

# Research Synthesis: Priority Review Vouchers

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## Introduction

The literature on priority review vouchers is considerable\*, especially with regards to the implementation and efficacy of the US priority review voucher (PRV) program. The literature seems to continue to expand since the program's introduction in 2007.

## Search terms

Priority Review Voucher

## Synthesis of the literature

### Legislative History of PRV

In 2006, Ridley et al. (2006) proposed the use of PRVs to encourage the development of medicines for neglected diseases. This paper developed a list of criteria for which a PRV should be issued, estimated the value of a PRV in relation to a “potential blockbuster drug” to be higher than USD 300 million, presented the dual benefit of PRVs as increasing access to drugs that are needed in developed and developing countries, respectively, and made a cost-benefit analysis of introducing the PRV incentive (Ridley, Grabowski, and Moe 2006).

Following support for the proposal from several members of the US Congress, the Food and Drug Administration Amendments Act (FDAAA) of 2007 introduced the PRV system in the US for the review of drug applications for neglected tropical diseases (Hamming 2013; Gaffney, Mezher, and Brennan 2018). In 2012, the Creating Hope Act of 2011 (CHA) added rare pediatric diseases to the list of PRV-eligible diseases (Hamming 2013).

The CHA also made the PRV transferable, e.g. by sale, and revocable for failure to market the product in a timely manner; it also shortened the application notice period to ninety days from one year (Abdel-Rahman et al. 2014). The PRV was also extended to medical countermeasures for pathogens of pandemic potential in 2016 through the 21st Century Cures Act (Gaffney, Mezher, and Brennan 2018). The same legislation also extended the PRV program for rare pediatric diseases for an additional 3 years (Ekins and Wood 2016). It has been noted that the PRV mechanism has received significant political support (Ravvin 2008).

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## Features of PRVs

Most of the literature discuss the basic features of the PRV including (i) that the award of a PRV is granted upon a successful approval of a medicine for any of the eligible diseases or conditions, (ii) the privilege of expedited review, that is 6 months instead of the usual 10 months or so review period, of any medicine application brought by virtue of the awarded PRV, (iii) the ability to sell the awarded PRV to other entities (transferability) and (iv) the absence of or minimal direct financial costs to taxpayers with respect to the implementation of the PRV program. In order to be eligible for a PRV the tropical disease medicine application must pertain to a new chemical entity that is not yet offered for sale in the US (Berman and Radhakrishna 2017).

Other PRV features include: the provision permitting the list of eligible diseases to be updated (Anderson 2009), the requirement to pay user fees when claiming the PRV privilege and the corresponding amounts paid from 2011 to 2018, the proviso that the PRV does not guarantee an affirmative decision on the application nor that the decision of the review process will be issued within the target six-month period (Hamming 2013; Gaffney, Mezher, and Brennan 2018), considering that certain applications may require further clarifications or tests (Moe, Grabowski and Ridley 2009). It is noted that the user fee covers the cost for implementing the program and thus, removes the direct financial burden from the government and taxpayers (Hoffman and So 2015). Berdud, Towse and Kettler (2016), focusing on malaria research and development, argued that the PRV user fees may be steep for some entities such as small and medium enterprises or not-for-profit organizations (Berdud, Towse and Kettler 2016).

## Expected Benefits

Among the expected benefits of the PRV are an increase in R&D activities for the target diseases (Ehrenheld 2008) and accelerated access to the resulting medicines by patients in developing countries (Sonderholm 2009). Dimitri (2010) provided an economic analysis of the efficacy of PRVs and concluded that, given certain conditions, PRVs would be likely to increase R&D activities (Dimitri 2010). The proponents of the PRV also noted the direct benefits from the PRV for drug developers in the form of expedited review of their applications, or the monetary proceeds from the sale of a PRV (Moe, Grabowski and Ridley 2009). Further, PRVs are also expected to complement other drug development initiatives (Grabowski, Ridley, and Moe 2008).

## PRVs as Issued and Market Value

Gaffney, Mezher, and Brennan (2018) listed the PRVs that were issued by the FDA from 2009 to 2018, including for which diseases and their respective status (whether they have been used, sold or remain to be used) (Gaffney, Mezher, and Brennan 2018). They compiled the known amounts for which the issued PRVs had been purchased. It was noted that, until 2015, the sales price of a PRV increased but starting in 2016 the prices decreased. Prices have ranged between USD 67 million and USD 350 million (Gaffney, Mezher, and Brennan 2018). Stefanakis et al. (2012) determined that there are 35 drugs under clinical development that would qualify under the PRV program between 2011 to 2020, yielding an estimated 1 or 2 PRVs annually (Stefanakis et al. 2012). Robertson estimated the floor price of a PRV, (upon sale to a third-party), depending on the number of PRVs awarded per year (Robertson 2016).

Robertson et al. (2012) conducted an online survey of for-profit companies that run programs dealing with diseases covered by the PRV. The survey results indicated that the PRV is one, but

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not the only, factor companies consider when deciding to engage in R&D for neglected tropical diseases (Robertson et al. 2012).

Ekins and Wood (2016) argued that the PRV is the main expected source of financial return for a small company engaged in drug R&D for rare diseases such as Sanfillipo Syndrome, which does not have a large patient base (Ekins and Wood 2016). It was also noted that the possibility of a PRV award upon approval of moxidectin for the treatment of onchocerciasis was a consideration for the Global Health Investment Fund in funding the drug's US FDA registration by the non-profit organization Medicines Development for Global Health (Kuesel 2016).

### Critiques

Some papers have made several critiques of PRVs. Mostaghim and Kesselheim (2016) and Sinha and Kesselheim (2016) argued that the PRV program has not yet shown any quantifiable impact with respect to increasing R&D on tropical diseases. It has also been observed that a survey of drugs being developed for neglected diseases from 2000 to 2014 indicated that “[t]he proportion of neglected tropical disease drugs among all products in development decreased by 1.74% per year (95% CI, -13.86% to 12.87%) before the voucher was created and decreased by 1.73% per year (95% CI, -12.75% to 10.27%) after the voucher was created” (Jain et al. 2017).

Other critiques include: that the PRV system more possibly functions as a reward for organizations that already have medicines at the late stages of the development pipeline and not as an incentive for the conduct of new R&D activities on neglected disease medicines (Ravvin 2008). It is also seen as an unsustainable mechanism because it mainly relies on US patients paying indirectly for the PRV (Sonderholm 2009). Another criticism of the PRV program is that, while it may boost drug development on the eligible diseases and conditions, this does not necessarily translate into availability or affordability of the drugs to the populations in need of them (Gaffney, Mezher, and Brennan 2018; Sonderholm 2009; Kesselheim, Maggs, and Sarpatwari 2015). Kesselheim (2008) argued that the PRV is an inefficient incentive tool since research on neglected tropical diseases is usually made by small, rather than large, pharmaceutical companies having “limited drug portfolios” and who will not likely use the awarded PRV (Kesselheim 2008) (this argument was made before the PRV was revised to become transferable).

The question has also been raised as to whether loopholes in the legislation allow companies to obtain a PRV without having conducted any R&D. For example, Sunyoto, Potet, and Boelaert (2018) and Doshi (2014) questioned whether the company Knight Therapeutics should have received a PRV for the approval of the drug miltefosine (for treating leishmaniasis), considering that public and philanthropic actors largely funded the development of this drug, and that it had already obtained regulatory approval outside the US (Sunyoto, Potet, and Boelaert 2018; Doshi 2014). Kesselheim (2009) proposed that funding be granted directly to those entities and individuals conducting medicines research for neglected diseases instead of spending the additional amounts on medicines that obtained faster marketing approval with a PRV (Kesselheim 2009). Lexchin (2010) concluded that the PRV system, with respect to neglected diseases, may be best replaced with another incentive mechanism for R&D (Lexchin 2010). This latter view was echoed by Muthyala (2011) as to the suitability of the PRV for orphan drugs (Muthyala 2011).

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## PRVs in the Future

Proposals for changes to improve the PRV system include: (i) the imposition of “access commitments” on the PRV awardee, (ii) requiring that the medicine eligible for PRV award be newly introduced worldwide instead of just in the United States market (Mostaghim and Kesselheim 2016), (iii) three PRVs should be awarded instead of just one to increase its “economic incentive”; (iv) that no orphan drug tax credit be granted on top of a PRV award; and (v) that the future PRV law require a waiver of patent rights over the neglected tropical disease medicine (Sonderholm 2009).

The adoption of the PRV system in Europe has been proposed, with the estimated value of the PRV expected to be similar to that in the US (Ridley and Sánchez 2010), but experts on orphan drug development caution that the expected benefits of adopting this program must be weighed against significant costs related to the system (Picavet, Cassiman, and Simoens 2012). PRVs have also been suggested as an incentive to develop new antibiotics for antimicrobial resistance (AMR) (Sciarretta et al. 2016).

The website <http://www.priorityreviewvoucher.org/> provides extensive information on the PRV, and is maintained by David Ridley (one of the original proponents of the PRV).

## Research gaps

- Analysis regarding the extent to which PRVs increase R&D efforts over business-as-usual in targeted diseases, and whether or how they shape R&D decision-making
- Research on the extent to which products covered by PRVs are made available, manufactured and distributed to the public, and at what price

## Cited papers with abstracts

Abdel-Rahman, Susan, Jasziane Tolbert, Jennifer Goldman, and Ralph Kauffman. 2014. “The Creating Hope Act: What Is Old Is New Again.” *Pediatric Health, Medicine and Therapeutics*, June, 49. <https://doi.org/10.2147/PHMT.S46069>.

Abstract: The Creating Hope Act, passed as part of the Food and Drug Administration Safety and Innovation Act of 2012, is among the newest laws intended to foster drug development for rare and neglected diseases in children. The act expands the priority review voucher incentive that first appeared in the Food and Drug Administration Amendments Act of 2007 and was intended to stimulate the development of products for the prevention and treatment of tropical diseases. Notably, legislative and regulatory initiatives aimed at enhancing drug development both for use in children and for rare diseases have intermittently emerged over the past 3 decades. This manuscript provides an overview of related legislation that has preceded the Creating Hope Act and examines the potential impact of the new act in the context of the outcomes that have been observed with the earlier initiatives.

Link: <https://www.dovepress.com/the-creating-hope-act-what-is-old-is-new-again-a17096>

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Anderson, Gerard F. 2009. "Spurring New Research For Neglected Diseases." *Health Affairs* 28 (6): 1750–59. <https://doi.org/10.1377/hlthaff.28.6.1750>.

**Abstract:** A very small proportion of global spending for biomedical research is for neglected diseases. However, neglected diseases account for a sizable percentage of the global burden of disease, especially in low-income countries. For-profit pharmaceutical and biotech companies are unlikely to conduct significant additional research on neglected diseases without financial incentives. This paper examines the benefits of providing a tax credit to encourage companies to conduct preclinical research on neglected diseases in the laboratory or in animals. This strategy could lead to a new generation of treatment options for the people in low-income countries who are susceptible to neglected diseases.

Link: <https://www.healthaffairs.org/doi/pdf/10.1377/hlthaff.28.6.1750>

Berdud, Mikel, Adrian Towse, and Hannah Kettler. 2016. "Fostering Incentives for Research, Development, and Delivery of Interventions for Neglected Tropical Diseases: Lessons from Malaria." *Oxford Review of Economic Policy* 32 (1): 64–87. <https://doi.org/10.1093/oxrep/grv039>.

**Abstract:** Making existing medical technologies accessible and incentivizing the development of new medicines for neglected diseases are major global health policy challenges. Where market incentives are not enough, additional policies and incentives are required to engage the private and public sectors. There have been major advances in tackling global health issues in the last decade with increasing funding for R&D for neglected diseases from high-income countries and from private foundations. Malaria is an illustrative example of both great progress and of continuing challenge. This paper reviews relevant incentives for progress towards malaria control, elimination, and eradication. We describe in depth the most relevant incentives—product development partnerships (PDPs), open source databases (OSDs), priority review vouchers (PRVs), and advance market commitments (AMCs). Finally we evaluate their achievements—existing anti-malarial tools and interventions—and discuss the R&D incentives required to generate further interventions to meet the malaria eradication goal and tackle neglected diseases.

Link: <https://academic.oup.com/oxrep/article/32/1/64/2452866>

Berman, Jonathan, and Tanya Radhakrishna. 2017. "The Tropical Disease Priority Review Voucher: A Game-Changer for Tropical Disease Products." *The American Journal of Tropical Medicine and Hygiene* 96 (1): 11–13. <https://doi.org/10.4269/ajtmh.16-0099>.

**Abstract:** The Neglected Tropical Disease Voucher Program is a Congressionally-mandated program intended to promote approval of products for tropical diseases because it provides spectacular financial compensation consequent to FDA approval of a priority product. Three drug approvals—artemether/lumifantrine for malaria, bedaquiline for multidrug resistant tuberculosis, miltefosine for leishmaniasis—have received Tropical Disease Vouchers to date. We give our view of the type of products that might qualify for a Tropical Disease Voucher, financial considerations in venturing capital to support product development, clinical ramifications of a successful product approval, and an overall evaluation of the Program.

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Abstract: Not available

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Ekins, Sean, and Jill Wood. 2016. "Incentives for Starting Small Companies Focused on Rare and Neglected Diseases." *Pharmaceutical Research* 33 (4): 809–15. <https://doi.org/10.1007/s11095-015-1841-9>.

Abstract: Starting biotech or pharmaceutical companies is traditionally thought to be based around a scientist, their technology platform or a clinical candidate spun out from another company. Between us we have taken a different approach and formed two small early stage companies after initially leveraging the perspective of a parent with a child with a life-threatening rare disease. Phoenix Nest (<http://www.phoenixnestbiotech.com/>) was co-founded to work on treatments for Sanfilippo syndrome a devastating neurodegenerative lysosomal storage disorder. In the space of just over 3 years we have built up collaborations with leading scientists in academia and industry and been awarded multiple NIH small business grants. The second company, Collaborations Pharmaceuticals Inc. (<http://www.collaborationspharma.com/>) was founded to address some of the other 7000 or so rare diseases as well as neglected infectious diseases. The Rare Pediatric Disease Priority Review Voucher is likely the most important incentive for companies working on rare diseases with very small populations. This may also be partially responsible for the recent acquisitions of rare disease companies with late stage candidates. Lessons learned in the process of starting our companies are that rare disease parents or patients can readily partner with a scientist and fund research through NIH grants rather than venture capital or angel investors initially. This process may be slow so patience and

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perseverance is key. We would encourage other pharmaceutical scientists to meet rare disease parents, patients or advocates and work with them to further the science on their diseases and create a source of future drugs.

Link: <https://link.springer.com/article/10.1007/s11095-015-1841-9>

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Abstract: Not available

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Hamming, Lesley. 2013. "The Promise of Priority Review Vouchers as a Legislative Tool to Encourage Drugs for Neglected Diseases." *Duke Law & Technology Review*, 11 (2): 390-412.

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

Link: [https://heinonline.org/HOL/Page?handle=hein.journals/dltr11&div=15&g\\_sent=1&casa\\_token=&collection=journals](https://heinonline.org/HOL/Page?handle=hein.journals/dltr11&div=15&g_sent=1&casa_token=&collection=journals)

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**Abstract:** Background: There is widespread recognition that the existing global systems for innovation and access to medicines need reform. Billions of people do not have access to the medicines they need, and market failures prevent new drugs from being developed for diseases that primarily affect the global poor. The World Health Organization's Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG) analyzed numerous proposals for reform. The aim of this article is to build on these previous inquiries.

**Methods:** We conducted a structured analysis that grouped proposals into five broad opportunities for global policy reform to help researchers and decision makers to meaningfully evaluate each proposal in comparison with similar proposals. Proposals were also analyzed along three important dimensions — potential health impact, financial implications, and political feasibility — further facilitating the comparison and application of this information.

**Findings:** Upon analysis, no one solution was deemed a panacea, as many (often competing) considerations need to be taken into account. However, some proposals, particularly product development partnership and prizes, appeared more promising and feasible at this time and deserve further attention.

**Conclusion:** More research is needed into the effectiveness of these mechanisms and their transferability across jurisdictions.

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Abstract: Onchocerciasis is a parasitic, vector borne disease caused by the filarial nematode *Onchocerca volvulus*. More than 99% of the population at risk of infection live in Africa. Onchocerciasis control was initiated in West Africa in 1974 with vector control, later complemented by ivermectin mass drug administration and in the other African endemic countries in 1995 with annual community directed treatment with ivermectin (CDTI.) This has significantly reduced infection prevalence. Together with proof-of-concept for onchocerciasis elimination with annual CDTI from foci in Senegal and Mali, this has resulted in targeting onchocerciasis elimination in selected African countries by 2020 and in 80% of African countries by 2025. The challenges for meeting these targets include the number of endemic countries where conflict has delayed or interrupted control programmes, cross-border foci, potential emergence of parasite strains with low susceptibility to ivermectin and co-endemicity of loiasis, another parasitic vector borne disease, which slows down or prohibits CDTI implementation. Some of these challenges could be addressed with new drugs or drug combinations with a higher effect on *Onchocercavolvulus* than ivermectin. This paper reviews the path from discovery of new compounds to their qualification for large scale use and the support regulatory authorities provide for development of drugs for neglected tropical diseases. The status of research for new drugs or treatment regimens for onchocerciasis along the path to regulatory approval and qualification for large scale use is reviewed. This research includes new regimens and combinations of ivermectin and albendazole, antibiotics targeting the *O. volvulus* endosymbiont *Wolbachia*, flubendazole, moxidectin and emodepside and discovery of new compounds.

Link:

<https://reader.elsevier.com/reader/sd/pii/S221132071630015X?token=1FAI78ECB586A9F9AF23CB8BED3142E76123758FD28001930D0D219F7F64A34FD4600FCCE727B8BA12AADA52B7824BB2>

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**Abstract:** Background: There is general agreement, including from the pharmaceutical industry, that current market based methods of generating research into the development of pharmaceutical products that are relevant for developing countries do not work. This conclusion is relevant not just for the most neglected diseases such as leishmaniasis but even for global diseases such as cancer and cardiovascular disease.

**Discussion:** Stimulating research will mean overcoming barriers such as patent thickets, poor coordination of research activities, exclusive licensing of new technologies by universities and the structural problems that inhibit conducting appropriate clinical trials in developing countries. In addition, it is necessary to ensure that the priorities for research reflect the needs of developing countries and not just donors. This article will explore each of these issues and then look at three emerging approaches to stimulating research -paying for innovation, priority review sales or vouchers and public-private partnerships, - and evaluate their strengths and weaknesses.

**Summary:** All of the stakeholders agree that there is a pressing need for a major expansion in the level of R&D. Whatever that new model turns out to be, it will have to deal with the 5 barriers outlined in this paper. Finally, none of the three proposals considered here for expanding research is free from major limitations.

**Link:** <https://bmcinthealthhumrights.biomedcentral.com/articles/10.1186/1472-698X-10-20>

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**Abstract:** To encourage the development of orphan drugs, the European Union has implemented specific policies in 2000. However, the political, social, scientific and economic context has changed since the implementation of these policies. For that reason, the aim of this article is to evaluate orphan drug policies in Europe. Firstly, key issues on the orphan drug policy were identified based on desk research. Secondly, a Delphi policy study with 47 European orphan drug experts from different backgrounds was carried out to explore these issues. In the round one of the Delphi, responses were received from 18 experts (38.3%) and from ten (55.5%) in the round two. Experts agree that the orphan drug policies in Europe have not outlived their usefulness. Additionally, the importance of reducing country-dependent inequalities in patient access to orphan drugs has been emphasized. Still, there is room for further refinement of the orphan drug policies. Within that context, we formulated several policy recommendations (e.g. enforcing the policy that is in place to reduce the period of market exclusivity for profitable orphan drugs, stating the level of clinical evidence needed to authorize orphan drugs, etc.) with the overall goal to optimize patient access to orphan drugs.

Link: <https://www.sciencedirect.com/science/article/pii/S0168851012002461>

Ravvin, M. 2008. "Incentivizing Access and Innovation for Essential Medicines: A Survey of the Problem and Proposed Solutions." *Public Health Ethics* 1 (2): 110–23. <https://doi.org/10.1093/phe/phn017>.

**Abstract:** The existing intellectual property regime discourages the innovation of, and access to, essential medicines for the poor in developing countries. A successful proposal to reform the existing system must address these challenges of access and innovation. This essay will survey the problems in the existing pharmaceutical patent system and offer critical analysis of some reform proposals. I will argue that existing mechanisms that are intended to mitigate the harms of the current pharmaceutical patent system, such as bulk buying, differential pricing and compulsory licenses, are inadequate and perhaps even counter-productive over the long-term. Other incentive mechanisms based on push funding, such as government research grants, are inefficient and limited in scope. Pull mechanisms, which offer some reward for successful pharmaceutical innovations, offer a more promising incentive mechanism. I will evaluate three pull mechanisms -- Priority Review Vouchers, Advance Market Commitment (AMC) and the Health Impact Fund -- on the basis of their capacity to incentivize access and innovation, as well as their efficiency and political feasibility. Though the Health Impact Fund appears to be the most promising proposal, more work must be done to overcome challenges of its implementation.

Link: <https://academic.oup.com/phe/article/1/2/110/1449014>

Ridley, David B., Henry G. Grabowski, and Jeffrey L. Moe. 2006. "Developing Drugs For Developing Countries." *Health Affairs* 25 (2): 313–24. <https://doi.org/10.1377/hlthaff.25.2.313>.

**Abstract:** Infectious and parasitic diseases create enormous health burdens, but because most of the people suffering from these diseases are poor, little is invested in developing treatments. We propose that developers of treatments for neglected diseases receive a "priority review voucher." The voucher could save an average of one year of U.S. Food and Drug Administration

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(FDA) review and be sold by the developer to the manufacturer of a blockbuster drug. In a well-functioning market, the voucher would speed access to highly valued treatments. Thus, the voucher could benefit consumers in both developing and developed countries at relatively low cost to the taxpayer.

Link: [https://www.healthaffairs.org/doi/abs/10.1377/hlthaff.25.2.313?url\\_ver=Z39.88-2003&rfr\\_id=ori%3Arid%3Acrossref.org&rfr\\_dat=cr\\_pub%3Dpubmed](https://www.healthaffairs.org/doi/abs/10.1377/hlthaff.25.2.313?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed)

Ridley, David B, and Alfonso Calles Sánchez. 2010. "Introduction of European Priority Review Vouchers to Encourage Development of New Medicines for Neglected Diseases." *The Lancet* 376 (9744): 922–27. [https://doi.org/10.1016/S0140-6736\(10\)60669-1](https://doi.org/10.1016/S0140-6736(10)60669-1).

Abstract: Not available

Link: <https://www.sciencedirect.com/science/article/pii/S0140673610606691>

Robertson, Andrew S. 2016. "Preserving an Incentive for Global Health R&D: The Priority Review Voucher Secondary Market." *American Journal of Law & Medicine* 42 (2-3): 524-542. <https://doi.org/10.1177/0098858816658278>.

Abstract: In December 2014, the United States government expanded the Priority Review Voucher ("PRV" or "voucher") program to include Ebola and other related Filoviruses. By doing so, lawmakers provided a potentially powerful incentive for drug companies to invest time and money in the development of novel medicines for terrifying diseases. This expansion is one of several additions made to the PRV programs since 2012. Many companies rely on voucher resale to recoup research and development ("R&D") costs; however, it is unclear whether the PRV program could be overextended, thereby diluting the value of the incentives. In this paper, I use historical approval data from the Food and Drug Administration ("FDA") and United States drug revenue data to better understand the secondary market value of a PRV. The data suggests that that purchase prices of a PRV could continue to climb; despite this, the market size for these vouchers is limited. The implications of these findings are discussed further.

Link: <http://journals.sagepub.com/doi/abs/10.1177/0098858816658278>

Robertson, Andrew S., Rianna Stefanakis, Don Joseph, and Melinda Moree. 2012. "The Impact of the US Priority Review Voucher on Private-Sector Investment in Global Health Research and Development." Edited by Timothy G. Geary. *PLoS Neglected Tropical Diseases* 6 (8): e1750. <https://doi.org/10.1371/journal.pntd.0001750>.

Abstract: Not available

Link: <https://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0001750>

Sciarretta, Kimberly, John-Arne Røttingen, Aleksandra Opalska, Arjon J. Van Hengel, and Joseph Larsen. 2016. "Economic Incentives for Antibacterial Drug Development: Literature Review and Considerations From the Transatlantic Task Force on Antimicrobial Resistance: Table 1." *Clinical Infectious Diseases* 63 (11): 1470–74. <https://doi.org/10.1093/cid/ciw593>.

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Abstract: The Trans-Atlantic Task Force on Antimicrobial Resistance (TATFAR) in 2015 was tasked with exploring economic incentives for antibacterial drug development and providing recommendations for potential global implementation. Due to the continual decline of pharmaceutical companies investing in new antibiotic development and the rise in antimicrobial resistance, there is an urgent need to examine market mechanisms that are appropriate to encourage small, medium, and large companies to reinvest in this space. This review provides a summary of the various models that have been proposed and highlights positions posed by several policy documents, peer-reviewed publications, organization proposals, and government-sponsored reviews. The findings support a form of a de-linkage model and a combination of push and pull incentive mechanisms. This level of consensus could culminate in global coordination of incentives that strike a balance of rewarding innovation and ensuring appropriate antibiotic use.

Link: <https://academic.oup.com/cid/article/63/11/1470/2526231>

Sinha, Michael S., and Aaron S. Kesselheim. 2016. "Regulatory Incentives for Antibiotic Drug Development: A Review of Recent Proposals." *Bioorganic & Medicinal Chemistry* 24 (24): 6446–51.

Abstract: Two primary regulatory mechanisms have been proposed to incentivize new antibiotic development: (1) changing Food and Drug Administration (FDA) approval processes to expedite antibiotic approval; and (2) offering enhanced possibilities for market exclusivity. Changes to the FDA regulatory approval process include greater reliance on surrogate endpoints such as biomarkers, use of noninferiority hypothesis designs for key preapproval clinical trials, and development of an expedited development track specific for antibiotics called the Limited Population pathway. The second strategy intended to encourage new antibiotic development has been to provide additional market exclusivity incentives based on regulatory approval. While these pathways have some positive attributes, they also present enhanced risks to patients associated with lower regulatory barriers and the market exclusivity incentives may not efficiently direct resources to the true origins of antibiotic innovation.

Link: <https://www.sciencedirect.com/science/article/pii/S096808961630640X>

Sonderholm, Jorn. 2009. "IN DEFENCE OF PRIORITY REVIEW VOUCHERS." *Bioethics* 23 (7): 413–20. <https://doi.org/10.1111/j.1467-8519.2009.01753.x>.

Abstract: Infectious and parasitic diseases cause enormous health problems in the developing world whereas they leave the developed one relatively unscathed. Research and development (R&D) of drugs for diseases that mainly affect people in developing countries is limited. The problem that relatively few drugs are available for diseases that cause an enormous burden of disease in the developing world is called the 'availability problem'. In recent years, the availability problem has received quite a bit of attention. A number of proposals have been fielded as to how this problem might be minimized. Wild-card patent extensions, advance market commitments, cash prizes and the Health Impact Fund are prominent examples of such proposals. These proposals can be thought of as pull-mechanisms for R&D. (2006), is described. A number of objections to this scheme are thereafter presented. A few

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amendments to the original scheme are then suggested, and it is argued that with these amendments in place, the priority review voucher scheme constitutes an attractive way of stimulating R D of drugs for neglected diseases. What has been coined a 'priority review voucher' is another pull-mechanism. This paper is a critical discussion of this pull-mechanism. First, the original priority review voucher scheme, as proposed by Ridley et al. of drugs for neglected diseases.

Link: <https://onlinelibrary.wiley.com/doi/full/10.1111/j.1467-8519.2009.01753.x>

Stefanakis, Rianna, Andrew S. Robertson, Elizabeth L. Ponder, and Melinda Moree. 2012. "Analysis of Neglected Tropical Disease Drug and Vaccine Development Pipelines to Predict Issuance of FDA Priority Review Vouchers over the Next Decade." Edited by Henry Grabowski. *PLoS Neglected Tropical Diseases* 6 (10): e1803. <https://doi.org/10.1371/journal.pntd.0001803>.

Abstract: Not available

Link: <https://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0001803>

Sunyoto, Temmy, Julien Potet, and Marleen Boelaert. 2018. "Why Miltefosine—a Life-Saving Drug for Leishmaniasis—Is Unavailable to People Who Need It the Most." *BMJ Global Health* 3 (3): e000709. <https://doi.org/10.1136/bmjgh-2018-000709>.

Abstract: Miltefosine, the only oral drug approved for the treatment of leishmaniasis—a parasitic disease transmitted by sandflies—is considered as a success story of research and development (R&D) by a public-private partnership (PPP). It epitomises the multiple market failures faced by a neglected disease drug: patients with low ability to pay, neglect by authorities and uncertain market size. Originally developed as an anticancer agent in the 1990s, the drug was registered in India in 2002 to treat the fatal visceral leishmaniasis. At the time, miltefosine was considered a breakthrough in the treatment, making it feasible to eliminate a regional disease. Today, access to miltefosine remains far from secure. The initial PPP agreement which includes access to the public sector is not enforced. The reality on the ground has been challenging: shortages due to inefficient supply chains, and use of a substandard product which led to a high number of treatment failures and deaths. Miltefosine received orphan drug status in the USA; when it was registered there in 2014, a priority review voucher (PRV) was awarded. The PRV, meant to facilitate drug development for neglected disease, was subsequently sold to another company for US\$125 million without, to date, any apparent impact on drug access. At the heart of these concerns are questions on how to protect societal benefit of a drug developed with public investment, while clinicians worldwide struggle with its lack of affordability, limited availability and sustainability of access. This article analyses the reasons behind the postregistration access failure of miltefosine and provides the lessons learnt.

Link:

[https://gh.bmj.com/content/3/3/e000709?int\\_source=trendmd&int\\_medium=trendmd&int\\_campaign=tr endmd](https://gh.bmj.com/content/3/3/e000709?int_source=trendmd&int_medium=trendmd&int_campaign=tr endmd)

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*\* For the purposes of this review, we have established three categories to describe the state of the literature: thin, considerable, and rich.*

- *Thin: There are relatively few papers and/or there are not many recent papers and/or there are clear gaps*
- *Considerable: There are several papers and/or there are a handful of recent papers and/or there are some clear gaps*
- *Rich: There is a wealth of papers on the topic and/or papers continue to be published that address this issue area and/or there are less obvious gaps*

*Scope: While many of these issues can touch a variety of sectors, this review focuses on medicines. The term medicines is used to cover the category of health technologies, including drugs, biologics (including vaccines), and diagnostic devices.*

*Disclaimer: The research syntheses aim to provide a concise, comprehensive overview of the current state of research on a specific topic. They seek to cover the main studies in the academic and grey literature, but are not systematic reviews capturing all published studies on a topic. As with any research synthesis, they also reflect the judgments of the researchers. The length and detail vary by topic. Each synthesis will undergo open peer review, and be updated periodically based on feedback received on important missing studies and/or new research. Selected topics focus on national and international-level policies, while recognizing that other determinants of access operate at sub-national level. Work is ongoing on additional topics. We welcome suggestions on the current syntheses and/or on new topics to cover.*

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