July 10, 2023

The Honorable Bernard Sanders
Chair, Senate Health, Education, Labor, and Pensions Committee

The Honorable Bill Cassidy, MD
Ranking Member, Senate Health, Education, Labor, and Pensions Committee

Chairman Sanders and Ranking Member Cassidy,

Thank you for the opportunity to comment on the discussion draft for reauthorization of the Pandemic and All-Hazards Preparedness Act (PAHPA).

We write on the behalf of the Yale Collaboration of Regulatory Rigor, Integrity, and Transparency (CRRIT), an interdisciplinary initiative at Yale University where faculty and trainees study medical product regulation, approval, and coverage toward advancing policies that improve patient outcomes and enable access to truly safe and effective therapies.

In our comments, we focused on the two draft proposals and recommend the following:

1. The committee should adopt Senator Sanders' proposal that would include reasonable pricing clauses within licensing agreements and other transactions for products developed by BARDA and CDC such that their prices are as low or lower than that of other G7 countries.

2. The committee should oppose Senator Cassidy's proposal to authorize and expand the medical countermeasure priority review voucher as it is an unnecessary incentive and could lead to patient harm.

Below, we have elaborated further on these recommendations. We welcome the opportunity to meet with you to further discuss these recommendations and the PAHPA Discussion Draft.

All the best,
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Regarding "Section 601. BARDA Reasonable Pricing Requirements" and "Section 602. CDC Reasonable Pricing Requirements"

COVID-19 has highlighted the importance of ensuring affordability of federally funded products.

The federal government's experience during COVID-19 highlights the critical need for reasonable pricing clauses as a mechanism for ensuring affordability of publicly funded vaccines and drugs. Despite having played an outsized role in the discovery, development, manufacturing, and procurement of COVID-19 vaccines, therapeutics, and diagnostics, the federal government has generally not exercised any leverage in ensuring fair pricing and affordable access of these transformational medical products.[1,23] During the pandemic, COVID-19 vaccine and drug manufacturers successfully negotiated prices with the federal government well above the cost of production,[4,5] allow the companies to garner multiple billions in profit. Now, following the end of the public health emergency period for COVID-19 and in anticipation of an upcoming vaccination campaign for prevention of COVID-19 as well as the likelihood of resurgence of COVID-19 infections later this year necessitating the use of antiviral treatments for particular patient populations, manufacturers have announced significant price increases for their products that without intervention, will create significant access barriers for patients, especially for those who are uninsured.[678] Thus, the proposal to include reasonable pricing clauses for medical products developed by the Biomedical Advanced Research and Development Authority (BARDA) and the Centers for Disease Control and Prevention (CDC) is a critical step towards implementing lessons learned from COVID-19 and requiring that manufacturers of such products ensure the federal government and the American public a fair return on their investment.

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[1] Taxpayers Paid Billions For It: So Why Would Moderna Consider Quadrupling the Price of the COVID Vaccine? | The U.S. Senate Committee on Health, Education, Labor & Pensions," March 22, 2023, https://www.help.senate.gov/hearings/taxpayers-paid-billions-for-it-so-why-would-moderna-consider-quadrupling-the-price-of-the-covid-vaccine.

[2] ChangWon C. Lee et al., "Origins and Ownership of Remdesivir: Implications for Pricing," *The Journal of Law, Medicine & Ethics* 48, no. 3 (September 1, 2020): 613–18, https://doi.org/10.1177/1073110520958890.

[3] Lalani HS, Nagar S, Sarpatwari A, et al. US public investment in development of mRNA covid-19 vaccines: retrospective cohort study. *BMJ*. 2023;380:e073747. doi:10.1136/bmj-2022-073747

[4] Zoltán Kis and Zain Rizvi, "How to Make Enough Vaccine for the World in One Year" (Washington, D.C.: Public Citizen, May 26, 2021), https://www.citizen.org/article/how-to-make-enough-vaccine-for-the-world-in-one-year/.

[5] Melissa J Barber and Dzintars Gotham, "Estimated cost-based generic prices for investigational COVID-19 antivirals," *Working Paper*, April 12, 2023. https://scholar.harvard.edu/sites/scholar.harvard.edu/files/melissabarber/files/estimated_cost-based_generic_prices_for_investigational_covid-19_antivirals_12_april_2023.pdf

[6] Pfizer, "Pfizer Reports Second-Quarter 2021 Results," July 28, 2021, https://investors.pfizer.com/investor-news/press-release-details/2021/PFIZER-REPORTS-SECOND-QUARTER-2021-RESULTS/default.aspx.

[7] Wingrove P. Moderna expects to price its COVID vaccine at about $130 in the US. *Reuters*. https://www.reuters.com/business/healthcare-pharmaceuticals/moderna-expects-price-its-covid-vaccine-about-130-us-2023-03-20/. Published March 21, 2023. Accessed July 9, 2023.

[8] Hannah Recht, "COVID-19 Treatment Paxlovid Has Been Free so Far. Next Year, Sticker Shock Awaits," *PBS NewsHour*, December 18, 2022, https://www.pbs.org/newshour/health/covid-19-treatment-paxlovid-has-been-free-so-far-next-year-sticker-shock-awaits.

Little evidence has been found that reasonable pricing clauses chill innovation.

In 1989, the U.S. Public Health Service and the National Institutes of Health (NIH) incorporated a fair pricing condition as part of cooperative research and development agreements (CRADAs) that established partnerships between the NIH and pharmaceutical manufacturers. This clause was rescinded in 1995 by NIH Director Dr. Harold Varmus citing lack of benefit and a "chilling-effect" on innovation.[9] However, no compelling evidence has been found to suggest that the reasonable pricing clauses do, in fact, have such an undue impact on federal government collaboration with the pharmaceutical industry.

NIH convened CRADA forums in 1994, which also included industry participants to discuss several issues related to the impact of fair pricing conditions on CRADAs.[10] These forums found that since 1990, there had not been a decline in the number of CRADAs.[11] There was simply a concern that such a condition would be *perceived* by industry to be a barrier.[12] Although NIH leadership had then asserted that there was a rebound increase in the number of CRADAs after the fair pricing condition was rescinded, this effect was likely due to other confounding factors. For instance, private and public investment in pharmaceutical innovation increased dramatically following the removal of the fair pricing condition. Between 1995 and 200, the NASDAQ Biotechnology Index increased by 37% and the average NIH budget was $55 billion higher between 1996 and 2000 compared to between 1990 and 1994. This increase in investment likely had a more significant impact than removal of fair pricing conditions.

The other likely explanation for the "rebound effect" of CRADAs was that after NIH rescinded the fair pricing clause in 1995, the NIH added a new category of CRADA known as materials CRADA (mCRADA). The number of standard CRADAs remained roughly consistent, indicating that this rebound effect was due to a change of categorization rather than a substantiated effect on innovation.[13] Instead, the criticism of the original fair pricing condition should be directed to vague and ambiguous language, as well as the lack of any enforcement mechanism.[14] The ambiguity of the original condition of establishing a "reasonable relationship" between price and public investment, may have been a dissuading factor for the pharmaceutical industry than a clear "Most Favored Nation" price as outlined in the proposed reasonable pricing clauses for BARDA and CDC medical products within the PAHPA Discussion Draft. In fact, during the CRADA forum panels in 1994, there was no suggestion that the reasonable pricing

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[9] Wolitz RE. The Pay-Twice Critique, Government Funding, and Reasonable Pricing Clauses. *Journal of Legal Medicine*. 2019;39(2):177-211. doi:10.1080/01947648.2019.1648942

[10] *Reports of the NIH Panels on Cooperative Research and Development Agreements: Perspectives, Outlook, and Policy Development*. National Institutes of Health; 1994. Accessed July 10, 2023. https://www.techtransfer.nih.gov/sites/default/files/documents/pdfs/NIH_%20CRADA_Report_on_Reasonable-Pricing_Clause_1994.pdf

[11] id at 8

[12] id at 8,9

[13] Sarpatwari A, LaPidus AK, Kesselheim AS. Revisiting the National Institutes of Health Fair Pricing Condition: Promoting the Affordability of Drugs Developed With Government Support. *Ann Intern Med*. 2020;172(5):348-350. doi:10.7326/M19-2576

[14] id at 8, 9

clauses should be rescinded, but rather revisions of the clause were necessary.[15] Having a clearer reasonable pricing clause would send a stronger signal of certainty to manufacturers.

During COVID-19, the federal government had implemented reasonable pricing clauses and with this language, were still able to successfully negotiate contracts with manufacturers.

Several examples where reasonable pricing conditions were implemented and had no chilling effect on innovation exist, particularly during the COVID-19 pandemic. The federal government had secured several bulk purchasing agreements with COVID-19 drug and vaccine manufacturers, even ahead of market authorization by the FDA and have included provisions requiring that the federal government receive the lowest price from the manufacturer in comparison to procurement prices paid by other countries. A collaboration between the U.S. Department of Defense and Novavax held that the manufacturer would provide the lowest, best price for a period of five years in the U.S.[16] In their contract for Paxlovid, the federal government negotiated a "most-favored nation" pricing clause with Pfizer that allowed them to receive a lower price if one of six other high-income countries negotiated a better deal.[17] Neither instance resulted in innovation failures or delays.

For medical products developed by BARDA and the CDC, significant federal investment has effectively removed the risk of development, thus incentivizing manufacturers to enter into agreements with the federal government and complete development of these products, carrying them through market authorization and commercialization. As the COVID-19 pandemic demonstrated, manufacturers are willing to accept contractual terms around reasonable pricing when coupled with other financial incentives including direct or indirect public investment as well as advance purchasing agreements guaranteeing them revenues following market authorization. Similarly, as the federal government will be the primary purchaser for products developed by BARDA and the CDC and will continue to provide significant support for the development of countermeasures and pandemic or epidemic products, manufacturers would likely not be dissuaded from entering into agreements with the federal government that include such reasonable pricing provisions.

Additional considerations for reasonable pricing clauses

- The proposal states that reasonable pricing clauses would be included into licenses or other transactions for products that are either a "qualified countermeasure, qualified pandemic or epidemic product, security countermeasure, or related technology" developed by BARDA or "covered product" developed by CDC. This should be broadened further to encompass all medical countermeasures addressing material and military threats developed by the agencies. As we discuss further in the next section, medical countermeasures receive significant federal support for their discovery,

[15] id at 8
[16] Kathryn Ardizzone, "Novavax and Inovio COVID-19 Vaccine Contracts Limit Prices Companies Can Charge for Their Products," *Knowledge Ecology International* (blog), January 28, 2021, https://www.keionline.org/35185.
[17] Sydney Lupkin, "Feds' Contract with Pfizer for Paxlovid Has Some Surprises," *NPR*, February 1, 2022, sec. Treatments, https://www.npr.org/sections/health-shots/2022/02/01/1075876794/feds-contract-with-pfizer-for-paxlovid-has-some-surprises.

development, and production as well as guaranteed revenue through federal procurement contracts. Thus, to ensure that the American public receives a fair return on all investment of these products, the definition of applicable products for which reasonable pricing clauses would be included within their contracts should be broadened.

- The proposal within the discussion draft outlines several factors to be taken into account when considering whether the price of a BARDA or CDC applicable medical product is fair and reasonable. These factors as well as the agency's rationale for determining whether a price is fair and reasonable should be made publicly available to allow for independent experts to also review these factors.
    - Another factor should also be taken into consideration is the non-monetary support provided by the federal government such as technical assistance from agency experts at the U.S. Food and Drug Administration, NIH, BARDA, CDC, and others and clinical trial networks. Such factors also offset development and manufacturing costs for manufacturers and should be weighed in assessing whether a price is fair and reasonable.

Regarding Section 611. Priority Review to Encourage Treatments for Agents that Present National Security Threats

The medical countermeasure priority review voucher, especially in its expanded form under the new proposal is an unnecessary incentive.

Introduced in 2016 under the 21st Century Cures Act, the medical countermeasure priority review voucher (MCM PRV) is an additional incentive awarded to sponsors to encourage the development of new drug and biological MCMs.[18] Awarded at the time of FDA approval, manufacturers can redeem a PRV for another product in their portfolio or transfer the PRV to another manufacturer for a price. The newly introduced proposal within the PAHPA Discussion Draft not only reauthorizes the MCM PRV program, but also expands the scope of the vouchers.

First, the new proposal expands the scope of MCM products that would be eligible to receive a PRV to also include drugs and biologics that could address material threats "against the Armed Forces sufficient to affect national security" in addition to those material threats that pose a risk to the United States population. Second, under the new proposal, FDA would grant manufacturers of eligible medical products not just one, but two vouchers – one of which could not be sold to another manufacturer. Unfortunately, the continuation and expansion of the MCM PRV program is misguided as there is little evidence that such a voucher is effective or necessary for its intended goal of stimulating innovation of such drugs and biologics.

In 2020, the Government Accountability Office published an analysis of the three existing priority review voucher programs including for medical countermeasures. For this analysis, they reviewed the existing (albeit limited) literature examining PRV programs, finding that these studies all came to the same conclusion: these federally awarded vouchers had little or

[18] *Material Threat Medical Countermeasure Priority Review Vouchers (Draft Guidance)*. Food and Drug Administration; 2018. https://www.fda.gov/media/110193/download

no effect in stimulating development of the medical products they were intended for.[19] One study specifically on MCMs found that 25 of the 26 such products in clinical trials had received either direct or indirect public funding support, raising questions on the necessity of such vouchers to incentivize innovation. While industry sponsors unsurprisingly said that PRVs were a factor in drug development, most said it was one of many factors; other factors for drug development were whether the drug or biologic candidate had received direct public financing for development and whether the company already had a production the pipeline that could qualify for and benefit from a PRV.

In 2021, we published a study on the MCM PRV in the *American Journal of Public Health* examining the drugs and biologics that had been awarded a voucher by the FDA as of June 2021. [20,21] We found that all five medical countermeasures awarded a priority review voucher were initially developed through public funding; the discovery of four of the five products was underwritten by the federal government and the remaining one by the German government (Table 1[22]).The U.S. government also sponsored late-stage clinical trials supporting FDA approval of all five products; for three, federal agencies designed and conducted these trials. FDA also granted all five medical countermeasures additional regulatory incentives including designations allowing these drugs and vaccines to receive expedited review of their products allowing for earlier market entry of their products. Additionally, FDA awarded further intellectual property protections in the form of exclusivity periods, barring generic entry for variable periods of time, ranging from five to 12 years. Finally, the federal government also guaranteed revenues for these products through bulk advance purchase agreements, often secured before regulatory approval. As the federal government has granted several financial, regulatory, and intellectual property incentives along the medical countermeasure development pipeline, issuance of an additional incentive in the form of an MCM PRV is unnecessary.

[19] Government Accountability Office, "DRUG DEVELOPMENT: FDA's Priority Review Voucher Programs," January 2020, https://www.gao.gov/assets/710/704207.pdf.
[20] Reshma Ramachandran, Ravi Gupta, and Jing Luo, "An Unnecessary Gift for COVID-19 Vaccines and Therapeutics: The Medical Countermeasure Priority Review Voucher," *American Journal of Public Health*, October 14, 2021, e1–4, https://doi.org/10.2105/AJPH.2021.306495.
[21] When the Ramachandran et al study on MCM PRVs was conducted, Ebanga indicated for Ebola was not posted on the FDA.gov website despite it having been approved by the FDA in late December 2020. The FDA website lists all MCM PRVs to date.
[22] id 19

TABLE 1— Research and Development and Procurement Support for FDA-Approved Medical Countermeasures Having Received Priority Review Vouchers

Product and Commercial Sponsor	Material Threat	Discovery of Product (Sponsor)	Conducted Pivotal Trial (Sponsor)	Expedited Review Pathway	Exclusivity Granted (Years)	Public Procurement	Date MCM Priority Review Voucher Issued
TPOXX (tecovirimat)—SIGA Technologies, Inc.	Smallpox	NIAID (NIH)[6]	SIGA (NIH and BARDA)[7]	Fast-track, priority review	Orphan (7)	BARDA: Sep 2018: $629.0 million[8]	Jul 13, 2018
Jynneos (smallpox and monkeypox vaccine)—Bavarian Nordic A/S	Smallpox, monkeypox	Bavarian State Vaccination Institute (German Government)[9]	USAMRIID (BARDA)[10]	Priority review	Biologic (12)	BARDA: Sep 2017: $299 for 13.0 million doses[11]; Apr 2020: $202 million for 1.4 million doses	Sep 24, 2019
INMAZEB (atoltivimab, maftivimab, odesivimab-ebgn)—Regeneron Pharmaceuticals	Ebola	Regeneron (BARDA)[12]	NIAID, WHO, and INRB in DRC, and African Coalition for Epidemic Research, Response, and Training (NIH)[13]	Breakthrough therapy, priority review	Orphan (7); Biologic (12)	BARDA: Jul 2019: $345 million for 6-y contract[14]	Oct 14, 2020
VEKLURY (remdesivir)—Gilead Sciences, Inc.	COVID-19	NIAID (NIH)[15]	NIAID (NIH)[16]	Fast-track, priority review	New chemical entity (5)	HHS: Jun 2020: $500 million for 500 000 doses[17,18]	Oct 22, 2020
STRATAGRAFT (allogeneic cultured keratinocytes and dermal fibroblasts in murine collagen-dsat)—Stratatech Corporation	Thermal burns	University of Wisconsin-Madison (NIH)[19]	StrataTech (BARDA)[20]	Regenerative medicine advanced therapy, priority review	Orphan (7); Biologic (12)	BARDA: Oct 2015: $247 million for 5-y contract[21]	Jun 15, 2021

Note. BARDA = Biomedical Advanced Research and Development Authority; DRC = Democratic Republic of Congo; FDA = US Food and Drug Administration; HHS = US Health and Human Services; INRB = Institut National de Recherche Biomédicale; MCM = medical countermeasures; NIAID = National Institute of Allergy and Infectious Diseases; NIH = National Institutes of Health; USAMRIID = US Army Medical Research Institute of Infectious Diseases; WHO = World Health Organization.

The superfluous nature of these vouchers is made even more obvious when considering the medical products since our last analysis that have received the voucher.[23] As of today, the three additional products that have received the MCM PRV include COVID-19 vaccines and therapeutics including Comirnaty (mRNA COVID-19 vaccine marketed by Pfizer), Spikevax (mRNA COVID-19 vaccine marketed by Moderna and co-developed by the NIH[24]), and Paxlovid (COVID-19 antiviral marketed by Pfizer). Through federal initiatives such as Operation Warp Speed and others, all three products received significant direct and indirect public funding and resources for their discovery and development, additional regulatory incentives including early market entry through emergency use authorization as well as expedited review designations ahead of full FDA approval, and guaranteed revenues from multiple advance purchasing agreements.[25,26,27]

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[23] 21st Century Cures Act: MCM-Related Cures Provisions. FDA. Published May 25, 2023. Accessed July 9, 2023. https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/21st-century-cures-act-mcm-related-cures-provisions

[24] Ramachandran R, Rizvi Z. Opinion | Will Moderna Ever Learn to Share? MedPage Today. Published November 28, 2021. https://www.medpagetoday.com/opinion/second-opinions/95877

[25] Lalani HS, Nagar S, Sarpatwari A, et al. US public investment in development of mRNA covid-19 vaccines: retrospective cohort study. *BMJ*. 2023;380:e073747. doi:10.1136/bmj-2022-073747

[26] Ryan P. Joyce, Vivian W. Hu, and Jun Wang, "The History, Mechanism, and Perspectives of Nirmatrelvir (PF-07321332): An Orally Bioavailable Main Protease Inhibitor Used in Combination with Ritonavir to Reduce COVID-19-Related Hospitalizations," *Medicinal Chemistry Research* 31, no. 10 (2022): 1637–46, https://doi.org/10.1007/s00044-022-02951-6.

[27] Morten CJ. *Written Statement of Christopher J. Morten, J.D., Ph.D. Associate Clinical Professor of Law, Columbia Law School Before the United States Senate Committee on Health, Education, Labor & Pensions (HELP)*

Moreover, under the recently launched Project NextGen, a collaborative effort between BARDA and the National Institute of Allergy and Infectious Diseases (NIAID) within the NIH, the federal government will be supporting the next generation of MCMs.[28] Like prior MCMs, these will also be likely eligible for additional regulatory incentives and receive federal procurement contracts. Thus, considering the availability of several other public incentives, the reauthorization and expansion of MCM PRVs becomes redundant.

The medical countermeasure priority review voucher puts patients at greater risk of potential harm.

Manufacturers redeem the PRV with the FDA for a drug or biologic that would otherwise be ineligible for priority review. Outside of redeeming a voucher, drugs and biologics are only eligible to receive priority review by the FDA if the drug or biologic treats a serious condition and if approved, demonstrates a "significant improvement in safety or effectiveness."[29] If a therapeutic receives a priority review designation, then the regulatory review time between when the sponsor submits an application and when FDA makes an approval decision is shortened from 10 months under standard review to six months.

In addition to being unnecessary for incentivizing innovation, PRVs could also put patients at increased risk of harm. When a manufacturer redeems a PRV, the voucher then forces the FDA to more rapidly assess the safety and efficacy of a medical product that would have not otherwise met the eligibility criteria for priority review as described above. Previous studies have found that products that received priority review or were approved near the regulatory deadline were more often associated with safety events including product withdrawals as well as boxed warnings and safety communications issued by the FDA.[30,31]

Moreover, such expedited review designations have also been associated with lower standards of evidence including fewer pivotal trials, fewer enrolled pivotal trial participants, and more frequent use of surrogate endpoints instead of more clinically relevant ones.[32] Thus, the issuance of multiple PRVs could lead to the increased number of potentially unproven and unsafe drugs and biologics being more hastily reviewed and approved by the FDA. Finally, this

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Hearing Entitled "Taxpayers Paid Billions For It: So Why Would Moderna Consider Quadrupling the Price of the COVID Vaccine?"; 2023. Accessed July 10, 2023. https://www.help.senate.gov/imo/media/doc/Morten%20-%20Full%20written%20statement.pdf

[28] Project NextGen: Next Generation Medical Countermeasures. Accessed July 10, 2023. https://medicalcountermeasures.gov/nextgen

[29] FDA - Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research. Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics. Published online May 2014. Accessed October 19, 2021. https://www.fda.gov/media/86377/download

[30] Nicholas S. Downing et al., "Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010," *JAMA* 317, no. 18 (May 9, 2017): 1854–63, https://doi.org/10.1001/jama.2017.5150.

[31] Carpenter D, Zucker EJ, Avorn J. Drug-Review Deadlines and Safety Problems. *New England Journal of Medicine*. 2008;358(13):1354-1361. doi:10.1056/NEJMsa0706341

[32] Audrey D. Zhang et al., "Assessment of Clinical Trials Supporting US Food and Drug Administration Approval of Novel Therapeutic Agents, 1995-2017," *JAMA Network Open* 3, no. 4 (April 21, 2020): e203284, https://doi.org/10.1001/jamanetworkopen.2020.3284.

also introduces an additional level of administrative burden on the agency in forcing FDA to meet the six-month priority review deadline for an approval decision and potentially having to reallocate their already limited resources towards reviewing products that may not treat serious conditions or demonstrate greater safety or efficacy than other products already available to patients. As examination of this incentive has failed to effectively promote the development of medical countermeasures and may instead lead to the hasty approval of potentially unsafe medical products of uncertain benefit, the committee should reconsider the expansion of the MCM PRV and sunset this program altogether.