

**Written Testimony of Reshma Ramachandran, M.D., M.P.P., M.H.S. of
Yale School of Medicine**

Hearing on “Preparing for the Next Public Health Emergency: Reauthorizing the Pandemic and
All-Hazards Preparedness Act”

Senate Health, Education, Labor, and Pensions (HELP) Committee

May 4, 2023

Chairman Sanders, Ranking Member Cassidy, and distinguished members of the committee, thank you for the invitation to testify today. My name is Reshma Ramachandran. I am an Assistant Professor at Yale School of Medicine where I co-direct an interdisciplinary research and policy program called the Yale Collaboration for Regulatory Rigor, Integrity, and Transparency (CRRIT). Through CRRIT, we study medical product evaluation, regulation, and coverage and translate these findings with the aim of improving patient health outcomes.

I am also a primary care physician at a federally qualified health center where I see and take care of patients, many of whom are uninsured or underinsured and face significant, but unnecessary barriers to accessing the treatments I prescribe. Additionally, I lead the Doctors for America Food and Drug Administration (FDA) Task Force, which is an independent group of physicians across specialties who provide unbiased expertise in evaluating and responding to the FDA regulatory process in a way that maximizes meaningful clinical outcomes for our patients. My written remarks reflect my own views and not that of my employers nor the organizations I work with.

The past three years of the COVID-19 public health emergency have demonstrated the incredible capability of the federal government in fostering and supporting targeted innovation to rapidly develop and make available novel health technologies amid a devastating pandemic. Not only did American taxpayers contribute billions in direct funding for the discovery, development, production, and distribution of COVID-19 diagnostics, vaccines, and drugs,^{1,2} they also indirectly contributed resources, personnel, and expertise through federal agencies that enabled the successful innovation of these technologies.^{3,4} Now, in just one week, the declaration of COVID-19 as a public health emergency will come to an end. With this year’s reauthorization of the Pandemic All-Hazards Preparedness Act (PAHPA) comes an opportunity to reflect on this period and utilize the lessons learned from disbursing this significant public investment. To inform this impending legislation, Congress can answer the following fundamental question:

¹ “COVID-19: Federal Efforts Accelerate Vaccine and Therapeutic Development, but More Transparency Needed on Emergency Use Authorizations” (Washington, D.C.: Government Accountability Office, November 2020), <https://www.gao.gov/assets/720/710691.pdf>.

² Biomedical Advanced Research and Development Authority, “BARDA’S Rapidly-Expanding COVID-19 Medical Countermeasure Portfolio,” accessed May 2, 2023, <https://www.medicalcountermeasures.gov/app/barda/coronavirus/COVID19.aspx>.

³ “NIH Launches Clinical Trials Network to Test COVID-19 Vaccines and Other Prevention Tools,” NIH.gov, July 8, 2020, <https://www.nih.gov/news-events/news-releases/nih-launches-clinical-trials-network-test-covid-19-vaccines-other-prevention-tools>.

⁴ U.S. Food and Drug Administration, “Coronavirus Treatment Acceleration Program (CTAP),” FDA.gov (FDA, January 24, 2023), <https://www.fda.gov/drugs/coronavirus-covid-19-drugs/coronavirus-treatment-acceleration-program-ctap>.

how can we ensure that the American public has equitable access to medical countermeasures developed in response to public health emergencies in the future?

In my written testimony, I will outline a few select principles and policies for lawmakers to consider as part of PAHPA towards enabling a fair return for the federal government as well as the American public for the significant public investment made to address public health emergencies.

The federal government must require rigorous evidence to be generated of medical countermeasures demonstrating safety and efficacy.

During a public health emergency (PHE) when the American public is at grave risk of disease, FDA can employ flexibilities such as emergency use authorization (EUA) to quickly evaluate and authorize unapproved medical products. Over the course of the COVID-19 PHE, FDA awarded numerous EUAs to vaccines, diagnostics, and drugs while continuing to assess additional safety and efficacy data to determine if the product should remain on or be withdrawn from the market.⁵ Amid an ongoing PHE, it may be necessary for the FDA to allow market access to medical countermeasures despite having residual uncertainty of their safety and efficacy at the time of authorization or approval. However, this must be coupled with requirements for pharmaceutical companies to conduct studies to confirm that their medical products are indeed safe and meaningfully effective.

For COVID-19 vaccines, FDA established rigorous regulatory standards for EUA of potential candidates, requiring large and diverse participant enrollment into randomized-controlled trials with clinical endpoints.⁶ The agency also set parameters for the clinical trial design, calling for them to be placebo-controlled and double-blinded with adequate follow-up of participants. These standards were also discussed publicly with independent experts through the Vaccines and Related Biologic Products Advisory Committee (VRBPAC) and others.⁷ FDA also issued draft guidance on these regulatory standards allowing for feedback through a public comment period.⁸

The National Institutes of Health (NIH) also played a pivotal role in ensuring rigorous clinical trial design, particularly through their Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) program.⁹ Within ACTIV, NIH worked closely alongside other agencies and the biopharmaceutical industry to develop and implement a coordinated research strategy to

⁵ Office of the Commissioner, “Emergency Use Authorization,” FDA.gov (FDA, May 2, 2023), <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization>.

⁶ U.S. Food and Drug Administration, “Development and Licensure of Vaccines to Prevent COVID-19: Guidance for Industry,” June 2020, <https://www.fda.gov/media/139638/download>.

⁷ Ravi Gupta et al., “During COVID-19, FDA’s Vaccine Advisory Committee Has Worked To Boost Public Trust – It Can Still Do More,” *Health Affairs Forefront*, accessed May 1, 2023, <https://doi.org/10.1377/forefront.20210225.712221>.

⁸ U.S. Food and Drug Administration, “Guidance Documents Related to Coronavirus Disease 2019; Availability,” August 3, 2020, <https://www.govinfo.gov/content/pkg/FR-2020-08-03/html/2020-16852.htm>.

⁹ “Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV),” National Institutes of Health (NIH), accessed January 19, 2022, <https://www.nih.gov/research-training/medical-research-initiatives/activ>.

move promising technologies more expeditiously from the preclinical to clinical trial stage. Under ACTIV, NIH also established several working groups where they convened public agencies and manufacturers to develop clinical trial protocols and harmonize efficacy trial designs for therapeutics and vaccines. Additionally, NIH funded and led several clinical trials in coordination with pharmaceutical company sponsors, providing critical scientific expertise and access to NIH’s own clinical trial networks and others.^{10,11}

However, such regulatory rigor across medical countermeasures has not been consistent. For instance, remdesivir was initially granted an EUA in May 2020 based on evidence that it may be effective for the treatment of severe COVID-19.¹² Just months later in October 2020, FDA granted its first full approval¹³ for remdesivir despite conflicting evidence of its effect on time to recovery for patients who are hospitalized and diagnosed with COVID-19. At the time of traditional approval, infectious disease experts could only conclude that remdesivir might work.¹⁴ Although FDA attempted offset this uncertainty through 29 additional required and voluntarily committed studies (more than three to four times the number typically required or requested)^{15,16}, none of the required studies addressed the key question of whether in light contradictory results across clinical studies, remdesivir did indeed decrease time to recovery for hospitalized COVID-19 patients with less severe disease or reduce mortality.¹⁷

Less than a year later, researchers from the Veterans Health Administration published a study finding that remdesivir was not associated with improved 30-day survival and that instead, it was associated with an increase in time to hospital discharge.¹⁸ Had the FDA required further evidence of the drug’s efficacy ahead of traditional approval or had imposed postmarketing requirements to confirm its efficacy with adequate oversight to ensure timely completion, the

¹⁰ “NIH Launches Clinical Trials Network to Test COVID-19 Vaccines and Other Prevention Tools.”

¹¹ Francis Collins et al., “The NIH-Led Research Response to COVID-19,” *Science* 379, no. 6631 (February 3, 2023): 441–44, <https://doi.org/10.1126/science.adf5167>.

¹² “Coronavirus (COVID-19) Update: FDA Issues Emergency Use Authorization for Potential COVID-19 Treatment,” FDA.gov (FDA, May 4, 2020), <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-emergency-use-authorization-potential-covid-19-treatment>.

¹³ “FDA Approves First Treatment for COVID-19,” FDA.gov (FDA, October 22, 2020), <https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19>.

¹⁴ Paul Sax, “Does Remdesivir Actually Work?,” *NEJM Journal Watch*, October 18, 2020, <https://blogs.jwatch.org/hiv-id-observations/index.php/does-remdesivir-actually-work/2020/10/18/>.

¹⁵ Joshua D. Wallach et al., “Postmarketing Commitments for Novel Drugs and Biologics Approved by the US Food and Drug Administration: A Cross-Sectional Analysis,” *BMC Medicine* 17, no. 1 (June 17, 2019): 117, <https://doi.org/10.1186/s12916-019-1344-3>.

¹⁶ Joshua D. Wallach et al., “Postmarket Studies Required by the US Food and Drug Administration for New Drugs and Biologics Approved between 2009 and 2012: Cross Sectional Analysis,” *BMJ* 361 (May 24, 2018): k2031, <https://doi.org/10.1136/bmj.k2031>.

¹⁷ John Farley, “NDA Approval Letter for Veklury,” October 22, 2020, https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2020/214787Orig1s000ltr.pdf.

¹⁸ Michael E. Ohl et al., “Association of Remdesivir Treatment With Survival and Length of Hospital Stay Among US Veterans Hospitalized With COVID-19,” *JAMA Network Open* 4, no. 7 (July 15, 2021): e2114741, <https://doi.org/10.1001/jamanetworkopen.2021.14741>.

federal government could have possibly saved a substantial amount rather than spending on excessive procurement and reimbursement.^{19,20}

Besides maintaining rigorous standards for FDA regulatory review and approval, the federal government could also ensure that further studies are conducted that are scientifically meaningful for public health. For instance, although the federal government made several investments across various vaccine candidates and provided scientific guidance, personnel, and additional resources including access to clinical trial networks, manufacturers were not required to conduct head-to-head vaccine trials to compare efficacy and safety were conducted. Such studies would allow the federal government to better understand if vaccine products have differential effects across populations. Moreover, this would also allow the federal government to be a better steward of public funding when negotiating procurement contracts with manufacturers for bulk purchase agreements to ensure that the American public has access to the most appropriate medical countermeasures.

Case Study: Low FDA regulatory standards for FDA approval of antibiotics have yielded drugs of unclear clinical benefit

Updated estimates paint a sobering picture of the human and economic toll of antimicrobial resistance. In 2019, 1.27 million deaths globally were estimated to be attributable to bacterial antimicrobial resistance²¹ and the CDC estimates that 35,000 in the U.S. die because of resistant bacterial infections.²² Additionally, the CDC in collaboration with academic researchers has estimated that treatment of the six most alarming antibiotic resistant pathogens contribute to more than \$4.6 billion in health care costs each year.²³

While exigency is certainly warranted for addressing antimicrobial resistance, this global public health threat differs from COVID-19 in terms of urgency of action and disbursement of federally funded incentives. COVID-19 with its rapid spread and resulting substantial mortality and morbidity required immediate action with the acceptance of some level of uncertainty in evaluating and authorizing new diagnostics, vaccines, and drugs. In contrast, for antimicrobial resistance, the federal government can take strategic steps in allocating public funding and resources to ensure equitable access for the American public to truly effective and safe treatments and other health technologies.

¹⁹ Eric M Tichy et al., “National Trends in Prescription Drug Expenditures and Projections for 2022,” *American Journal of Health-System Pharmacy* 79, no. 14 (July 15, 2022): 1158–72, <https://doi.org/10.1093/ajhp/zxac102>.

²⁰ Karyn Schwartz and 2020, “How Could the Price of Remdesivir Impact Medicare Spending for COVID-19 Patients?,” *KFF* (blog), July 14, 2020, <https://www.kff.org/coronavirus-covid-19/issue-brief/how-could-the-price-of-remdesivir-impact-medicare-spending-for-covid-19-patients/>.

²¹ Christopher JL Murray et al., “Global Burden of Bacterial Antimicrobial Resistance in 2019: A Systematic Analysis,” *The Lancet* 0, no. 0 (January 19, 2022), [https://doi.org/10.1016/S0140-6736\(21\)02724-0](https://doi.org/10.1016/S0140-6736(21)02724-0).

²² “COVID-19: U.S. Impact on Antimicrobial Resistance, Special Report 2022” (National Center for Emerging and Zoonotic Infectious Diseases, June 14, 2022), <https://doi.org/10.15620/cdc:117915>.

²³ Richard E Nelson et al., “National Estimates of Healthcare Costs Associated With Multidrug-Resistant Bacterial Infections Among Hospitalized Patients in the United States,” *Clinical Infectious Diseases* 72, no. Supplement_1 (January 15, 2021): S17–26, <https://doi.org/10.1093/cid/ciaa1581>.

Instead, stakeholders including the pharmaceutical industry have urgently called for the adoption of costly pull incentives for drug manufacturers without clear assurance or safeguards that the antimicrobials yielded are clinically beneficial or effective against future resistant pathogens.^{24,25} Under the Pioneering Antimicrobial Subscriptions To End Up surging Resistance (PASTEUR) Act, manufacturers of newly-approved antimicrobials would be eligible to receive as much as \$3 billion in regular installments over a five to 10 year contract period for an individual drug.²⁶ An additional \$1 billion could also be allocated as an extension of the initially contracted period or given ahead of FDA approval for a promising antimicrobial drug candidate. However, absent from this lucrative award for drug manufacturers is a requirement that eligible drugs improve patient health outcomes. Instead, it is one of several “favored characteristics”; among these is that a drug would be eligible for valuable subscription contract if it has received a prior “transitional subscription contract.” Eligibility for such a transitional includes that the drug has received the FDA “qualified infectious disease product” (QIDP) designation and has been developed to treat resistant infections listed within CDC’s most recent “Antibiotic Resistant Threats in the United States” report.

Examination of recently approved antimicrobials including those granted the QIDP designation by the FDA has shown that the agency approves treatments of unclear benefit and at worst, antimicrobials that are less effective than what is currently available. Prior characterization of pivotal clinical trials for FDA-approved antibiotics (including a small number awarded the qualified infectious disease product or QIDP designation) between 2010 and 2015 have shown that most of these trials were noninferiority studies with none evaluating direct patient outcomes as a primary endpoint.²⁷ A more recent study of antibiotics approved by the FDA between 2016 and 2019 found that all drugs, many of which were designated as QIDPs, were approved based on surrogate endpoints. More than half of the pivotal trials supporting their approval also used a non-inferiority design, which means that the drugs can be either marginally better or worse by some amount than older, effective alternatives.²⁸ The study authors also found these new antibiotics despite uncertainty of their clinical benefit at the time of approval were frequently more expensive than other effective alternatives.

In an ongoing research study examining the evidentiary basis for approval of QIDP indications, we found that over 20% were approved based on *in vitro* studies and a majority were tested in non-inferiority pivotal trials, which as noted earlier, allow for intervention drugs to be

²⁴ Andrew Jack, “Drugmakers Eye Government Money to Combat Antibiotic Resistance,” *Financial Times*, October 27, 2022.

²⁵ Reshma Ramachandran and John H. Powers, “Why the PASTEUR Act Is No Cure for Antimicrobial Resistance | The Hill,” *The Hill*, December 13, 2022, <https://thehill.com/opinion/healthcare/3773180-why-the-pasteur-act-is-no-cure-for-antimicrobial-resistance/>.

²⁶ Michael F. Bennet, “PASTEUR Act of 2021,” Pub. L. No. S. 2076 (2021), <https://www.congress.gov/bill/117th-congress/senate-bill/2076/text>.

²⁷ Dalia Deak et al., “Progress in the Fight Against Multidrug-Resistant Bacteria? A Review of U.S. Food and Drug Administration–Approved Antibiotics, 2010–2015,” *Annals of Internal Medicine* 165, no. 5 (September 6, 2016): 363, <https://doi.org/10.7326/M16-0291>.

²⁸ Mayookha Mitra-Majumdar et al., “Evidence at Time of Regulatory Approval and Cost of New Antibiotics in 2016-19: Cohort Study of FDA Approved Drugs,” *BMJ Medicine* 1, no. 1 (December 1, 2022), <https://doi.org/10.1136/bmjmed-2022-000227>.

less effective compared with older, effective antimicrobials by a prespecified margin.²⁹ Moreover, nearly half of the QIDP indication pivotal trials failed to enroll patients with potential or confirmed resistance. In fact, the FDA only confirmed efficacy against any resistant pathogens for less than a third of these indications based on their pivotal clinical trials. Moreover, FDA has not required manufacturers to conduct further studies after approval to confirm clinical benefit, superiority compared to other effective alternatives, or clinical efficacy against resistant bacterial infections. This suggests that these financial incentives in the form of assured high revenues may be misaligned, rewarding manufacturers of QIDPs for unclear effectiveness against resistant pathogens, despite receiving this special designation intended for this purpose.

Proponents of the PASTEUR Act claim that the legislation would delink the price of newly approved antimicrobial as well as the volume of doses administered from the drug’s development costs. However, the legislation has several fundamental flaws in its design including that it would fail to guarantee the American public access to truly effective and safe antimicrobials. Instead, PASTEUR would guarantee that pharmaceutical companies would be awarded a multi-billion-dollar contract funded by taxpayers. Alternatively, as with COVID-19, the federal government should set higher standards for regulatory approval that would lead to novel and effective innovation and focus taxpayer investments earlier in the pipeline including for late-stage clinical trials to yield treatments with proven public health and clinical impact.

Summary of Key Points:

- During COVID-19, the federal government through its agencies including FDA, CDC, and NIH demonstrated that even during a public health emergency period, parameters for robust clinical trial design could be set to ensure greater certainty of efficacy and safety of novel medical countermeasures.
- While during the public health emergency period federal agencies may allow for regulatory flexibility of novel medical countermeasures, they must also put in place requirements for sponsors to provide further data even after initial authorization or approval to confirm the product’s efficacy and safety.
- In return for significant public investment and resources directed toward the development of novel medical countermeasures, the federal government should require sponsors to conduct additional studies of medical countermeasures to answer important public health questions and more efficiently allocate public funding and resources.
- When developing medical countermeasures outside of a public health emergency, the federal government should take strategic steps to ensure that any such public investment yields products that are proven to be safe and effective throughout rigorous and well-designed clinical studies.
 - Erosion of FDA regulatory standards has led to the approval of new antimicrobials of unclear clinical benefit and efficacy against resistant threats with no safeguards in place to confirm whether these drugs are truly effective after approval.

²⁹ Food and Drug Administration, “Non-Inferiority Clinical Trials to Establish Effectiveness: Guidance for Industry,” November 2016, <https://www.fda.gov/media/78504/download>.

- Pull incentives such as the recently re-introduced PASTEUR Act fail to guarantee the American public access to truly novel, effective, and safe antimicrobials, but guarantee pharmaceutical manufacturers revenues under multi-billion-dollar subscription contracts.

The federal government must ensure that the American public has affordable access to medical countermeasures.

The federal government has played an outsized role in financing and supporting the development of medical countermeasures. Yet it has exercised very little leverage in ensuring affordable access and fair pricing of these medical products. As discussed at the recent hearing held by the Senate HELP Committee on March 22, 2023, COVID-19 vaccine manufacturers received significant public funding support for discovery, development, production, and manufacturing activities through Operation Warp Speed and other initiatives.³⁰ Even predating the pandemic, the U.S. government invested an estimated \$337 million toward early and late stages of development as well as manufacturing capacity of mRNA vaccines.³¹ Ahead of confirmation of efficacy and safety, several manufacturers were granted advanced purchase agreements for hundreds of millions of doses without necessitating FDA authorization or approval.³² Essentially, the federal government de-risked several stages of vaccine development and production for manufacturers.

Despite this, COVID-19 vaccine manufacturers have been able to negotiate prices with the federal government well above the cost of production,³³ reaping multiple billions in profits. Now, as the PHE period comes to an end, these companies have also announced significant price increases to their products.³⁴ Coupled with the likelihood that COVID-19 will be considered an endemic disease possibly requiring regular booster doses,³⁵ similar to that of influenza, these anticipated price hikes will translate to significant costs for patients and the federal government. Without intervention, uninsured populations will directly face these anticipated vaccine price hikes and deterring many from receiving a potentially necessary prevention measure.

³⁰ “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>.

³¹ Hussain S. Lalani et al., “US Public Investment in Development of MRNA Covid-19 Vaccines: Retrospective Cohort Study,” *BMJ* 380 (March 1, 2023): e073747, <https://doi.org/10.1136/bmj-2022-073747>.

³² Leila Abboud and Hannah Kuchler, “Why the Three Biggest Vaccine Makers Failed on Covid-19,” *Financial Times*, February 16, 2021, <https://www.ft.com/content/657b123a-78ba-4fba-b18e-23c07e313331>.

³³ 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/>.

³⁴ 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>.

³⁵ U.S. Food and Drug Administration, “FDA Briefing Document: Future Vaccination Regimens Addressing COVID-19,” January 26, 2023, <https://www.fda.gov/media/164699/download>.

For these populations, manufacturers have promised to establish patient assistance programs.³⁶ However, to ensure access, these programs as they have been traditionally established and implemented will not be adequate. Not only do such programs often lack a standardized application process, but their applications are onerous and complex often requiring assistance from health professional personnel.³⁷ Additionally, supply is typically allocated through patients’ providers, necessitating an extra step and potentially, an additional payment for a clinic visit to obtain the needed treatment. To realize the intention of these programs of providing equitable and free access to COVID-19 vaccines for uninsured patients, the federal government must set minimum requirements for manufacturers to make these products easily accessible without any cost.

Manufacturers have also argued that insured populations will not see these costs in the form of out-of-pocket payments. While this is certainly true under the Affordable Care Act and the Inflation Reduction Act, the federal government and private insurers will likely bear the burden of higher post-pandemic prices, which could lead to higher premiums for the insured American public.³⁸ The federal government could continue to purchase vaccine doses in bulk at a lower price as anticipated in the near-term;³⁹ however, as evidenced by the case of the influenza vaccine which similarly was developed and manufactured with public funding support,⁴⁰ even the initial public procurement price will become a floor for continued price increases.

For COVID-19 treatments, pricing following the PHE is less certain. Public procurement prices for antivirals such as molnupiravir (Lagevrio), nirmatrelvir-ritonavir (Paxlovid), and remdesivir (Veklury) have far exceeded their production costs^{41,42,43} and despite their manufacturers also having received federal funding support and resources for their development.^{44,45,46} The CEO of Pfizer, which markets nirmatrelvir-ritonavir referred to the

³⁶ “Moderna’s Commitment to Patient Access in the United States,” [modernatx.com](https://investors.modernatx.com/Statements--Perspectives/Statements--Perspectives-Details/2023/Modernas-Commitment-to-Patient-Access-in-the-United-States/default.aspx), February 15, 2023, <https://investors.modernatx.com/Statements--Perspectives/Statements--Perspectives-Details/2023/Modernas-Commitment-to-Patient-Access-in-the-United-States/default.aspx>.

³⁷ Niteesh K. Choudhry et al., “Drug Company–Sponsored Patient Assistance Programs: A Viable Safety Net?,” *Health Affairs* 28, no. 3 (May 1, 2009): 827–34, <https://doi.org/10.1377/hlthaff.28.3.827>.

³⁸ 2023, “How Much Could COVID-19 Vaccines Cost the U.S. After Commercialization?,” *KFF* (blog), March 10, 2023, <https://www.kff.org/coronavirus-covid-19/issue-brief/how-much-could-covid-19-vaccines-cost-the-u-s-after-commercialization/>.

³⁹ “Fact Sheet: HHS Announces ‘HHS Bridge Access Program For COVID-19 Vaccines and Treatments’ to Maintain Access to COVID-19 Care for the Uninsured,” Text, HHS.gov, April 18, 2023, <https://www.hhs.gov/about/news/2023/04/18/fact-sheet-hhs-announces-hhs-bridge-access-program-covid-19-vaccines-treatments-maintain-access-covid-19-care-uninsured.html>.

⁴⁰ Reshma Ramachandran et al., “Future of Covid-19 Vaccine Pricing: Lessons from Influenza,” *BMJ* 373 (June 22, 2021): n1467, <https://doi.org/10.1136/bmj.n1467>.

⁴¹ Prepared Melissa J Barber and Dzintars Gotham, “Estimated Cost-Based Generic Prices for Molnupiravir for the Treatment of COVID-19 Infection,” *Working Paper*, October 1, 2021.

⁴² Prepared Melissa J Barber and Dzintars Gotham, “Estimated Cost-Based Generic Prices for Nirmatrelvir/Ritonavir (Paxlovid),” *Working Paper*, January 12, 2023.

⁴³ Andrew Hill et al., “Minimum Costs to Manufacture New Treatments for COVID-19,” *Journal of Virus Eradication* 6, no. 2 (n.d.): 61–69.

⁴⁴ 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>.

\$530 per course price point the federal government was able to receive through its initial bulk purchasing agreement as “really very attractive” and indicated the drug will cost significantly more on the commercial market.⁴⁷ For these and other COVID-19 treatments, the burden of potentially unaffordable access will fall onto disproportionately on the most vulnerable populations who are at higher risk of developing severe illness.

Other medical countermeasures developed to address public health emergencies have also benefitted from significant public funding and resource support for their discovery, basic and preclinical studies, and clinical trials supporting regulatory authorization or approval.⁴⁸ The federal government has also often secured bulk purchasing agreements ahead of market authorization from the FDA. Such agreements have given the federal government leverage to negotiate a likely more reasonable price point with manufacturers. However, few contracts have included provisions guaranteeing such reasonable pricing, particularly in comparison to procurement prices paid by other countries. As part of their agreement with Novavax, the Department of Defense stated that it should receive the lowest, best price for a period of five years for purchase of doses administered in the U.S.⁴⁹ In exchange for \$1.8 billion, Sanofi had been prohibited in its agreement to sell its vaccine to any member of the G7 or Switzerland at a price lower than that of the federal government.⁵⁰ In their contract with Paxlovid, the federal government including a “most-favored nation” pricing clause that would allow them to receive a lower price if one of six other high-income countries were to negotiate a better deal.⁵¹ Such conditions that better safeguard affordable access both during the PHE period as well as afterward should be applied across medical countermeasures by the federal government.

Besides conditions directly focused on pricing, the federal government should also ensure that public funding and resources granted to pharmaceutical companies and others do not include flexibilities that could preclude access. During COVID-19, the Biomedical Advanced Research and Development Authority (BARDA) along with the Department of Defense routinely utilized

⁴⁵ Travis Whitfill, “A Likely New Treatment for Covid-19 Was Made Possible by Government-Funded Innovation,” *STAT* (blog), October 5, 2021, <https://www.statnews.com/2021/10/05/government-funding-backed-molnupira-vir-possible-new-covid-19-treatment/>.

⁴⁶ Ryan P. Joyce, Vivian W. Hu, and Jun Wang, “The History, Mechanism, and Perspectives of Nirnatrelvir (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>.

⁴⁷ 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>.

⁴⁸ Michael S. Sinha et al., “Expansion of the Priority Review Voucher Program Under the 21st Century Cures Act: Implications for Innovation and Public Health,” *American Journal of Law & Medicine* 44, no. 2–3 (May 2018): 329–41, <https://doi.org/10.1177/0098858818789430>.

⁴⁹ 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>.

⁵⁰ Kathryn Ardizzone, “\$1.8 Billion Sanofi Vaccine Contract Contains International Reference Pricing Clause, Preserves Standard IP and Data Rights,” *Knowledge Ecology International* (blog), December 2, 2020, <https://www.keionline.org/34776>.

⁵¹ 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>.

the mechanism of Other Transaction Agreements (OTAs) to attract private partners to enter into government contracts granting federal funding support for the development and production of various medical products.⁵² While such flexibilities are employed to hasten contracting with private sector partners, they also remove potentially important safeguards that would enable affordable access. For instance, OTAs are not subject to conditions under the Bayh-Dole Act, which means that when pricing of publicly funded medical countermeasures hinders reasonable access of these products, federal agencies are unable to exercise march-in rights that would compel the patent owner to license the pertinent patents to another company such as a generic drug manufacturer.⁵³ BARDA has proposed as part of their 2022-2026 Strategic Plan to leverage OTAs further as part of their contracting process⁵⁴ putting at risk the ability of the federal government to intervene to ensure affordable access.

Summary of Key Points:

- Although the federal government has played an outsized role in financing and supporting the development of medical countermeasures, it has exercised very little leverage in ensuring affordable access and fair pricing of these medical products even during public health emergency periods.
- Untethered price hikes of COVID-19 vaccines and therapeutics following the public emergency period will have a disproportionate and undue impact on those populations who are uninsured and at higher risk of severe illness unless the federal government intervenes.
- Although manufacturers argue that insured patients will not face barriers in accessing COVID-19 vaccines due to anticipated price hikes due to policies that prevent cost-sharing of CDC-recommended vaccines for those who are insured, they may face these costs in the form of higher premiums. Additionally, the federal government and private insurers in procuring doses from the manufacturers may also face these significant price hikes, precluding allocation of such funds for other necessary public health interventions.
- Although the federal government could mitigate the impact of such price hikes through bulk purchasing agreements at a negotiated lower price, the initial public procurement price following the public health emergency period will likely be the floor as evidenced by trends in public and private influenza vaccine pricing over time.
- In a few contracts, the federal government has been able to include provisions guaranteeing reasonable pricing in comparison to other wealthy countries, which should also be included in all future purchasing agreements.
- The federal government should also ensure that such agreements do not include provisions that remove access safeguards at the expense of flexibility and speed.

⁵² Eric Steinberg, “Use of Other Transactions at ASPR,” accessed May 3, 2023, <https://doi.org/10.1037/e658332011-001>.

⁵³ Stuart W. Turner, “Other Transactions Authority (OTA): Protests and Disputes,” Arnold & Porter, June 28, 2018, <https://www.arnoldporter.com/en/perspectives/advisories/2018/06/other-transactions-authority-ota-protests>.

⁵⁴ Assistant Secretary for Preparedness and Response and Biomedical Advanced Research and Development Authority, “BARDA Strategic Plan 2022–2026” (Department of Health and Human Services, May 2022), <https://www.medicalcountermeasures.gov/media/38717/barda-strategic-plan-2022-2026.pdf>.

The federal government must continuously evaluate the success of publicly awarded incentives and sunset those that fail to generate truly innovative, effective, and safe medical countermeasures.

Along the drug and vaccine development pipeline, agencies have awarded various incentives to pharmaceutical companies and other stakeholders ranging from push incentives that lower the cost of development to pull incentives that ensure or increase revenue. While the purpose of such incentives is to enable greater participation from stakeholders including private partners in the development of novel medical countermeasures, there has been little effort to evaluate these incentives once implemented and sunset those that have not been proven to be effective.

One such incentive is the medical countermeasure priority review voucher, created under the 21st Century Cures Act in 2016.⁵⁵ Awarded at the time of FDA approval, manufacturers can redeem priority review vouchers allowing for another product in their portfolio. Under the traditional review process, these products would be reviewed by the FDA within 10 months; with a voucher, the product would instead receive priority review without having to meet specific eligibility criteria, shortening regulatory review time to a maximum of six months and allowing for earlier market entry. The Government Accountability Office (GAO) analysis of three existing priority review voucher programs including for medical countermeasures generally did not find any effect of these vouchers on innovation.⁵⁶ The GAO report also noted another analysis, which found that 25 of the 26 medical countermeasures in clinical trials received public funding for their development, raising questions on the necessity of such vouchers to incentivize innovation.

In a study we published in 2021,⁵⁷ we found that all five medical countermeasures initially 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. 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. Additionally, FDA awarded further intellectual property protections in the form of exclusivity periods, barring generic entry for variable periods of time. Finally, the federal government also ensured a market for these products through bulk advance purchase agreements, often secured before regulatory approval. Considering that the federal government has granted several financial, regulatory, and intellectual property incentives along the medical countermeasure development pipeline, issuance of an additional priority review voucher is likely unnecessary.

⁵⁵ “Material Threat Medical Countermeasure Priority Review Vouchers: Draft Guidance” (Rockville, MD: Food and Drug Administration, January 17, 2018), <https://www.fda.gov/media/110193/download>.

⁵⁶ Government Accountability Office, “DRUG DEVELOPMENT: FDA’s Priority Review Voucher Programs,” January 2020, <https://www.gao.gov/assets/710/704207.pdf>.

⁵⁷ 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>.

Moreover, there may be undue impacts from the awarding of such priority review vouchers, creating an undue burden for patients and clinicians. Redeeming the priority review voucher forces the FDA to more rapidly access the safety and efficacy of a medical product that would otherwise be ineligible for this expedited review designation. Such designations have been associated with increased risk of FDA safety actions after approval⁵⁸ as well as 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.⁵⁹ 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, legislators should reconsider and even sunset this program altogether.

For antimicrobials, other incentives have been introduced to encourage the development of novel drugs with limited evaluation of their value. Entering into a “subscription” contract under the PASTEUR Act would not disqualify manufacturers from receiving other financial incentives. One such other financial incentive is that of new technology add-on payments from the Centers for Medicare and Medicaid Services (CMS), which in 2019 modified these to be higher and removed the eligibility criteria of “substantial clinical improvement”, thus lowering the bar for receiving this additional reimbursement. This payment received by manufacturers when the antimicrobial is dispensed to a patient is effectively a volume-based incentive that is antithetical to the need to conserve these drugs to prevent against further resistance.

Therefore, should the PASTEUR Act be included as part of PAHPA, manufacturers of new antimicrobials would not only be eligible to receive billions in federally awarded subscription contracts, but also additional revenue through new technology add-on payments. This may create a perverse situation in which health systems and hospitals would be incentivized to prescribe more of a new antimicrobial that should be conserved as a last line treatment. Moreover, as the PASTEUR Act only addresses public remuneration of new antimicrobials in the form of regular lump sum payments, manufacturers of these drug products would also potentially be able to receive private payer reimbursement separately as additional revenue, which may incentivize the overuse or misuse of these new treatments.

Such financial incentives that may prompt health systems and hospitals to inappropriately prescribe novel antimicrobials encompassed by the PASTEUR Act would not be offset by the stewardship provisions in the bill.⁶⁰ As written, the legislation does not tie specific stewardship efforts to antimicrobials for which a “subscription” contract has been issued, making it unclear how these treatments will be conserved to prevent further antimicrobial resistance. Any such

⁵⁸ 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>.

⁵⁹ 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>.

⁶⁰ Bennet, PASTEUR Act of 2021.

incentive awarded to antimicrobial manufacturers must fully delink the development costs from both the price as well as volume to ensure equitable, affordable access and not excess.⁶¹

Summary of Key Points:

- The federal government has supported the development of several medical countermeasures through push incentives that lower the cost of development as well as pull incentives that ensure or increase revenues. Following the implementation of these incentives, there has been limited evaluation of their success as well as efforts to sunset those that have not been found to be effective.
- There is little evidence that the medical countermeasure priority review voucher is effective in promoting the development of novel products as the federal government has granted several other financial, regulatory, and intellectual property incentives to these same health technologies. Granting priority review vouchers may instead lead to the hasty approval of potentially unsafe medical products of uncertain benefit. Therefore, legislators should reconsider and even sunset this program altogether.
- For antimicrobials, pull incentives such as the recent increase in new technology add-on payments awarded by CMS and removal of the “substantial clinical improvement” criteria may incentivize hospitals and health systems to overuse these drugs, which need to be conserved to prevent exacerbating antimicrobial resistance.
- Any incentive awarded to antimicrobial manufacturers must fully delink the development costs from both the price as well as volume to ensure equitable, affordable access and not excess.

Considering Opportunity Costs and Conclusion

Resulting from any allocation of funding and resources by the federal government to promote the development of novel medical products will be opportunity costs. For public health emergencies, the wager of awarding financial and other resource incentives can be risky as targeting these toward particular health technologies would preclude their use for other purposes including public health interventions not involving individual products. For instance, much of the focus of federal funding support to address COVID-19 has been largely for promoting the development of individual diagnostic, vaccine, and therapeutic products with comparatively less federal investment allotted for other public health prevention strategies.

For antimicrobial resistance, significantly more has also been spent and proposed for innovation of individual drugs compared to other strategies that would prevent the emergence and spread of bacterial resistance and in turn, the need for continuous development of novel antimicrobials effective against the next future resistant pathogen. In fact, the OECD has estimated that three out of four deaths due to antibiotic resistance could be prevented by

⁶¹ Anthony D. So and Tejen A. Shah, “New Business Models for Antibiotic Innovation,” *Upsala Journal of Medical Sciences* 119, no. 2 (March 19, 2014): 176–80, <https://doi.org/10.3109/03009734.2014.898717>.

spending \$2 per individual annually on non-pharmacologic interventions such as handwashing, stewardship of antibiotics, and rapid testing.⁶²

In view of the federal government and taxpayers as critical investors in addressing future public health emergencies, variation within their investment portfolio with balanced allotments for both prevention as well as treatment independent of non-pharmacologic measures will be necessary to ensure a truly effective response. Nevertheless, the federal government should continue to support through direct funding and resources across agencies the development of novel medical countermeasures in the form of therapeutics and vaccines. However, the success of these efforts should not be hinged on the authorization or approval of these products, but rather on whether the federal government can be an effective steward of taxpayer funds and ensure equitable access to truly effective and safe health technologies.

⁶² “Stemming the Superbug Tide: Just A Few Dollars More,” OECD Health Policy Series (OECD, November 7, 2018), <https://www.oecd.org/health/stemming-the-superbug-tide-9789264307599-en.htm>.