PORTAL
Program On Regulation, Therapeutics, And Law

Division of Pharmacoepidemiology and Pharmacoeconomics
Harvard Medical School | Brigham & Women's Hospital

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

July 9, 2023

To: Senate HELP Committee
From: Aaron S. Kesselheim, M.D., J.D., M.P.H.; Matthew J. Martin, M.A.; Ameet Sarpatwari, J.D., Ph.D.

From the Program On Regulation, Therapeutics, And Law (PORTAL), Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts

We are responding to a request for comments on the discussion draft to reauthorize the Pandemic and All-Hazards Preparedness Act (PAHPA). The Committee sought feedback on two staff proposals in particular: (a) policy to require that all BARDA and CDC-supported products be sold to the Federal Government or in the US commercial market at the lowest price among G7 countries (Canada, France, Germany, Italy, Japan, and the United Kingdom) and at a reasonable price, and (b) policy to incentivize the development of more medical countermeasures (MCMs) by extending the Priority Review Voucher (PRV) program through the duration of PAHPA and providing a new, non-transferrable priority review voucher to companies that develop new military or material threat MCMs in addition to the transferrable voucher they currently receive. We will review these two proposals in turn.

I. Requiring all BARDA- and CDC-supported products be sold at the lowest price among G7 countries and at a reasonable price.

We agree with the proposal that all BARDA- and CDC-supported products be sold at a reasonable price, and no higher than that charged to other G7 countries. As one of us (ASK) explained in previous Congressional testimony,[1] the US government is the greatest source of pharmaceutical innovation in the world. According to one review, every single drug approved by the FDA from 2010 to 2016 could be traced back to federal funding in some way.[2] In a more recent review of 356 drugs FDA-approved from 2010 to 2019, investigators linked federal funding to 354 (99.4%), calculating that, on average, public funding of basic or applied research contributed about $1.44 billion per approval.[3]

Perhaps the most highly visible example of publicly-funded drug development occurred with the development of the transformative mRNA COVID-19 vaccines. The US government invested at least $31.9 *billion* to develop, produce, and purchase these vaccines, including sizeable investments in the three decades before the pandemic relating to development of lipid nanoparticles as a drug delivery system, synthesis and modification of mRNA and small interfering ribonucleic nucleic acid, definition of the

[1] These comments draw from prior testimony, which can be found in its entirety here: Kesselheim AS. How the government supports meaningful drug and device innovation: funding development of transformative therapies and avoiding excessive prices for new products with limited benefits. Hearing before the House Subcommittee on Health of the Committee on Ways and Means (Rep. Buchanan, Chairman). 11 May 2023. United States Congressional Record. Available on-line at: http://waysandmeans.house.gov/wp-content/uploads/2023/05/Kesselheim-Testimony.pdf

[2] Galkina Cleary E, Beierlein JM, Khanuja NS, McNamee LM, Ledley FD. Contribution of NIH funding to new drug approvals 2010-2016. Proceedings of the National Academy of Sciences of the USA 2018;115(10):2329-2334

[3] Galkina Cleary E, Jackson MJ, Zhou EW, Ledley FD. Comparison of Research Spending on New Drug Approvals by the National Institutes of Health vs the Pharmaceutical Industry, 2010-2019. JAMA Health Forum 2023;4(4):e230511.

prefusion "spike" protein structure of SARS-CoV-2, and development of RNA vaccine biotechnology for use in humans.[4] In this case, not only did the NIH and US government substantially support the key discoveries and development of the mRNA vaccine technology, but they also provided a guaranteed market for the final stages of development. These highly effective vaccines have helped protect millions of people from the complications of COVID-19, and they would not have been discovered or disseminated as quickly in the first years of the pandemic without government participation.

As we have previously pointed out, "public research grants, including NIH, BARDA, and DoD, traditionally do not include provisions to safeguard public access or affordability of future inventions. They also do not typically include provisions for equitable global access for inventions of public health significance. Instead, US technology transfer policy has allowed recipients of public funding, such as academic research centers, to manage any intellectual property and licensing arrangements directly with commercial partners. As a result, products developed with public funding are often sold at high prices both in the US and around the world. For example, the antiretroviral combination of emtricitabine/tenofovir (Truvada) was shown to be effective in preventing HIV using $50 million in federal grants, and yet was priced at $2,100 per month by its manufacturer, sparking a 2019 Congressional oversight investigation."[5]

Despite the significant US public funding and advanced market commitment, the US paid Pfizer-BioNTech $19.50 per dose in 2020, $24.00 in 2021, and $30.48 in 2022 for the bivalent booster;[6] and Moderna $15.25 per dose (monovalent) for the first order and $26.36 per dose (bivalent) in 2022. At these prices, both companies reaped unprecedented revenue and profit. However, they failed to adequately supply low-income countries, resulting in gross global inequities in access through the first two years of the pandemic.[7]

We, therefore, support the idea that CDC- or BARDA-supported products should be available at a reasonable price to ensure fair access. We think that the draft bill describes appropriate factors that might go into determining whether a price is reasonable. It is clear from the bill that the goal is not to make products available for free but to ensure that the price is set according to the product's development costs and public value. We believe that using prices in the G7 countries as a proxy for this measure is also a reasonable approach, since the health systems in those countries are designed to ensure that drugs are reimbursed in line with the level of clinical benefit they provide while maintaining adequate patient access to essential products.

We also recommend the Committee consider the following elements that would strengthen the reasonable pricing provisions. First, in discussing the countermeasure, covered product, or technology to which the reasonable pricing requirements are applicable, the Committee could consider expanding the definition of said products to include derivatives (e.g., reformulations, changes in delivery mechanism, etc.) that may not have directly been developed in collaboration with BARDA or CDC, but for which the originator product relied heavily on federal funding. In addition, the Committee could consider clarifying the definition of an eligible product's "value" to include the price's impact on access as well as its impact on federal health care spending. Third, the Committee could consider clarifying whether the government's research and development costs associated with an eligible product are limited to costs to the specific agency (i.e., CDC or BARDA), or are intended to encompass costs to *all* federal contributions. This is important as some technologies may receive financial support from other taxpayer-supported research agencies (NIH, DoD,

[4] Lalani HS, Nagar S, Sarpatwari A, Barenie RE, Avorn J, Rome BN, Kesselheim AS. US Public investment in the development of mRNA COVID-19 vaccines: retrospective cohort study. BMJ 2023;380:e073747.
[5] Id.
[6] Id.
[7] Sarpatwari A, Pandya A, Hyle EP, Persad G. COVID-19 Vaccine boosters for all adults: an optimal U.S. approach? Annals of Internal Medicine. 2021.

NSF, ARPA-H). Research and development spending should also be presented relative to the sponsoring agency's federal budget.

Beyond BARDA and CDC, the Committee may also consider expanding reasonable pricing requirements to products developed in collaboration with other federal entities involved in public health and pandemic preparedness. In particular, the network of laboratories affiliated with the Department of Defense may advance novel technologies that have initial military applications yet could have broad commercial applicability in public health emergencies. ARPA-H may be another entity to which these provisions could apply to maximize their system-wide impacts.

We also feel it is critical to address a widespread, misguided understanding of a prior effort to introduce a reasonable pricing clause. As we have previously noted, "In 1989, the US Public Health Service—the parent organization of the NIH—incorporated a fair pricing condition into its model cooperative research and development agreement (CRADA), which allows private institutions to work with government agencies and negotiate exclusive licenses for inventions stemming from such work."[8] The NIH removed this condition 5 years later, with critics citing an uptick in CRADAs upon the condition's removal as evidence that it chilled innovation,[9] but this is an erroneous view. Our investigation of the history of the NIH's fair pricing condition revealed two important points of context that contradict this framing of the circumstances surrounding the removal of the reasonable pricing clause policy. First, around the same time the policy was revoked, the NIH created a materials CRADA (mCRADA) pathway, "fashioned to accelerate negotiations about NIH's receipt of propriety research materials . . . . Although some pre-1996 CRADAs may have qualified for the mCRADA pathway, it clearly spurred agreements that otherwise would not have been executed, accounting for the dramatic rise in total CRADAs."[10] Second, the reasonable pricing condition was frequently not included in the CRADAs executed between the NIH and its commercial partners.[11] Thus, past NIH experience should not deter efforts to move forward with a fair reasonable pricing clause policy.

II. Extending the PRV program for MCMs and adding a new non-transferable voucher.

We disagree with the proposal to extend the priority review voucher (PRV) program for MCMs because there is no evidence that the PRV for MCMs—or any PRV program—incentivizes innovation in drug development. Rather, there is evidence that PRVs complicate the FDA regulatory approval process to the detriment of public health.

As one of us (ASK) explained in previous Congressional testimony,[12] PRVs were devised in 2007 as a way to incentivize private investment in neglected tropical disease research and development. 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 to be reviewed by the FDA on the 6-month 'priority review' timeline instead of the standard 10-month process. This faster-to-market potential was estimated to be worth over $300 million to drugmakers.[13] The voucher program was extended to include drugs treating rare pediatric diseases in 2012 and medical countermeasures in 2016.

---

[8] Sarpatwari A, LaPidus AK, Kesselheim AS. Revisiting the National Institutes of Health fair pricing condition: promoting the affordability of drugs Ddveloped with government support. Annals of Internal Medicine. 2020;172(5):348-350.
[9] Id.
[10] Id.
[11] Id.
[12] Much of these comments draw from that prior testimony, which can be found in its entirety here: Kesselheim AS. Congress Should Support Development of New Treatments for Pediatric Rare Diseases, But Not with Priority Review Vouchers. Hearing before the House Committee on Energy and Commerce Subcommittee on Health (Rep. Eshoo, Chairwoman). July 29, 2020. https://docs.house.gov/meetings/IF/IF14/20200729/110949/HMTG-116-IF14-Wstate-KesselheimA-20200729.pdf
[13] Ridley DB, Grabowski HG, Moe JL. Developing Drugs For Developing Countries. Health Affairs. 2006;25(2):313-324.

There were 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.[14] 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.[15] 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 consider the fact that it was potentially dangerous, since too-speedy FDA review may lead to poor regulatory decision making. The priority review designation was meant to shorten the review time of products that were major treatment advances or that treat conditions for which no adequate therapy exists, such as certain types of cancer and HIV infection.[16] 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.[17] 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; have a major safety warning added to its labeling; and/or have one or more dosage forms discontinued by the manufacturer.[18] 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 clinical advantages (if any), even though high prices can still make them very profitable in the US.

Almost immediately after the original PRV was approved, 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 abroad.[19] Experience with the PRV since then has shown that there is no evidence that the neglected tropical disease PRV—or *any* PRV—actually works to improve innovation. For example, to empirically test the question of whether increased early-stage neglected tropical disease product development was observed after the voucher program was created, our colleagues conducted a system-wide review of clinical trials for voucher-eligible neglected tropical diseases.[20] We first identified products potentially eligible for a priority

---

[14] Darrow JJ, Kesselheim AS. Drug development and FDA approval, 1938-2013. New England Journal of Medicine 2014;370(26):e39.
[15] Jenkins JK. CDER drug review: 2016 update. December 14, 2016. Available from: https://www.fda.gov/media/101930/download.
[16] Kesselheim AS. Encouraging drug development for neglected diseases — the trouble with FDA review vouchers. New England Journal of Medicine 2008;359:1981-1983.
[17] Id.
[18] Carpenter D, Zucker EJ, Avorn J. Drug-review deadlines and safety problems. New England Journal of Medicine 2008:358(13):1354-1361.
[19] 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.
[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.

review voucher entering Phase 1 trials between January 2000 and 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, as these initial 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. We concluded that the program did not increase the rate of companies starting clinical development of new neglected tropical disease drug products.[23]

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 such vouchers for rare pediatric diseases. In a study we published 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.[24] As with the neglected tropical disease PRV example, 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.[25]

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 too many vouchers are on the market, the amount a drugmaker would be willing to pay for them diminishes. By 2019, after over a dozen such vouchers had been granted, vouchers were consistently being sold on the market for approximately $80-110 million.[26] The most recent PRV sale occurred on July 5, 2023, in which a rare pediatric disease PRV was sold for just $102 million.

The rare pediatric disease PRV also highlighted the strain that the voucher program puts on the FDA.[27] 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 unremarkable products that would not otherwise merit an expedited timeline.[28] 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.[29]

Despite no good evidence that PRVs work, and credible concerns from the FDA that they were actually problematic, 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 MCMs.[30] To assess the potential impact of the MCM 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

---

[21] Id.
[22] Id.
[23] Id.
[24] Id.
[25] Id.
[26] Id.
[27] 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.
[28] Government Accountability Office (GAO-16-319). Rare diseases: too early to gauge effectiveness of FDA's pediatric voucher program. 2016. Available from: https://www.gao.gov/products/gao-16-319.
[29] Id.
[30] USC § 360bbb-4a(a)(4)(A)(i)-(ii).

the voucher. In a 2018 study, we reported a total of 26 MCM products undergoing clinical trials.[31] As expected, virtually all (25, 96%) of these medical countermeasure products had already received direct or indirect public funding. It is also likely that the US government would be a major buyer of many of these products.[32] In such a market, the importance of a PRV in providing incentive is unclear. However, adding more priority vouchers to the market increases the strain on the FDA's resources.

Given this background, **we recommend the MCM PRV *not* be reauthorized for the duration of PAHPA**. The risks such vouchers pose to the robustness of FDA review by expediting review timelines for non-innovative drugs and wasting federal resources outweigh any hypothesized innovation benefits. As such, these PRV programs, including that for MCMs, should be allowed to sunset. Instead, PAHPA should be revised to offer greater up-front funding or tax credits for MCM development, or to provide greater public funding for late-stage development led by non-profit organizations working in this area. Incentives for private manufacturers to become involved could take the form of advance-purchasing promises for truly effective and important new products. 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 a successful example of this model.[33]

We also recommend a new, non-transferable voucher for military or material threat MCMs ***not* be created.** In making this recommendation, we considered certain guardrails that could perhaps make a new voucher more acceptable. For example, prior to the consideration of this second PRV, both the MCM sponsor and the relevant federal entity (likely DoD) could be required to submit a determination that all other public-private mechanisms to stimulate MCM development (i.e., contracts, grants, other transactions) have been exhausted or are otherwise inapplicable. Congress could also require that sponsors of material threat/military MCM applications submit alongside any request for a PRV a plan to ensure adequate access to the MCM. Such filings could also require disclosure of any additional federal investments or collaborations that supported the development of the MCM. Alternatively, Congress could limit awarding of secondary PRVs to MCMs that are truly novel (i.e., not already licensed/in use outside the U.S.) and have demonstrated efficacy in clinical trials or well-designed animal studies (for circumstances in which an RCT may be unethical). Finally, Congress could require that the Secretary of Defense maintain a limited list of "material threats" most in need of innovation that would earn a PRV and for a product to qualify, the sponsor would have to initiate relevant pre-clinical development of the MCM within two years of the announcement of a material threat being added to the designated list.

However, we do not think that any of these incremental improvements are ideal. Rather, the best solution would be to finally admit that the PRV was a failed policy and, as described before, provide direct logistical and financial support for the development of MCMs that effectively protect U.S. national security and public health.

[31] 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.
[32] Milne C et al. Landscape for Medical Countermeasure Development. Nature Reviews Drug Discovery 2017;16:448.
[33] Lalani HS, Nagar S, Sarpatwari A, Barenie RE, Avorn J, Rome BN, Kesselheim AS. US Public investment in the development of mRNA COVID-19 vaccines: retrospective cohort study. BMJ 2023;380:e073747.