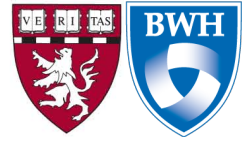




PORTAL
Program on Regulation, Therapeutics, And Law



Division of Pharmacoepidemiology and Pharmacoeconomics
Harvard Medical School and Brigham & Women's Hospital
Aaron S. Kesselheim, M.D., J.D., M.P.H., Director
Jerry Avorn, M.D., Co-Director
Ameet Sarpatwari, J.D., Ph.D, Assistant Director

Phone: 617-278-0930
Fax: 617-232-8602
www.PORTALresearch.org

Congress Should Support Development of New Treatments for Pediatric Rare Diseases, But Not with Priority Review Vouchers

Testimony of:

Aaron S. Kesselheim, M.D., J.D., M.P.H.

Professor of Medicine, Harvard Medical School

Director, Program On Regulation, Therapeutics, And Law (PORTAL)

Division of Pharmacoepidemiology and Pharmacoeconomics

Department of Medicine, Brigham and Women's Hospital

Boston, MA

www.PORTALResearch.org

United States House of Representatives
House Energy and Commerce Committee
Subcommittee on Health
Wednesday, July 29, 2020
Washington, D.C.

Summary of major points

- Priority review vouchers were devised in 2007 as a way of incentivizing private investment in research and development for neglected tropical diseases. A drugmaker that gets FDA approval for a neglected tropical disease indication earns a voucher that entitles it to have one of its otherwise unremarkable and not clinically innovative drugs—that would have been reviewed by the FDA on a standard timeline of 10 months—to be reviewed on the ‘priority review’ timeline of 6 months. This faster-to-market potential was estimated to be worth over \$300 million to drugmakers. The voucher program was extended to include drugs treating rare pediatric diseases in 2012 and drug treating medical countermeasures in 2016.
- Since that time, there has been no evidence that priority review vouchers have stimulated development of new treatments for any of the diseases to which they apply. In particular, in a Health Affairs study, my colleagues and I at Harvard Medical School showed no increases after 2012 in the rate of new drugs entering clinical trials for rare pediatric diseases when compared to drugs for rare adult diseases, which did not earn a voucher.
- The voucher incentive’s economic value was substantially overestimated, and in recent years has dropped to about \$80-110 million in part because of numerous vouchers on the market arising from all the types of drugs that can now earn them. The program also does not assure access to drugs that earn the voucher, which are often priced at extremely high levels by their manufacturers.
- Vouchers are potentially dangerous because they force the FDA to accelerate review of drugs that are otherwise unremarkable and/or non-innovative, which increases the risk of problematic regulatory decisions relating to these products. The FDA has also reported that the voucher strains its limited resources and disrupts its public health-based approach to prioritizing drug reviews.
- **Thus, the priority review voucher program was ill-conceived and in the 14 years since it was devised, there has been no systematic, rigorous evidence that it has proven useful in achieving its goals.**
- It is time to let the rare pediatric disease priority review voucher sunset, and instead direct efforts towards better solutions with a known track record in successfully leading to transformative drugs for medical conditions for which current market incentives have proven inadequate. For example, Congress could provide greater up-front public funding or tax credits for research into rare pediatric diseases. Another approach would be to provide greater support for late-stage development through public-private partnerships with non-profit organizations. Naturally, such partnerships should include guarantees about affordable access to the rare pediatric disease drugs that emerge because of the public’s involvement in reducing the risks and costs of research and development.

Chairwoman Eshoo, Ranking Member Burgess, and Members of the Subcommittee:

My name is Aaron Kesselheim; I am an internal medicine physician, lawyer, and health policy researcher and a Professor of Medicine at Harvard Medical School in the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women’s Hospital in Boston, one of the main Harvard teaching hospitals. I lead its Program On Regulation, Therapeutics, And Law (PORTAL), an interdisciplinary research group that studies the intersections between prescription drug affordability and use, laws and regulations related to medications, and the development and cost of drugs. I am here today to talk about the rare pediatric disease priority review voucher, which will sunset in 2020, and how the government can best support research into prescription drugs to treat rare pediatric diseases.

Priority Review Vouchers

To understand why the priority review voucher was proposed to serve as an incentive for drug development, it is necessary to review basic information about the review process undertaken by the Food and Drug Administration (FDA) for new prescription drugs. Before a new drug can be marketed in the US, it must be tested for efficacy and safety and the clinical trials reviewed by the FDA to determine that the benefits of the drug appear to outweigh its risks. The FDA’s review process includes dozens of scientists poring over extensive databases of studies in animals, toxicologic evaluations, and clinical trials.¹ It is extremely important that this process be done carefully and thoroughly because of the importance of prescription drugs in the management of certain critical diseases and because of the potentially severe side effects that can result from routine use of prescription drugs. Under the Prescription Drug User Fee Act (PDUFA), as revised in 2002, the FDA is supposed to make a decision on all new drug applications within 10 months of receiving a full application. Drugs that appear to represent a “therapeutic advance” or meet an unmet medical need may qualify for priority review, which reduces the FDA review goal to 6 months. The FDA meets its review goals over 90% of the time, and approves about 80% of the applications it receives. The remaining drugs qualifying for standard review are expected to have therapeutic qualities similar to those of already-marketed drugs, and to lack any sort of special innovative or clinical quality that would lead the FDA to agree to speed up the normal timeframe of its review.²

In 2006, economists proposed that it would be valuable for pharmaceutical manufacturers sponsoring these kind of run-of-the-mill drugs to be able to short-circuit FDA’s usual processes and have their non-innovative drugs reviewed faster, on a priority time frame.³ Getting earlier entry into the market would allow manufacturers to start earning revenues sooner on these drugs, some of which might bring in a billion dollars of revenue or more per year. These revenues would be earned due in large part to taxpayer spending through government insurance programs such as Medicare and Medicaid, which cover drug costs for over 100 million people in the US. It could also allow them to enjoy a longer period of market exclusivity before their patents would expire and give way to price-lowering generic competition.

Thus, a plan was put in place to address another drug development problem: lack of new drugs for neglected tropical diseases. Neglected tropical diseases are infectious diseases such as tuberculosis, dengue, leishmaniasis, and malaria that occur predominantly in resource-poor settings around the world. Since these diseases occur primarily in settings with underdeveloped health care systems that have limited ability to pay for drug treatments, the for-profit pharmaceutical industry has invested little in treatments for these conditions.⁴ Despite their global public health importance, neglected tropical diseases were estimated to account for less than

¹ Kesselheim AS and Avorn J. Pharmaceutical promotion to physicians and First Amendment rights. *New England Journal of Medicine* 2008;358:1727-1732.

² Darrow JJ, Avorn J, Kesselheim AS. New FDA breakthrough-drug category—implications for patients. *New England Journal of Medicine* 2014;370:1252-1258.

³ Ridley DB, Grabowski HG, Moe JL. Developing drugs for developing countries. *Health Affairs* 2006;25:313-324.

⁴ Trouiller P, Olliaro P, Torreele E, Orbinski J, Laing R, Ford N. Drug development for neglected diseases: a deficient market and a public-health policy failure. *Lancet* 2002;359: 2188-2194.

1% of pharmaceutical research and development expenditures.⁵ The plan was devised to grant new manufacturers of neglected tropical disease drugs priority review vouchers that they could use to accelerate the review of another, non-innovative standard-review drug, or sell to another manufacturer that had such a drug in its pipeline. The economists estimated that this earlier time to market could be worth up to \$325 million per drug for a lucrative product of the company that bought this queue-jumping priority review voucher from the innovator company that brought the neglected tropical disease drug to market. The hope was that winning and then re-selling these vouchers could create a powerful economic incentive to draw companies into research that would lead to treatments for neglected tropical diseases.

There were some important limitations to those economic calculations that caused the market value number to be excessively optimistic at the time of the original article, and certainly make it an overestimate now. For example, the \$325 million prediction only applied to the highest-grossing tenth of drugs; it is less likely that a non-innovative drug that does not offer a therapeutic advance would eventually go on to earn blockbuster sales. That is even more true in the current era, when about 60% of drugs already qualify for priority review; by contrast, in 2006, only 10 out of 22 approved drugs – less than half – qualified for priority review, so the pool of standard review drugs was larger.⁶ In addition, the economic estimate from the Duke economists was based on an assumption that the average FDA review time would be reduced by from 18.4 months for standard review drugs to 6.4 months for priority review drugs. But according to the FDA, the actual difference in median review times between standard and priority review drugs had fallen to only about 4 months in 2015.⁷ With a smaller difference in review times, the value of the voucher in the private market would be much less.

The original conception of the priority review voucher also did not take into account the fact that it was potentially dangerous, since too-speedy FDA review may lead to bad regulatory decision making. The priority review designation was meant to shorten the review time of products that were major advances in treatment or that treat conditions for which no adequate therapy exists, such as certain types of cancer and HIV infection.⁸ In such circumstances, accelerating the review process is reasonable, given the serious problems faced by patients. But the voucher program can allow drugs for which there is little or no clinical urgency to be subject to accelerated deadlines.⁹ That could increase the chances that products would be approved without giving FDA adequate time to evaluate them. A review published in the *New England Journal of Medicine* in 2008 found that drugs approved in the 2 months before their normal PDUFA deadlines were more likely to be withdrawn for safety reasons than drugs approved without such a looming deadline, or to have a major safety warning added to its labeling, and/or to have one or more dosage forms discontinued by the manufacturer.¹⁰ This study highlighted the risk of imposing arbitrarily short deadlines on FDA review times for drugs that did not deserve such acceleration. Since most clinically important drugs now already get priority review, the priority review voucher would most likely be sold to a company making a product with less clinical urgency, that offered only small if any clinical advantages, even though high prices can still make them very profitable in the US. Accelerating review of these products could also waste scarce FDA regulatory time and resources by pushing more critical drugs further back in the queue.

Outcomes of the Neglected Tropical Disease Priority Voucher

As I said, the developers of the priority review voucher concept proposed that the value generated by forcing the FDA to review non-innovative drugs faster could be used as an incentive to encourage manufacturers

⁵ World Health Organization. Neglected Tropical Diseases: Hidden Successes, Emerging Opportunities. 2006. Available from: http://apps.who.int/iris/bitstream/10665/69367/1/WHO_CDS_NTD_2006.2_eng.pdf.

⁶ Darrow JJ, Kesselheim AS. Drug development and FDA approval, 1938-2013. *New England Journal of Medicine* 2014;370(26):e39.

⁷ Jenkins JK. CDER drug review: 2016 update. December 14, 2016. Available from: <https://www.fda.gov/media/101930/download>.

⁸ Kesselheim AS. Encouraging drug development for neglected diseases — the trouble with FDA review vouchers. *New England Journal of Medicine* 2008;359:1981-1983.

⁹ Id.

¹⁰ Carpenter D, Zucker EJ, Avorn J. Drug-review deadlines and safety problems. *New England Journal of Medicine* 2008;358(13):1354-1361.

to invest in research and development for neglected tropical diseases. Congress was persuaded that a priority review voucher could address this gap between investment and disease burden and thus spur innovation for neglected tropical disease. It therefore legislatively created neglected tropical disease priority review vouchers in the FDA Amendments Act of 2007.¹¹ The original statute allowed the voucher to be transferred or sold once, required 365 days of notice to the FDA, and provided that the manufacturer had to pay FDA an additional user fee (currently about \$2 million) to account for the additional work that the FDA would have to do in accelerating review. But it could still be a boon for a company seeking to speed up review of an otherwise unremarkable but potentially lucrative product.

Almost immediately, important flaws started emerging. One was that the voucher could be applied to drugs that may have been new to the FDA, but had been long sold in other places around the world.¹² For example, the first voucher was awarded to Novartis for artemether/lumefantrine (Coartem),¹³ an antimalarial that had previously been approved years earlier in over eighty countries.¹⁴ Five years later, Knight Therapeutics received a voucher for the leishmaniasis drug miltefosine (Impavido),¹⁵ for which clinical trials had been conducted several years earlier by the World Health Organization.¹⁶ In fact, at the time of FDA approval, these two drugs were already widely available where these tropical diseases were common.¹⁷ Thus, when a voucher is awarded to a company based on a drug that has already been widely approved around the world, or one that was developed through publicly-funded research, the voucher clearly did not help stimulate research and development. Novartis used its voucher earned for the marketing of artemether/lumefantrine to buy accelerated FDA review of one of its own products, canakinumab (Ilaris). The company proposed it as a supplemental indication for gouty arthritis, although the FDA in the end did not approve the drug for this indication. Knight won its voucher for the approval of miltefosine, and reportedly sold it in 2014 for \$125 million to Gilead. That company then used to speed FDA review of its potentially lucrative HIV combination product emtricitabine/rilpivirine/tenofovir alafenamide (Odefsey).¹⁸

Despite these egregious misapplications of the priority review voucher, other examples suggested that the program may help manufacturers better engage investors in neglected tropical disease pharmaceutical development. For example, the CEO of the drugmaker Kineta reportedly stated, that the voucher “is critical in making the business case to our investors to advance this research.”¹⁹ To empirically test the question of whether increased early-stage neglected tropical disease product development was observed after the voucher program was created, my colleagues and I at Harvard conducted a system-wide review of clinical trials for voucher-eligible neglected tropical diseases.²⁰ We first identified products potentially eligible for a priority review voucher entering Phase 1 trials between 1 January 2000 and 31 December 2014 (7 years before and after the creation of the voucher).²¹ We focused on Phase 1 clinical testing as the first required stage of testing in humans: these initial

¹¹ FDA Amendments Act of 2007, § 1102 (codified at 21 U.S.C. § 524).

¹² Sinha MS, Jain N, Hwang T, Kesselheim AS. Expansion of the Priority Review Voucher program under the 21st Century Cures Act: implications for innovation and public health. *American Journal of Law and Medicine* 2018;44:329-341.

¹³ Kesselheim AS, Maggs L, Sarpatwari A. Experience with the Priority Review Voucher Program for Drug Development. *JAMA* 2015;16:1687-1689.

¹⁴ *Id.*

¹⁵ *Id.*

¹⁶ *Id.*

¹⁷ Sinha MS, Jain N, Hwang T, Kesselheim AS. Expansion of the Priority Review Voucher program under the 21st Century Cures Act: implications for innovation and public health. *American Journal of Law and Medicine* 2018;44:329-341.

¹⁸ Mezher M, Brennan Z, Gaffney A. Regulatory explainer: everything you need to know about FDA’s priority review vouchers. *Regulatory Focus*, 25 Feb 2020. Available from: <https://www.raps.org/regulatory-focus/news-articles/2017/12/regulatory-explainer-everything-you-need-to-know-about-fdas-priority-review-vouchers>.

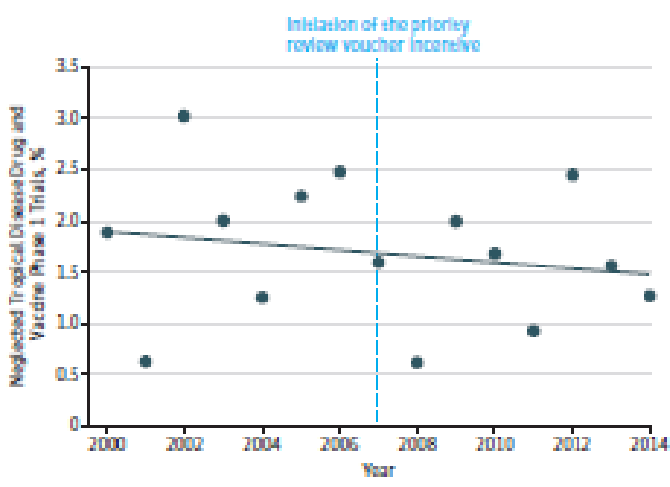
¹⁹ Ridley DB, Dent J, Egerton-Warburton C. Efficacy of the Priority Review Voucher Program. *JAMA* 2016;315:1659-1660.

²⁰ Jain N, Hwang TJ, Franklin JM, Kesselheim AS. Association of the priority review voucher with neglected tropical disease drug and vaccine development. *JAMA* 2017;318(4):388-389.

²¹ *Id.*

trials are an important signal of new pharmaceutical innovation.²² We found that the percentage of new Phase 1 trials for drugs with primary or secondary neglected tropical disease indications was 1.9% from 2000-2007, and 1.5% from 2008-2014. That is, we found no significant changes in the trend before or after the voucher program was created (see Figure). We concluded that the program did not increase the rate of companies starting clinical development of new neglected tropical disease drug products.²³

Figure. Neglected Tropical Disease Phase I Trial Initiation, 2000-2014



From Jain et al., *JAMA*, 2017

Rare Pediatric Disease Priority Voucher and Its Outcomes

Although there was no evidence at the time that the original priority review voucher was promoting research and development in neglected tropical diseases, Congress nonetheless extended the program in 2012 to allow priority review vouchers to be issued for rare pediatric diseases. This version of the voucher was based on the neglected tropical disease priority review voucher, although it could be sold multiple times and required only 90 days notice to the FDA before it could be used. (These differences were ultimately erased in 2014, when the multiple transfers and shorter notice provisions were extended to neglected tropical disease priority review vouchers as well.)

Certainly, children suffering from rare diseases need more attention to their conditions from medical researchers and the pharmaceutical industry. From 2012 to 2018, the FDA awarded 14 rare pediatric disease priority review vouchers.²⁴ Despite this seemingly large number of vouchers being awarded, the actual evidence collected indicates that the pediatric rare disease priority review voucher did not succeed any better in promoting research and development in this field. In a study we published in the health policy journal *Health Affairs* in 2019, we sought to measure the effect of these new vouchers by comparing how drugs treating rare pediatric diseases progressed through development before and after the voucher policy with how drugs treating rare adult diseases (which would not earn a voucher) progressed during the same time period.²⁵ We found no significant change in the rate at which drugs eligible for a pediatric priority review voucher were introduced into clinical testing, compared to the rate of drugs for rare diseases affecting adults.²⁶ We also found no significant differences in the rate at which

²² Id.
²³ Id.
²⁴ Hwang TJ, Bourgeois FT, Franklin JM, Kesselheim AS. Impact of the priority review voucher program on drug development for rare pediatric diseases. *Health Affairs* 2019;38(2):313-319.
²⁵ Id.
²⁶ Id.

such pediatric drugs progressed from Phase II to Phase II and from Phase III to approval, although we did find a statistically significant effect on the timing of drugs moving from Phase I to Phase II.²⁷ We concluded that since the program was not associated with a change in the number or rate of new drugs starting clinical testing, other policies may be needed to expand the pipeline of therapies for rare pediatric diseases.²⁸

The rare pediatric disease priority review voucher program turned out to have similar limitations as the neglected tropical disease priority review voucher. For example, many vouchers were awarded to drugs that were being developed anyway, and did not require the voucher as an incentive. The first voucher was issued in February 2014 to BioMarin after FDA approval of elosulfate alfa for the treatment of Morquio A syndrome, an inherited metabolic disease affecting approximately 800 children in the US.²⁹ The pivotal Phase III trial for the drug was launched in February 2011, 17 months prior to the initiation of the program.³⁰ Another voucher was awarded to United Therapeutics for approval for dinutuximab, a drug to be used in combination for pediatric patients with high-risk neuroblastoma.³¹ This drug was developed by the National Cancer Institute, which synthesized it, conducted its initial preclinical studies, and then manufactured it through the Biopharmaceutical Development Program to perform pivotal phase 3 testing between 2001 and 2009.³²

The rare pediatric disease voucher also revealed new flaws in the priority review voucher concept. It became clear that the value of the voucher is dependent on the number of vouchers available in the market. That is, because there are limited supplies of potentially blockbuster standard-review drugs to which the voucher could apply, if there are too many vouchers on the market, the amount a drugmaker would be willing to pay for them would be diminished. Indeed, United Therapeutic sold its voucher in 2015 for \$350 million to Abbvie, which used it to accelerate the approval of upadacitinib (Rinvoq), yet another treatment for adults with moderate to severe rheumatoid arthritis.³³ However, by 2019, after over a dozen such vouchers were now granted, vouchers were consistently being sold on the market for approximately \$80-110 million.³⁴

The rare pediatric disease voucher also made clear that there is nothing in the voucher program that requires sponsors to make voucher-eligible therapies affordable to patients. High prices charged for products developed under the priority review voucher program contribute to limited access by patients for these therapies. For instance, the manufacturer of elosulfase alfa priced its product at \$380,000 per year.³⁵ This issue has also come up for products granted neglected tropical disease priority review vouchers, some of which their manufacturers price at alarmingly high levels.³⁶

The rare pediatric disease priority review voucher also highlighted the strain that the voucher program puts on the FDA.³⁷ In a report filed by the U.S. Government Accountability Office, FDA officials raised concerns that the priority review program impaired the FDA's ability to define its public health priorities by hastening review of

²⁷ Id.

²⁸ Id.

²⁹ Kesselheim AS, Maggs L, Sarpatwari A. Experience with the Priority Review Voucher Program for Drug Development. *JAMA* 2015;16:1687-1689.

³⁰ Id.

³¹ Id.

³² Id.

³³ Mezher M, Brennan Z, Gaffney A. Regulatory explainer: everything you need to know about FDA's priority review vouchers. *Regulatory Focus*, 25 Feb 2020. Available from: <https://www.raps.org/regulatory-focus/news-articles/2017/12/regulatory-explainer-everything-you-need-to-know-about-fdas-priority-review-vouchers>.

³⁴ Id.

³⁵ Philippidis A. The High Cost of Rare Disease Drugs. *GEN* March 4, 2014. Available from: <https://www.genengnews.com/gen-exclusives/the-high-cost-of-rare-disease-drugs/77900055>.

³⁶ Delaunay S, et al. Letter from Medicins Sans Frontieres, Drugs for New Diseases Initiative and TB Alliance to Hon. Tom Harkin and Hon. Lamar Alexander. July 30 2014. (On file with author)

³⁷ Sinha MS, Jain N, Hwang T, Kesselheim AS. Expansion of the Priority Review Voucher program under the 21st Century Cures Act: implications for innovation and public health. *American Journal of Law and Medicine* 2018;44:329-341.

unremarkable products that would not otherwise merit an expedited timeline.³⁸ The agency also reported that, despite the additional user fee associated with utilizing a voucher, the program strained the agency’s resources since the FDA cannot quickly hire and train new staff with the necessary expertise.³⁹

Medical Countermeasures Priority Voucher

Despite the compounding problems of having priority review vouchers apply to both neglected tropical diseases and rare pediatric diseases, Congress expanded the priority review voucher program yet again in 2016 in the 21st Century Cures Act by making a new category eligible for priority review vouchers treatments for “medical countermeasures.” These are drugs that prevent or treat harm from a biological, chemical, radiological, or nuclear agent.⁴⁰

To assess the potential impact of the medical countermeasure voucher program, we extracted information on investigational therapies currently in clinical development for the treatment or prevention of these threats, and would be eligible for the voucher. In a 2018 study we published in the *American Journal of Law and Medicine*, we reported a total of 26 medical countermeasure products were identified undergoing clinical trials.⁴¹ As expected, virtually all (25, 96%) of these medical countermeasure products had already received direct or indirect public support. It is also likely that the US government would be a major buyer of many of these products.⁴² In such a market, the role of a priority review voucher is unclear. However, adding more priority vouchers to the market is likely to reduce the value of the incentive—and increase the strain on the FDA’s resources.

Policy Recommendations

The priority review voucher program was ill-conceived initially and in the 14 years since it was devised, there has been no systematic, rigorous evidence that it has proven useful in achieving its goals—stimulating the generation of new treatments for neglected tropical diseases, rare pediatric diseases, or medical countermeasures. Indeed, the studies cited in these comments demonstrate that it has had virtually no measurable impact on the emergence of new treatments, although the sale of such vouchers has been enormously lucrative to the companies that were awarded them. Moreover, as the voucher program has expanded over that time, it has paradoxically undermined its own goals, as one of the economists who devised the voucher recently recognized, when he and a colleague concluded that “Congress should be cautious about expanding the voucher program, because increasing the number of vouchers sharply decreases the expected price” of each voucher issued.⁴³ At the same time, the voucher program has been criticized by the FDA for disrupting its public health-based process for prioritizing which drugs should get faster regulatory review and for putting an unnecessary strain on the agency’s already-limited resources.

One way to try to address these issues would be to make necessary improvements to the voucher program. For example, the user fee associated with the voucher could be substantially increased, or the drugs qualifying for the voucher could be limited to new, first-in-class products or products meeting unmet medical needs. Manufacturers should also not be able to earn a priority review voucher immediately for drugs approved via the “accelerated approval” pathway, since accelerated approval drugs have not yet demonstrated meaningful patient benefits and require confirmatory post-approval testing. More importantly, rare pediatric disease manufacturers earning a voucher could be required to ensure that the product is sold to US patients at value-based prices, or at no

³⁸ Government Accountability office (GAO-16-319). Rare diseases: too early to gauge effectiveness of FDA’s pediatric voucher program. 2016.

³⁹ *Id.*

⁴⁰ USC § 360bbb-4a(a)(4)(A)(i)-(ii).

⁴¹ Sinha MS, Jain N, Hwang T, Kesselheim AS. Expansion of the Priority Review Voucher program under the 21st Century Cures Act: implications for innovation and public health. *American Journal of Law and Medicine* 2018;44:329-341.

⁴² Milne C et al. Landscape for Medical Countermeasure Development. *Nature Reviews Drug Discovery* 2017;16:448.

⁴³ Ridley DB and Regnier S. The commercial market for priority review vouchers. *Health Affairs* 2016;35(5):776-783.

higher than prices sold to rare pediatric disease patients in other high-income countries. At a minimum, companies should publicly report on the affordability and availability of drugs that receive such vouchers.⁴⁴

But these incremental improvements will not change the fundamental problems with the voucher, including the risk from unnecessarily accelerating FDA review of non-innovative drugs and the waste of resources from government-sponsored drug insurance programs. The program reflects a growing trend in health policy toward excessive reliance on financial incentives to achieve social goals.⁴⁵ It is problematic to rely on pharmaceutical manufacturers' profit motive as the main key to developing drugs for essential and under-recognized public health issues, such as infectious diseases in resource-poor settings or drugs for rare pediatric diseases.⁴⁶ Effectively conducting research into treatments for these conditions involves a more sustained commitment than can be achieved simply by rationalizing the revenue that arises from it.⁴⁷ In addition, if any changes in the drug-development marketplace, such as initiation of federal drug-reimbursement guidelines in the US, diminish the perceived value of these vouchers, then any research started by private entities solely in anticipation of voucher revenue will again cease, to the detriment of the very patients it was intended to help.⁴⁸

Therefore, a better pathway forward for Congress would be to consider more direct ways to encourage drug development for medical conditions for which current incentives have proven inadequate. For example, the US government supports investment in pharmaceutical innovation by investing substantial amounts of taxpayer dollars each year in basic and translational science that identifies potential new compounds and drug targets, and that determines whether products that change molecular pathways can lead to health benefits. In 2019, the NIH's budget was about \$39 billion, the largest investment by any government in scientific research in the world. One study found that all new drugs approved from 2010-2019 or their molecular targets could be linked back to government-funded research, mostly through the NIH.⁴⁹ We recently published in *BMJ* a review of drugs approved from 2008-2017, which found that 25% (62/248) were based on patents or other late-stage intellectual contributions from publicly-supported research institutions.⁵⁰ The US government also offers various tax concessions and refunds directed at research and development spending by private firms. Thus, greater up-front funding or tax credits could be offered for research into rare pediatric diseases. Achieving real progress could be less expensive than expected. In the case of neglected tropical diseases, the non-profit Drugs for Neglected Diseases initiative (DNDi) spearheaded the development of 6 treatments (and early-stage testing of 12 new chemical entities) for patients with malaria, trypanosomiasis, visceral leishmaniasis, and Chagas disease at a total cost of around \$250 million in just its first 10 years of existence.⁵¹

Another approach would be to provide greater support for late-stage development through public funding, either directly to non-profit organizations such as medical schools or organizations such as DNDi. This route could be operationalized through expanded public-private partnerships. Such partnerships have been used to encourage manufacturers to bring investigational drugs, such as antibiotics, into trials that pharmaceutical manufacturers may not have pursued on their own. Incentives for the manufacturers to become involved could take the form of

⁴⁴ Ridley DB. How to put an Ebola treatment on drugmakers' radar. *SF Chronicle*. Oct 12 2014. Available from: <https://www.sfgate.com/opinion/openforum/article/Congress-should-offer-vouchers-to-develop-ebola-5818174.php>.

⁴⁵ Kesselheim AS. Encouraging drug development for neglected diseases — the trouble with FDA review vouchers. *New England Journal of Medicine* 2008;359:1981-1983

⁴⁶ *Id.*

⁴⁷ *Id.*

⁴⁸ *Id.*

⁴⁹ Galinka Cleary E, et al. Characterizing the public sector contribution to drug discovery and development: the role of government as a first investor. Institute for New Economic Thinking. Available from: <https://www.ineteconomics.org/uploads/papers/Public-sector-contribution-to-drug-discovery-and-development.pdf>.

⁵⁰ Nayak RK, Avorn J, Kesselheim AS. Public sector financial support for late stage discovery of new drugs in the United States: cohort study. *BMJ* 2019;367:15766.

⁵¹ Drugs for Neglected Diseases Initiative. Research and development for diseases of the poor: a 10-year analysis of impact of the DNDi model. http://www.dndi.org/images/stories/pdf_aboutDNDi/DNDiModel/DNDi_CostOfDev_FactsFigures.

advance-purchasing promises. Recent funding through the U.S. Department of Health and Human Services' Biomedical Advanced Research and Development Authority (BARDA) to support vaccines for COVID-19 is an example of this model. Naturally, such partnerships should include guarantees about affordable access to the rare pediatric disease drugs that emerge because of the public's involvement in reducing the risks and costs of research and development.

Conclusion

Children with rare diseases need more investment in scientific discovery and clinical trials to help get them the treatments they deserve. It is encouraging to see Congress take special interest in this patient population. However, the evidence is clear that enacting the pediatric rare disease priority review voucher program in 2012 has led to little change in innovation and drug development outcomes. Providing costly economic incentives to drugmakers has not proven to be a useful or cost-effective means of achieving such goals. It is time to move past that mistake and let it sunset, and instead direct efforts towards better solutions with a known track record in leading to transformative drugs, including direct public investment in research and development.