58 procedure, which enables the European Medicines Agency (EMA) to provide an “opinion” on products intended for use outside of the EU (see also [Cavaller Bellaubi et al., 2020](#)), and Swissmedic’s [Marketing Authorization for Global Health Products \(MAGHP\)](#) procedure, which serves a similar role. See also [EMA \(2015\)](#) for a somewhat dated review of EU-M4all and a comparison of the procedure to FDA review with TD PRV — and several other pathways — in greater detail (pp. 7-8, Exhibits 1-2).

Our discussion with Murray Lumpkin revealed several learnings from various European tropical disease programs that the FDA tropical disease review process could incorporate (independent of the TD PRV program). However, Lumpkin noted that the EU-M4all and MAGHP procedures hold specific legal mandates to dedicate institutional capacity to reviews that do not culminate in locally focused authorizations, whereas the FDA, when reviewing a tropical disease drug or vaccine and subsequently granting a PRV, is still officially reviewing the product for US authorization (often justified, Lumpkin said, under the premise that US military personnel and civilian travelers visit regions affected by tropical diseases and then return to the US). The below suggestions do not suppose deeper legislative reforms that would enable the FDA to play a role similar to the EMA and Swissmedic in performing non-locally focused reviews, but instead suggest reforms under the current setup.

**Invite LMIC regulators to attend FDA advisory committees:** Lumpkin suggested that countries affected by relevant tropical diseases could be invited to form part of advisory committees during the FDA review process of these products — specifically, the [Antimicrobial Drugs Advisory Committee](#) (previously known as the Anti-Infective Drugs Advisory Committee) and the [Vaccines and Related Biological Products Advisory Committee](#). However, when prompted with potential cases where a drug was not approved but could have been approved had the affected countries participated, Lumpkin said that no examples came to mind, as the FDA’s “hands are tied,” given that its current mandate is still to review and, if the data support, approve products for use in the US healthcare system. It cannot, for example, offer an opinion on a product for use elsewhere, as can the EMA.

**Reform commercial confidentiality rules to facilitate FDA links with the WHO and with LMIC national regulatory authorities:** Lumpkin said that FDA approvals of tropical disease products do not aid the WHO PQ process as much as they could, because commercial confidentiality and trade secret regulations prevent the FDA from providing the WHO and regulators in LMICs its review documents without significant redactions — the documents it provides, Lumpkin said, are thus “unusually unhelpful.” This stands in contrast to the EMA, which does not highly redact documents it provides to the WHO. Lumpkin cited the example of African countries’ approvals of COVID-19 vaccines, which were facilitated by the EMA’s authorizations and subsequent provision of documents to the WHO and LMIC regulators, which is a function that the FDA could not serve in the same way. He also mentioned a relevant *Science* editorial he co-authored ([Lumpkin et al., 2022](#)) that we did not have time to review.

## How we would spend more time

- Further investigate the integration of FDA approval and WHO PQ/EML registration:
  - In particular, we could build on our existing [table](#) comparing FDA approval times and WHO PQ/EML registration to find potential cases with which to explore the extent to which FDA approval per se may have contributed to earlier deployment of products in endemic countries.
- Further assess robustness of the academic evidence on the incentive effect of PRVs; specifically:
  - i. Identify data for all PRV-eligible diseases on [G Finder](#) to increase our certainty in the percentage of spending attributable to BMGF;
  - ii. Conduct the same exercise for the control groups in these studies to see if BMGF funding increased (to the same extent) for PRV-ineligible diseases, across jurisdictions eligible for PRV awards (on [ClinicalTrials.gov](#)) and those ineligible for PRV awards (other WHO ICTRP registries).
    - Option (ii) essentially suggests performing robustness tests we wish that [Aerts et al. \(2022\)](#) would have conducted, though we note that it is possible changes other than BMGF of which we are not aware would remain a potential source of bias.
  - iii. For a more qualitative approach, one could also attempt to trace the stages of drug development to assess the extent to which BMGF-funded research contributed to PRV-eligible innovations, despite or in addition to PRV eligibility.
  - iv. We would also review in greater detail the study methods of [Hwang et al. \(2019\)](#), a paper referred to us by David Ridley, which finds that the RPD PRV program may have accelerated clinical trials.
- Conduct more research into how PRV sales proceeds have been used by their beneficiaries to understand the post-award benefits of PRVs.
- Compare the potential incentive effects of PRVs to what we know about the incentive effects of [prizes](#), [market size](#), and/or the [Orphan Drug Act](#).



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