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Hearing on “The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight”

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Chairman Pallone, Ranking Member Rodgers, and distinguished members of the subcommittee, thank you for the invitation to testify today. My name is Reshma Ramachandran. I am a physician and researcher in the National Clinician Scholars Program at Yale School of Medicine. I also lead the Doctors for America Food and Drug Administration (FDA) Task Force, which is an independent group of physicians working together to support and strengthen the FDA towards ensuring meaningful clinical outcomes for our patients. I am honored to testify before you today. My remarks reflect my own views and not that of my employers nor the organizations I work with.

As a practicing physician, FDA approval signals that the agency has undertaken a rigorous review process to ensure that the benefits of an approved treatment outweigh its risks such that it can be prescribed safely by myself and my colleagues to our patients. However, continued erosion of FDA’s regulatory standards that ultimately led to the controversial approval of aducanumab for Alzheimer’s disease has shaken our trust in the agency, overshadowing its laudable work during ongoing COVID-19 pandemic that has enabled the authorization and approval of multiple effective and safe vaccines, therapies, and diagnostics. Nevertheless, with the impending reauthorization of the Prescription Drug User Fee Authorization Act, there is an opportunity for Congress to recenter the FDA’s role around its core mission to protect patients above all else.

In my written testimony below, I discuss only a portion of the many important legislative proposals before the subcommittee as follows:

1) Resetting the Balance Between Earlier Access and Ensuring Confirmation of Efficacy and Safety of Accelerated Approval Drugs

The accelerated approval pathway is intended to provide our patients with earlier access to potentially promising new treatments based on the success of a surrogate endpoint thought to be predictive of clinical benefit.¹ In exchange for this ability to market drugs earlier to patients as granted under the accelerated approval pathway, drug manufacturers are required to complete additional postapproval studies to confirm that the drug does indeed demonstrate the predicted clinical benefit. Should the confirmatory trials fail to do so or the manufacturer fail to initiate required postapproval studies in a timely manner or initiate them at all, the FDA can withdraw marketing authorization the accelerated approval treatment. However, the lack of adequate oversight and enforcement authority by the FDA has allowed industry sponsors to continue to market these drugs and make them available for patients despite negative confirmatory trials or delays in conducting required postapproval studies.

A recent analysis by the medical journal, *The BMJ*, found that nearly half (n=112) of the 253 drugs approved through the accelerated approval pathway between 1992 and 2020 have not been confirmed to be clinically effective.² Of these, one-fifth (n=24) have been on the market for more than five years. Only sixteen of all accelerated approval drugs from this period were withdrawn, either due to a lack of efficacy or because the confirmatory trials were never conducted.

The application of accelerated approval for specific drug classes has also changed over time. Although accelerated approval was initially used to expedite approval of treatments for HIV/AIDS in the 1990s, the majority of drugs receiving accelerated approval over the last decade has been cancer drugs.³ Ten of the 35 oncology indications approved through the accelerated approval pathway in the last six years were considered “dangling” accelerated approvals – that is, accelerated approval drugs where their confirmatory trials had failed to confirm clinical benefit, but continued to remain on the market, available for patients to use and clinicians to prescribe.⁴ Four of these dangling approvals were voluntarily withdrawn by industry sponsors. The remaining six were discussed by the FDA Oncologic Drugs Advisory Committee (ODAC) in April 2021 when FDA convened this group of external advisors to review the data from the confirmatory postapproval studies and vote on whether to maintain marketing authorization for these drugs, despite failing to demonstrate clinical benefit. Ultimately, ODAC voted in favor of maintaining approval of four of the six indications.⁵

FDA could decide to make a regulatory decision that differs from that of their advisory committees. However, this rarely occurs.⁶ In fact, one study specifically examining FDA approval decisions of oncology drugs found that discordance between the FDA’s regulatory decision and ODAC vote only occurs when the agency decides to further expand access to a cancer drug with no prior occurrence of the FDA overruling ODAC’s vote to limit access to oncology treatment.⁷ As experts have noted, the FDA’s decision to uphold the ODAC’s vote to maintain a majority of the dangling acceleration approvals could have ramifications on future accelerated approvals.³ Industry sponsors may become less likely to voluntarily withdraw their drugs even when their postapproval studies fail to confirm clinical benefit as ODAC’s recommendations could signal to sponsors the likelihood of their accelerated approval drugs remaining on the market despite negative confirmatory trials.

Moreover, such a vote may have signaled to industry sponsors the acceptance of poorly designed postapproval studies. Prior studies have shown that such required confirmatory trials for accelerated approval drugs are small and short, with many lacking randomization, blinding, or concurrent controls⁸ – key characteristics of well-designed clinical trials. Additionally, postapproval studies for drugs granted accelerated approval continue to rely on surrogate endpoints despite the intention for the trial to confirm clinical benefit and their initial approval having been based on a surrogate endpoint. Researchers examining cancer drugs approved by the FDA between 1992 and 2017 through the accelerated approval pathway found that over 40% used a surrogate endpoint as the basis for confirming benefit. Of these, nearly one-half used the same surrogate endpoint as the associated preapproval pivotal clinical trial.⁹

The harms of allowing manufacturers to market drugs that have failed to demonstrate clinical benefits for both patients and clinicians are manifold. First, clinicians may

unknowingly be prescribing treatments of limited or no clinically meaningful benefit to patients. For those conditions where they may be an available and proven alternative including a non-pharmacological option, this may create an unfortunate opportunity cost for patients, both therapeutically and financially. Second, payers may be required to provide coverage for such treatments, causing patients prescribed these drugs to incur higher out-of-pocket payments and other beneficiaries to potentially pay higher premiums.¹⁰

Without a doubt, the controversial decision by the FDA to approve aducanumab for Alzheimer's disease under the accelerated approval pathway has led to significant scrutiny of this expedited review pathway. After a near unanimous vote by their independent advisory committee against aducanumab's approval, FDA allowed the sponsor to pursue accelerated approval on the basis of a surrogate marker – that is, the change in MRI findings of brain beta-amyloid, a protein hypothesized to be predictive of cognitive benefit.¹¹ While both pivotal trials showed a significant decrease in beta-amyloid, numerous studies have found that beta-amyloid changes do not predict clinical benefit in terms of reversing or slowing cognitive decline for patients. In fact, a review of data from more than two dozen clinical trials published in *Nature* examining beta-amyloid did not find any association with slowing or reversing the progression of Alzheimer's disease.¹² At the independent advisory committee meeting noted earlier, a senior FDA official even stated that they were not going to be using beta-amyloid “as a surrogate for efficacy.”¹³

Upon approval, even FDA's biostatisticians noted that there was no evidence of association between the beta-amyloid changes and cognitive or functional changes.¹¹ Moreover, this surrogate marker was evaluated in only approximately a third of trial participants in both pivotal clinical trials.¹⁴ The unusual nature of this approval has not only prompted public outcry, but also multiple investigations including by this Committee in collaboration with the House Committee on Oversight and Reform¹⁵ as well as by the Office of the Inspector General within the Department of Health and Human Services (HHS) specifically on how FDA implements accelerated approval.¹⁶

In the wake of aducanumab's approval, FDA officials and legislators have since committed to reforming the accelerated approval pathway. Just last month, Dr. Robert Califf, the recently confirmed FDA Commissioner had publicly committed to Senator Ron Wyden (D-OR) that he view it as a high priority for the FDA to “ensure that drug developers granted accelerated approval conduct confirmatory trials that demonstrate that the balance of clinical benefit and risk for intended use of the drug is positive” and that these trials are “done in a timely manner.”¹⁷

Policymakers within this committee from both sides of the aisle have introduced legislation to recenter accelerated approval to ensure a balance between timely access to new treatments for patients as well as oversight to ensure patients that these treatments are truly safe and beneficial.^{18,19} Importantly, provisions within these introduced bills would allow for FDA to review and approve the design of required postapproval studies within a certain period of time that will help prevent against any delays in initiating confirmatory trials. Additionally, the bills include provisions that would allow FDA to further expedite withdrawal of accelerated approval drugs that fail their confirmatory postapproval studies or for which their postapproval studies are either delayed or not conducted. This would prevent unproven accelerated approval drugs from remaining on the market, thereby curbing any potential clinical or financial harms for patients.

Besides these important provisions, the Accelerated Approval Integrity Act (H.R. 6963) includes several additional safeguards necessary to balance faster access to potentially promising treatments and prompt confirmation of their clinical benefit. They include:

- collaboration between the FDA and the sponsor to ensure well-designed confirmatory studies with oversight of the study protocol and study completion deadline;
- submission of progress reports on the status of such postapproval studies to the FDA to ensure timely completion of confirmatory trials and assistance should there be any barriers to their completion (similar to what other national regulatory authorities in other countries such as Europe, Australia, United Kingdom, and others already require for similar approval pathways²⁰);
- clear criteria for the FDA to employ in making decisions to withdraw an accelerated approval drug from the market;
- expediency in the process for FDA to withdraw an accelerated approval drug to prevent against unnecessarily prolonged marketing of unproven treatments to patients;
- automatic expiration within a specified period of time (1 year following the deadline established between the FDA and sponsor for completion of confirmatory studies; 5 years following initial accelerated approval of the drug) – again, similar to what other national regulatory authorities in other countries such as Europe, Australia, United Kingdom, and others already require for similar approval pathways²⁰; and
- enforcement authority in the form of monetary penalties should sponsors fail to submit their required, routine reports on progress in completing their postapproval studies or fail to conduct such studies with due diligence.

There are also additional opportunities to further strengthen this legislation so that patients and clinicians have greater certainty of the clinical effectiveness and safety of accelerated approval treatments across the following areas:

a. Improving the Design of Required Post-Approval Studies to Truly Confirm Clinical Benefit

- **Legislation should explicitly state that postapproval studies should use clinical endpoints, not surrogate endpoints. These endpoints should be prespecified explicitly within the agreement between the FDA and the drug sponsor.**
 - Under the accelerated approval pathway, manufacturers must confirm the clinical benefit of treatments initially approved based on surrogate endpoints thought to be predictive of clinical benefit in exchange for earlier marketing authorization to patients. **In order to establish that the drug has a clinically meaningful positive outcome, sponsors should use clinical endpoints, not surrogate endpoints.** Today, a significant proportion of accelerated approval drugs continue to use surrogate endpoints as the basis for confirming clinical benefit.⁹
 - There may be “validated” surrogate endpoints that the FDA has determined after robust evaluation to be predictive of meaningful clinical outcomes. **However, at the very minimum, use of surrogate endpoints for confirmatory clinical trials**

that mirror those used for accelerated approval should not be allowed.

Moreover, any surrogate endpoints used within postapproval studies should be those that are validated by the FDA. As noted earlier, nearly one-half of those cancer drugs that used surrogate endpoints to confirm clinical benefit used the *same* surrogate endpoint as in the preapproval pivotal clinical trial that led to their accelerated approval.⁹

- **FDA should draft guidance for sponsors for public comment regarding what classes of drugs or therapeutic areas for which initiating postapproval studies prior to approval may not be possible.**

- It is understandable that FDA may need flexibility in requiring postapproval studies to be underway prior to approving a drug under accelerated approval. **However, FDA should also draft guidance for sponsors for public comment regarding what classes of drugs and therapeutic areas for which initiating postapproval studies prior to approval may not be possible.** Not only would this offer anticipatory guidance for sponsors on the drugs and diseases that the FDA will be mandating timely initiation of postapproval studies, but will also allow for public accountability by patients, clinicians, payers, and policymakers of both the agency and sponsors in implementing such requirements.

- **FDA should ensure that postapproval studies abide by existing clinical trial reporting requirements.**

- Under the Food and Drug Administration Amendments Act (FDAAA) of 2007, sponsors are required to register clinical trials and report trial results information onto ClinicalTrials.gov.²¹ **This should be reinforced specifically related to required postapproval studies for accelerated approval drugs in stating that any proposed legislation does not obviate registration and reporting commitments for such trials under FDAAA.**

b. Clarifying Use of Automatic Expiration as a Necessary Safeguard and Backstop to Prevent Patients from Receiving Unproven Treatments

- **Aligning the deadlines for automatic expiration with previously demonstrated durations for other accelerated approval drugs.**

- The backstop of “automatic expiration” is a necessary safeguard and backstop to ensure that both patients and clinicians are not left with indefinite, continued uncertainty of the clinical benefit of an accelerated approval drug. **Nevertheless, the time period until which automatic expiration would take effect of five years as currently included in legislation should be shortened to two years after the date on which the product is approved should the required postapproval study fail to verify and describe the predicted clinical benefit or be conducted.** In examining drugs granted accelerated approval between 2009 and 2018, we found that the median postapproval study duration was 17 months.²²

We also determined that the median time from approval to FDA-established postapproval trial results reporting deadlines for sponsors was 50 months – a median of 30 months more than the postapproval trial durations. Thus, five years may be an excessive deadline for completing confirmatory trials, particularly if FDA does require that postapproval studies are underway upon granting accelerated approval.

- Nevertheless, this concern around the length of time an accelerated approval drug remains available for patients despite continued clinical uncertainty could be mitigated by the FDA setting more prompt trial completion dates in their agreements with sponsors. However, in the case of aducanumab, the FDA granted the manufacturer 9 years to complete the required confirmatory trial, which was an outlier as illustrated in the aforementioned study. Such a prolonged deadline may have set an unfortunate precedent for future accelerated approval treatments.

c. Strengthening FDA's Enforcement Capability to Ensure that Post-Approval Studies are Well-Designed and Completed in a Timely Manner

- The proposed legislation includes enforcement mechanisms to ensure that sponsors of accelerated approval drugs submit required reports of their progress in completing postapproval studies and conduct these required studies with due diligence. **However, the civil monetary penalties proposed to be levied against sponsors who fail to submit such reports or conduct postapproval studies as required could be increased to match those under the FDAAA (Section 303(f)(3)), which authorizes FDA to levy civil monetary penalties of “not more than \$10,000 for each day that the violation continued after such period until the violation is corrected.”**²³

d. Making Transparent FDA's Oversight of Accelerated Approval Treatments

- **FDA should make submitted progress reports of postapproval studies publicly available on the agency's website.**
 - As the drug would have been approved through the accelerated approval pathway and therefore, made available for patients in addition to the fact that the required postapproval studies are outlined within the publicly available FDA approval letter and action package, there should not be any commercially confidential information in these reports that would prevent FDA from making progress reports of such studies publicly available.
- **FDA should promptly release results from completed postapproval studies.**
 - As these accelerated approval treatments are already available for patients, it will be critical to know from a clinical care perspective what the findings of such postapproval studies are. Should the studies demonstrate no clinical benefit or benefit only in a more narrow patient population than those the drug has been indicated for, prompt availability of these results would help inform clinical care as well as practice guidelines. This may also help mitigate any potential

therapeutic or financial harms in preventing the use or prescribing of treatments where postapproval studies are found to be negative.

- **FDA should create public and complete database of all required postapproval studies.**
 - Under this legislation, the FDA could also be tasked to update its existing searchable, public database of all postmarketing requirements to be managed in perpetuity. Importantly, the database should not remove such postapproval studies from the database once the requirement is satisfied, as currently occurs now. It should also explicitly state what the status of the required postapproval study, linked to the trial registration and results information on ClinicalTrials.gov. This information is already available to do the FDA and increasing transparency of postapproval studies would greatly benefit patients, clinicians, and researchers in determining status of individual required trials as well as such studies over time.
- **FDA should clearly state what the regulatory review process is for accelerated approval drug and other associated information regarding pivotal as well as postapproval studies within drug labels and action packages.**
 - To make clear to both clinicians and patients the evidentiary underpinning approving a treatment through accelerated approval, the FDA drug label specifically state that the product was approved based on a biomarker thought to be predictive of clinical benefit in addition to stating that the “product is subject to postmarketing studies to verify clinical benefit.” Once the drug is converted from accelerated to standard approval based on positive postapproval studies, the label should be revised to clearly state what the confirmatory trial evidence is for clinical benefit.
 - Moreover, documentation regarding all drug approvals within the drug label and action package should include the National Clinical Trial (NCT) number for both preapproval and postapproval studies. Former FDA Commissioner Scott Gottlieb had announced a plan to do this,²⁴ but it has not yet been realized even though it would be a minor, but impactful fix.

2) Ensuring that FDA-Approved Treatments Are Tested in Trial Participants Representative of Patients Indicated

The controversial approval of the Alzheimer’s disease treatment, aducanumab has also raised attention on the longstanding, neglected issue of inadequate representation of patients within clinical trials. Not only did Biogen, the manufacturer of aducanumab fail to enroll participants representative of the Medicare beneficiary population mostly likely to be prescribed this medication within its pivotal clinical trials, it also neglected to enroll participants reflective of marginalized patient populations with a disproportionate and likely, underestimated burden of Alzheimer’s disease.²⁵ Only 0.6% (19 individuals) of participants identified as Black, 3% as Hispanic, 0.03% (1 person) as American Indian or Alaska Native, and 0.03% as Native Hawaiian

or Pacific Islander.¹⁴ Of the 9% identified as Asian, 94% were recruited in Asia. Older Black and Hispanic adults are estimated to have Alzheimer's disease incidence up to twice or 1.5 times the rates in older White people, respectively.²⁶ Despite this, Biogen reported that only 6 Black and less than two dozen Hispanic people were randomized to the treatment dose approved by the FDA.¹⁴

Well before aducanumab, clinical trials have had limited representation from non-White race and ethnic patient populations leading to continued uncertainty among patient and clinicians of the effect of treatments across patient populations.^{27,28} The FDA has proposed and taken steps to address these disparities in clinical trial enrollment, namely in 1) improving the completeness and quality of demographic subpopulation data; 2) identifying barriers to demographic subpopulation participation in clinical trials and employing strategies to encourage greater participation; and 3) making demographic subpopulation data more publicly available and transparent.²⁹ However, these measures have continue to fall short in moving sponsors to enroll participants of color within clinical trials. A recently published study examined data from FDA's Drug Trials Snapshots, a publicly available webpage with demographic information of pivotal trial participants for FDA-approved new molecular entities and original biologics. Although the FDA had required every pivotal trial for these drugs to include reporting of clinical benefits and risks by race, the authors found that only 20% provided such results reporting for Black patients – a figure that did not improve over the eight-year period assessed.³⁰

Industry sponsors are now echoing longstanding calls to increase representation in clinical trials, issuing public statements on the importance of such measures. In response to this ongoing concern that was further brought to light with the recent approval of aducanumab, policymakers within this committee have introduced legislation to increase representation in clinical trials including the Diverse and Equitable Participation in Clinical Trials (DEPICT) Act (H.R. 6584)³¹ and the Diversifying Investigations Via Equitable Research Studies for Everyone (DIVERSE) Act (H.R. 5030).³²

Under the DEPICT Act, the FDA would require sponsors to take specific, enforceable actions to increase representation in clinical trials including by:

- requiring sponsors to submit as part of their applications for investigational use of drugs and devices informational on the estimated prevalence for a disease/condition the investigational drug or device is intended for, the sponsor's targets for demographic subpopulation enrollment and rationale, and "diversity action plans" for how sponsors intend to meet their intended enrollment targets;
- empowering the FDA with the authority to mandate representative postapproval studies should the sponsor fail to meet their subpopulation enrollment targets;
- allowing sponsors to receive a waiver from the FDA to not complete representative postapproval studies should they provide "sufficient justification" for why enrollment targets cannot be reached; and
- requiring the FDA to publish annual reports of progress in increasing representation in clinical trials.

Beyond the FDA, the legislation would also task the National Institutes of Health (NIH) to engage with stakeholders within “underserved communities to facilitate the inclusion of underrepresented minorities in clinical trials.” Additionally, the bill would allocate grants to community health centers, often serving proportionally greater patients of color compared to other clinics, to allow them to participate in clinical trials.

Such proposed policies are long overdue towards enabling greater representation in clinical trials. Opponents to the legislation have stated that requiring sponsors to provide enrollment targets across demographic subpopulations as well as their justification, and plans to meet such enrollment targets may be too onerous for both sponsors and the FDA. However, sponsors already provide detailed information regarding their clinical trials upon registration as required under FDAAA to ClinicalTrials.gov including their overall enrollment targets, primary and secondary outcomes, clinical trial locations, and more.³³ This would be simply another necessary field for sponsors to provide to the FDA when pursuing drug or device development. The penalty for sponsors not providing such information is simply that the FDA would then require them to pursue postapproval studies examining efficacy and safety among different subpopulations. Within the legislation, FDA also has further flexibility in waiving such postapproval studies should the sponsor pursue a waiver, justifying why achieving enrollment targets may not be feasible. **To ensure that these waivers will not be pursued haphazardly by sponsors claiming to be unable to enroll diverse populations, FDA should issue guidance to clearly outline under what circumstances waiver applications would be appropriate and considered by the agency.**

There may be instances where epidemiological data regarding the prevalence of disease or condition may not be available and for which the gaps in data across subpopulations may be exacerbated by structural racism and other factors contributing to underdiagnosis among these marginalized groups. **In these situations, the FDA should set a floor for enrollment targets for clinical trials in calling for representation to reflect available national demographic subpopulation data.** Furthermore, **the legislation should also provide an opportunity for the FDA to partner with other agencies including the Centers for Disease Control and Prevention (CDC) and CMS in utilizing existing disease or condition demographic subpopulation data and to collect further data disaggregated by age, sex, and race and ethnicity.** Such data would inform sponsor’s enrollment targets toward ensuring a more representative trial that mirrors that patient population who would be indicated to receive the drug or device upon FDA approval. Moreover, FDA could also include the data required under the DEPICT Act to be collected and reported for their “Annual Report on Progress to Increase Diversity in Clinical Trials and Studies” as part of annual Prescription Drug User Fee Act performance metrics.

Provisions within the DEPICT Act also allow for the use of real-world evidence to fulfill required postapproval trials. **However, the legislation should specify this further to state that such real-world evidence would be allowed solely for examining the safety and efficacy of a drug or device for which the FDA has determined that reaching enrollment targets may be difficult.** As currently written, it may be interpreted that the FDA may allow the use of real-

world evidence for any required postapproval study. As detailed in a later portion of this testimony (see Part 3 on H.R. 6000 - Cures 2.0), there are significant limitations to the use of currently available real-world evidence in being unable to feasibly replicate data collected through robust randomized controlled trials.

Other proposed legislation such as the DIVERSE Act would enable essential resources to support education, outreach, and recruitment efforts for clinical trials studying the effect of drugs and devices on diseases with a disproportionate impact on underrepresented populations. Not only would this legislation build on existing infrastructure developed during the ongoing COVID-19 pandemic to collect data including on demographics and other structural determinants of health, but it would require the FDA to issue guidance on conducting decentralized trials with “meaningful demographic diversity.” Additionally, the legislation would further minimize barriers for lower-income patients, including those from communities of color to participate in clinical trials by relieving other incurred costs including for transportation or childcare.

Given that progress to date on inclusion of diverse populations into clinical trials has stalled despite FDA taking various non-enforceable measures including public reporting demographic subpopulation data of pivotal clinical trials, it is unlikely that trial sponsors will take action of their own accord without FDA oversight and enforcement capability. Thus, granting FDA the authority to require representation within clinical trials will be critical to ensuring the efficacy and safety of treatments across various demographic subpopulations are known to patients and clinicians.

3) Re-evaluating the Promises and Pitfalls of Cures 2.0

Like its predecessor, Cures 2.0 (H.R. 6000)³⁴ is a large legislative package containing a broad range of provisions, including a number of regulatory and financial incentives along the drug development value chain. There is no doubt that certain bill provisions would be beneficial for patients and clinicians including further allocation of funding for the study of “long COVID” or for educational awareness campaigns on the safety and importance of vaccines. However, alongside these positive proposals, Cures 2.0 also includes other provisions that would further erode evidentiary standards for FDA regulatory review, leading to continued uncertainty over whether approved drug products are truly clinically beneficial for patients. Other additional provisions would strip CMS of its discretion to review clinical trial evidence in making informed coverage and reimbursement decisions.

Specific provisions within Cures 2.0 that Congress should reconsider are:

a. Offering a Financial Incentive for Unproven Antimicrobials (PASTEUR Act)

Under the Pioneering Antimicrobial Subscriptions To End Up surging Resistance (PASTEUR) Act, manufacturers of newly-approved antimicrobials are eligible to receive as much as \$3 billion payments disbursed as regular installments over a five to 10 year contract period for an individual drug. 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.

From these payment installations, the total cost of doses used by public payers (i.e. Medicare, Medicaid, Veterans Affairs, Indian Health Service) would be deducted. Separately and unrelated to those drugs that receive financial incentives, a federal grant program would be established through the CDC to support hospital and inpatient efforts around antimicrobial stewardship, prioritizing those hospitals in rural areas, critical access hospitals, those serving tribal populations, and safety-net hospitals. Under the PASTEUR Act, additional resources are allocated to collect and publicly report data on antibiotic use and resistance.

Although PASTEUR seemingly attempts to delink the price of newly approved antimicrobial as well as the number of doses administered from the drug's research and development costs, the multi-billion financial incentives awarded would fail to address the fundamental flaw of these new drugs. As a result of eroding evidentiary standards for approval, the FDA has approved new antimicrobials of increasingly uncertain benefit to patients. Prior characterization of pivotal clinical trials for FDA-approved antimicrobials (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.³⁵

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 allow for intervention drugs to be less effective compared with older, effective antimicrobials by a prespecified margin.³⁶ 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. This suggests that these financial incentives may be misaligned, rewarding manufacturers of QIDPs for unclear effectiveness against resistant pathogens, despite receiving this special designation intended for this purpose.

Entering into such a "subscription" contract does not preclude other financial incentives. For instance, in 2019, the Centers for Medicare and Medicaid Services implemented increased new technology add-on payments and the removal of "substantial clinical improvement" criteria.³⁷ Therefore, should Cures 2.0 pass with the PASTEUR Act included, sponsors of new antimicrobial treatments would be eligible to not only receive \$3-4 billion per drug, but also additional new technology add-on payments. This may set up 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 lump sum payments, manufacturers of these drug products would also be eligible to receive private payer reimbursement separately as additional revenue, potentially incentivizing the overuse or misuse of these new treatments.

Such financial incentives that may prompt health systems and/or hospitals to inappropriately prescribe novel antimicrobials encompassed by the PASTEUR Act would not be offset by the stewardship provisions in the bill. As written, the legislation does not tie stewardship and surveillance efforts to antimicrobials for which a "subscription" contract has been issued, making

it unclear how these treatments will be conserved in order to prevent further antimicrobial resistance.

Rather than awarding costly financial incentives for unproven antimicrobial treatments, FDA should have further discretion in granting QIDP and other expedited review pathway designations. Instead, the agency should require sponsors of antimicrobial drug candidates to conduct pivotal clinical trials in clinically relevant patient populations including those are typically excluded and that are designed to prove superiority against known, effective alternatives. Further resources should instead be allocated to address the upstream scientific bottlenecks to novel antimicrobial drug development and other alternatives such as vaccines to prevent against infections.

a. Removing CMS's Discretion in Making Coverage Decisions of Breakthrough Devices

Last year, CMS rescinded the rule regarding coverage of breakthrough devices finalized under the prior administration establishing the Medicare Coverage of Innovative Technology (MCIT) pathway.³⁸ Under the MCIT pathway, CMS would guarantee up to four years of coverage for FDA-designated and approved breakthrough devices. For those breakthrough devices where reimbursement rates are short of the acquisition costs, CMS would also grant new technology add-on payments, no longer considering whether the device offers substantial improvement over existing alternatives as the agency had been doing previously. Within Cures 2.0, legislators are seeking to reinstate the MCIT Pathway, codifying the removal of CMS's discretion in making coverage decisions for breakthrough devices.

Prior research examining the burgeoning Breakthrough Devices Program within the FDA found that within its first three years, high-risk breakthrough devices were approved based on trials using surrogate, short-term endpoints not clearly associated with meaningful clinical benefits.³⁹ Researchers also found that FDA approved some breakthrough devices without consideration of efficacy, solely relying on safety data. FDA also authorized other devices with known significant safety risks including patient death. One example they noted was that of an implantable lung valve system approved for treatment of severe pulmonary emphysema, but caused pneumothorax (i.e. lung collapse) in over a quarter of patients treated compared to none who received the usual standard of care.³⁹ Not only would this breakthrough device receive additional reimbursement from CMS as the agency no longer considers where it offers a substantial improvement compared to other alternatives, but under the MCIT pathway, CMS would be required to provide four years of coverage. Given that use of these devices is coupled with higher reimbursement, health systems and hospitals may be incentivized to prescribe these devices of uncertain efficacy and safety.

Moreover, FDA has had difficulty ensuring the timely completion of postapproval studies to confirm the efficacy and safety of such devices with less than 20% of required studies being completed within three to five years after FDA approval.³⁹ Under the MCIT Pathway, CMS would not require companies to complete such postapproval studies including those that are required as a condition of coverage.³⁸ Moreover, the costs of coverage under the MCIT Pathway are substantial with estimated Medicare spending on MCIT coverage for two eligible

breakthrough devices increasing from \$300 million in 2021 to more than \$2 billion for 14 eligible breakthrough devices. However, as researchers have pointed out, this is likely an underestimate given that over 400 devices have been designated as a breakthrough devices. Should the MCIT Pathway be instated through Cures 2.0, this would place significant financial strain on the Medicare program, possibly leading to other downstream consequences to patients in raising their health insurance premiums.

Congress must not remove CMS’s discretion that protect patients, preventing them from receiving unproven and potentially unsafe breakthrough devices. Instead, legislators should require the FDA to revisit how it grants breakthrough device designation and apply more stringent conditions for this designation including mandating that sponsors meet prespecified efficacy and safety endpoints as a condition of approval. Additionally, FDA should mandate that sponsors complete postapproval efficacy and safety studies within specific periods of times. Should they fail to do so or make progress, their marketing authorization should be rescinded. Instead of guaranteeing blanket coverage for breakthrough devices of unproven benefit to patients, CMS should coordinate with FDA to incentivize completion of postapproval studies through the Coverage with Evidence Development program. Finally, CMS should apply prior discretion in awarding additional reimbursement for such devices by again applying the criteria that in order to be eligible for these additional payments, eligible breakthrough devices should demonstrate substantial improvement over other existing alternatives.

b. Inappropriately Allowing for Real-World Evidence as Adequate for Fulfilling Required Postapproval Study Requirements for Accelerated Approval Drugs

Under the 21st Century Cures Act, FDA has been examining the quality and acceptability of real world evidence (RWE) for regulatory decision-making. Cures 2.0 similarly includes such proposals for HHS to issue guidance and reports around the use of real-world evidence. The bill also would create a Real World Evidence Task Force including the HHS Secretary, CMS Administrator, FDA Commissioner, NIH Director, additional federal representatives, and private sector representatives. **Such a Task Force should also include independent representatives without financial ties to the pharmaceutical or biotechnology industries including consumer advocacy organizations and other public sector stakeholders as well as academic experts.**

Cures 2.0 also allows for RWE to be used to fulfill required postapproval studies for accelerated approval drugs. However, allowing for the use of such RWE sources may be premature and could further contribute to the clinical uncertainty of such treatments. My colleagues examined whether it would be feasible to use such RWE to emulate FDA-required postapproval confirmatory trials for all new drugs that received accelerated approval between 2009 and 2018.⁴⁰ Of the 50 confirmatory trials required by the FDA for these drugs, none could be feasibly emulated using currently available RWE sources in terms of medical claims or structured electronic health record data. This suggests that currently available RWE sources and observational methods are unlikely to replace postapproval confirmatory trial requirements as has been proposed. Other research has raised questions on the feasibility of using real world evidence to support certain regulatory decisions. One study found that only 15% of US-based

clinical trials published in high-impact medical journals could be feasibly replicated using the RWE sources of administrative claims or electronic health records data.⁴¹

When RWE has been used to emulate randomized controlled trials, it has underscored several complexities in designing such studies. One recently published study used medical claims data to emulate a randomized controlled trial examining the cardiovascular risk of prostate cancer treatment.⁴² Only one-quarter of real-life patients using the tested treatments met the randomized controlled trial's narrow inclusion and exclusion criteria. Additionally, the study authors were unable to use RWE to precisely emulate the endpoints examined within the randomized-controlled trial. Other considerations for designing such studies include the ability to assess follow-up with available RWE as well as appropriate statistical analyses as such data is not as well controlled as in traditional clinical trials.

Already, the FDA has been taking steps to carefully understand these complexities to identify appropriate study designs and characteristics for using RWE and the agency should invest in further research with public stakeholder engagement to clearly outline appropriate use conditions for RWE in making regulatory decisions. This should be done ahead of further statutory mandates that may preclude the agency's scientific and public health discretion in determine where RWE has been shown to benefit patients. **Moreover, just as sponsors of clinical trials are required under law to publicly register their studies, submit trial protocols, and report results information on ClinicalTrials.gov,^{33(p11)} sponsors of RWE studies should also be mandated to do the same – a provision that could be included as part of the Cures 2.0 package.**

4) Ensuring the American Public a Fair Return on their Public Investment Through ARPA-H

Finally, legislators have proposed establishing the Advanced Research Projects Agency for Health (ARPA-H)⁴³, modeled after the more flexible, nimble approach adopted by the Defense Advanced Research Projects Agency (DARPA) within the Department of Defense. The focus of this agency would be take a high-risk, high-reward approach to innovation to develop “high-need cures” in collaboration with other agencies including NIH, CMS, FDA, Biomedical Advanced Research and Development Authority (BARDA), National Center for Advancing Translational Sciences (NCATS), and more. Building on the success of significant public investment, both in terms of funding and resources, that have led to the successful, rapid development of novel COVID-19 vaccines, therapeutics, and diagnostics, ARPA-H would similarly allocate funding and other resources to addressing diseases of unmet medical need and burden among the American population.

Public investment has long since played a catalytic role in enabling transformative innovation. Studies have shown that NIH has contributed to the discovery and development of all 356 new drugs approved by the FDA between 2010 and 2019.⁴⁴ However, this figure is likely a significant underestimate of taxpayer contribution given the number of agencies beyond NIH engaged in drug development. Moreover, researchers have also found that public investment plays an outsized role in funding truly transformative health technology innovation.⁴⁵ Additionally, the

public sector is increasingly funding late stage clinical trials, particularly for more novel therapies including biologics and gene therapies.^{46,47,48}

Despite such public investment, access and affordability have largely been an afterthought in this innovation model. Today, nearly 40% of adults report difficulty affording the medications we prescribe.⁴⁹ Even with COVID-19 mRNA vaccines and therapeutics where the federal government contributed funding and resources for the discovery, development, and manufacturing of these products, procurement of doses were at prices set well above marginal cost leading to record-breaking profits for manufacturers.⁵⁰ Not only do manufacturers have control of the price for these publicly-funded health technologies, but also the supply, which has contributed to significant disparities in access that has only prolonged the ongoing pandemic.^{51,52} In the case of the COVID-19 mRNA vaccine manufactured by Moderna, the U.S. government financed nearly 100% of its development and continues to subsidize ongoing R&D of variant-specific and other vaccines that will be marketed by the company. The ongoing patent dispute between the NIH and Moderna highlights yet another failure with this innovation model of doling out blank checks to private and public sector partners such as universities without conditions to enable access and affordability, even during a public health emergency.⁵³

Without safeguards in establishing this new agency, ARPA-H will only repeat mistakes of the past in forcing taxpayers to pay multiple times to access the results of publicly-funded research.

Legislation creating this new agency must incorporate access and affordability as part of ARPA-H's innovation model, not as an afterthought when it may be too late. Such

safeguards should include:

- a publicly-available portal of all funding and resources allocated through ARPA-H including of clinical trial costs;
- adherence to NIH's recently adopted data-sharing policy to promote open science approaches and collaboration to more effectively steward public resources and prevent against unnecessary replication;
- timely release of funded trial registration and results information including through ClinicalTrials.gov as mandated under FDAAA;
- use of non-exclusive licenses for all publicly-funded health technologies to enable competition to lower prices and enable adequate supply;
- allocation of funds for end-to-end public discovery, development, manufacturing, and distribution of health technologies for therapeutic areas of unmet need and not viewed as commercially promises by the private sector such as antimicrobials or rare diseases; and
- investment in building a robust pipeline of researchers from communities of color.

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