Attachment—Additional Questions for the Record

Subcommittee on Health
Hearing on
" The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight "
March 17, 2022

Reshma Ramachandran, M.D., Chair, Doctors for America FDA Task Force, Physician-Fellow, Yale National Clinician Scholars Program, Yale School of Medicine

The Honorable Debbie Dingell (D-MI)

Thank you, Representative Dingell for these thoughtful questions. Please find my responses below. I would also be happy to meet with your office to discuss these questions and my responses further.

1. *Dr. Ramachandran, it was good to see the thoughtful feedback on Cures 2.0 that you put into your written testimony. As we consider Cures 2.0, what more can this Committee do to ensure we are preserving those high standards of evidence at FDA?*

   First, Title III of Cures 2.0 includes several provisions focused on the FDA with an emphasis on efforts to expedite regulatory review of novel health technologies where the Committee could further ensure preservation of rigorous evidentiary standards at FDA as follows:

   - **Section 302 ("Grants for Novel Trial Designs and Other Innovations in Drug Development")** – Under this section, the FDA would award grants for the incorporation of novel trial designs and other innovative mechanisms, prioritizing the use of digital health technologies and real-world evidence, as well as the collection of patience experience data into clinical protocols and applications for drugs. While pilot testing of such approaches is necessary to ascertain feasibility as well as the benefits and harms in doing so, FDA should enable public availability of the evidentiary data generated to allow for independent review outside of the agency. **At a minimum, FDA should release a briefing document with summary results and their interpretation of the data as they typically do for other drugs and devices to allow for further validation of these novel trial designs and innovative mechanisms by independent experts and to inform the feasibility of using these methods for regulatory decision-making. However, FDA could also convene a public stakeholder meeting to discuss the use of these novel mechanisms to elicit further feedback on the feasibility of such approaches and where there might be opportunities for enhancing such approaches to ensure robust evidentiary standards. Moreover, FDA in awarding such grants for use of incorporating complex, adaptive and other trial designs into clinical protocols could also enable public access to how**

these funds are used, offering insight on how such approaches affect clinical trial costs.

- **Section 303 ("FDA Cell and Gene Therapy) and Section 307 ("Accelerating Timeline for Breakthrough and RMAT Designations")** – Under these sections, FDA would be tasked for producing a report to Congress on the landscape of cell and gene therapies and how the agency intends to address any challenges in the regulatory review process of such therapies. Additionally, FDA would also be able to award the designations of "Breakthrough Therapies" or "Regenerative Medicine Advanced Therapies (RMAT)" earlier in the drug development process allowing sponsors to further expedite development as well as review of their candidate drugs and engage with the FDA more closely. **Within these sections, the Committee could request FDA also report on the evidentiary standards for approval as well as their oversight of postapproval studies for these novel therapies. Congress could also go further to ensure rigorous evidentiary standards for approval and also, require postapproval studies to confirm clinical benefit and safety.** Prior research has shown that FDA-approved drugs awarded breakthrough designations are approved more quickly based on weaker evidence including trials that lack randomization, double-blinding, or control groups, use surrogate endpoints, and enroll fewer patients.[1] Our examination of the five novel gene therapies approved by the FDA as of the end of 2020 and had received the RMAT designation were approved more quickly based on even weaker clinical trial evidence than breakthrough therapies – most were approved based on a single, one-arm, open-label trial using surrogate endpoints.[2] However, despite this lack of robust evidence, only for three of the five treatments did FDA require postapproval studies. Thus, the focus of the FDA cannot be solely on expediting approval of these treatments, especially at the expensive of scientific evidence to inform clinical decision making for both patients and clinicians.
- **Section 304 ("Increasing Use of Real World Evidence)** – Under this section, the FDA would be required to issue guidance on the use of real-world evidence (RWE) in evaluating the safety and efficacy of drugs that received breakthrough status, fast track, or accelerated approval designations. FDA would also be required to submit a report to Congress on approaches for using RWE with recommendations for other legislative proposals towards implementing such approaches. This section also establishes a Real World Evidence Task Force under the Department of Health and Human Services that would provide further recommendations. **While these recommendations may further enable FDA to increasingly consider RWE in their regulatory decision-making process, they must be balanced with ensuring that such utilization is robust, can feasibly provide insight on the safety and efficacy of treatment candidates as clinical trials do, and serves as a useful complement to traditional clinical trials.** Moreover, the Real World Evidence Task Force fails to include independent experts and other public stakeholders without ties to industry sponsors – these perspectives for such a task force are imperative for ensuring that FDA and other agencies in HHS carefully consider the use of RWE in regulatory decision-making.
- **Section 309 ("Post-Approval Study Requirements for Accelerated Approval)**

Under this section, required postapproval studies meant to confirm clinical benefit for accelerated approval drugs would be allowed to be based on RWE. However, prior research has shown such confirmatory studies for accelerated approval cannot be feasibly replicated using available RWE in the form of electronic health records and medical claims.[3] Other forms of RWE proposed in the section to be the basis of postapproval studies such as clinical care data repositories and patient registries are insufficient as they are often limited to a single episode of care, often limiting their ability to provide longitudinal data. Moreover, such registries often do not include a control group making it difficult to determine the safety and efficacy of products in comparison to placebo or comparator.[4] Finally, most registries are owned by medical professional societies, but are funded by the pharmaceutical industry and thus, fail to include data on comparative effectiveness to examine treatment effect in relation to the standard of care or other alternatives. **Thus, Congress should amend this section to remove this section or only allow the use of RWE as a complement to traditional clinical trials in confirming that an accelerated approval drug has proven clinical benefit.**

Transparency of FDA's Utilization of New Approaches to Evidence Generation in Regulatory Decision Making

As with its predecessor, the 21st Century Cures Act, Cures 2.0 has a focus around accelerating the development of medical products through use of complex, adaptive trials, decentralized trials, and real-world evidence. While these novel mechanisms hold promise in enhancing the efficiency of evidence generation to more quickly inform regulatory decision-making, Congress must also ensure that safeguards around the use of such approaches are also included in Cures 2.0 and other associated legislation. **These safeguards must be structured to ensure independent evaluation and determination that these methods can provide evidence of meaningful clinical benefit and safety of medical products.** These might include:

- Allowing public access to the data generated through these new approaches;
- Requiring FDA to publish their reviews evaluating data generated through these new approaches that informs regulatory decision-making (as the agency currently does for all new product approvals within their review documents that are publicly posted on the Drugs@FDA database; such reviews are only available for original indication approvals, but not supplemental indications approvals, thus obscuring FDA's rationale for such approval decisions);
- Mandating advance registration of non-traditional studies and results reporting onto ClinicalTrials.gov as required under the FDA Amendments Act of 2007 with similar enforcement penalties should sponsors not comply including warning letters, fines, and legal action;[5]
- Engaging independent experts and other public stakeholders, not solely government officials and industry representatives together to discuss how FDA should incorporate these new mechanisms in their regulatory decision-making; and

- Evaluation by independent experts (e.g. academic partners, National Academy of Medicine, etc.) to study the feasibility of such approaches in informing clinical decision-making.

Independent Assessment of FDA's Expedited Review Pathways

Increasingly, FDA has approved new drugs and devices through expedited review pathways that allow for shorter regulatory review times at the expense of ensuring rigorous evidentiary support. Prior research has shown that pivotal clinical trials supporting such approvals over time are often shorter, enroll fewer patients, and lack characteristics of rigor including randomization, double-blinding, or active comparators.[6] Several expedited review pathways now exist across therapeutic areas allowing for such a tradeoff between speed and certainty of a medical product's safety and efficacy. **Congress could call for an independent review of all of FDA's expedited review pathways to determine whether the pathways are meeting their intended goals of ensuring patients timely access to drugs with meaningful clinical benefit, addressing diseases of unmet need.**

Alignment between the Centers for Medicare and Medicaid Services (CMS) and FDA

Cures 2.0 as written seeks to harmonize decisions made by the FDA on regulatory approval of new medical products with that of the Centers for Medicare and Medicaid Services (CMS) – in the wrong direction. As mentioned previously, drugs and devices have been increasingly approved by the FDA more quickly, but based on lower standards of evidence, heightening uncertainty at the time of approval of their efficacy and safety for patients and clinicians.[6,7] For certain types of drugs, such as those approved under the accelerated approval pathway, FDA requires manufacturers to complete confirmatory postapproval studies demonstrating clinical benefit. For other drugs, FDA can issue postmarketing requirements upon approval that would mandate manufacturers complete additional studies by a certain date. For those medical products where there remains uncertainty of safety and efficacy, CMS has the authority to review preapproval clinical trial evidence in making coverage decisions for their beneficiaries. In the case of aducanumab, CMS employed such an approach under the Coverage for Evidence Development (CED) program to require the manufacturer conduct a randomized-controlled trial evaluating the clinical efficacy and safety of the drug in representative populations.[8] This offers an opportunity for CMS and FDA to further collaborate in ensuring alignment of postapproval studies, particularly for those medical products approved through expedited review pathways where confirmation of safety and efficacy has yet to be proven and additional studies may be required by CMS in making coverage decisions. **Congress could mandate such coordination between FDA in establishing postmarketing requirements for approved medical products and CMS in making coverage decisions that may necessitate further evidence for certain drugs and devices including those receiving Breakthrough Therapy/Breakthrough Device designations or accelerated approval where uncertainty of their efficacy and safety remains at the time of FDA approval.**

Lessons Learned from COVID-19

Finally, many legislators have called for the passage of Cures 2.0 in the setting of the ongoing COVID-19 pandemic, noting the successful development of multiple vaccines, therapies, and diagnostics. FDA's efforts to instill public trust through increased utilization of their independent expert advisory committees for reviewing clinical trial evidence for COVID-19 vaccines and other therapies as well as transparency of their decision-making process in these authorization and approval decisions should be applied beyond the public health emergency period to treatments of other diseases.[9] One recent study found that for other disease areas, FDA has less often referred approved drugs while they were being considered for regulatory review to the agency's independent expert advisory committees over the past decade, from 55% to 6% annually.[10] Moreover, as called for by the current FDA Commissioner prior to his current tenure,[11] timely public access to clinical trial results, particularly during a public health emergency, is urgently needed to prevent duplication of efforts, stewardship of federal research funds, and inform clinical decision-making.

2. *Some stakeholders have raised concerns that if we insist on program integrity in the accelerated approval pathway, it will limit the chances for a rare disease drug getting approved. The accelerated approval pathway was originally created to get at diseases where other treatments are unavailable, so I want to make sure we are clear about this. Dr. Ramachandran, is there any provision of the Accelerated Approval Integrity Act which could limit opportunities to approve drugs that treat rare diseases?*

The Accelerated Approval Integrity Act does not include any provisions that would limit opportunities to approve drugs that treat rare diseases. The bill does not propose changes in the process for granting accelerated approval for potentially promising treatments. Under this legislation, the accelerated approval pathway remains intact. Instead, the bill as written would ensure that manufacturers fulfill their mandate of conducting postapproval studies to confirm the predicted clinical benefit that their initial accelerated approval was based on. By allowing FDA adequate oversight of these required confirmatory studies to ensure their timely completion, patients with rare diseases (and clinicians who treat them) will have greater and more timely certainty of the drug's potential clinical benefit. This will prevent patients from prolonged exposure to any undue harms – both clinically and financially – of continuing to take a drug, which may not demonstrate meaningful therapeutic benefit and delaying their opportunity to switch to other potentially more effective options (pharmacological or otherwise). As an example, the rare disease drug, duvelisib, received accelerated approval by the FDA for thyroid cancer and had a black box warning of having "fatal and serious toxicities" in 2018.[12] The manufacturer made no effort to conduct the required postapproval study necessary to confirm clinical benefit, allowing the drug to continue to be prescribed with these serious side effects to patients on the hope of a clinical benefit that outweighed these risks. Only last year, did the FDA request the manufacturer withdraw the drug from the market, which they eventually did earlier this year after recouping millions of dollars from sales annually. Thus, the Accelerated Approval Integrity Act as originally written with the automatic expiration for accelerated approval drugs where manufacturers fail to

conduct confirmatory studies or fail to demonstrate proven clinical benefit would protect patients. The bill also includes flexibility for the FDA to work with sponsors in implementing its key provisions, recognizing that for certain diseases and drugs, there may be additional considerations in establishing their study protocol for such confirmatory studies and their deadlines for completion.

References:

1. Puthumana J, Wallach JD, Ross JS. Clinical Trial Evidence Supporting FDA Approval of Drugs Granted Breakthrough Therapy Designation. *JAMA*. 2018;320(3):301-303. doi:10.1001/jama.2018.7619

2. Puthumana J, Egilman AC, Ramachandran R, Naushad N, Shah N, Ross J. Early experience with the FDA's regulatory review of novel gene therapies. *BMJ Evid Based Med*. Published online October 11, 2021:bmjebm-2021-111720. doi:10.1136/bmjebm-2021-111720

3. Wallach JD, Zhang AD, Skydel JJ, et al. Feasibility of Using Real-world Data to Emulate Postapproval Confirmatory Clinical Trials of Therapeutic Agents Granted US Food and Drug Administration Accelerated Approval. *JAMA Network Open*. 2021;4(11):e2133667. doi:10.1001/jamanetworkopen.2021.33667

4. Dhruva SS, Ross JS, Desai NR. Real-World Evidence: Promise and Peril For Medical Product Evaluation. *P T*. 2018;43(8):464-472.

5. Food and Drug Administration. Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank. Published online August 2020. Accessed August 18, 2021. https://www.fda.gov/media/113361/download

6. Zhang AD, Puthumana J, Downing NS, Shah ND, Krumholz HM, Ross JS. Assessment of Clinical Trials Supporting US Food and Drug Administration Approval of Novel Therapeutic Agents, 1995-2017. *JAMA Netw Open*. 2020;3(4):e203284. doi:10.1001/jamanetworkopen.2020.3284

7. Johnston JL, Dhruva SS, Ross JS, Rathi VK. Early experience with the FDA's Breakthrough Devices program. *Nat Biotechnol*. 2020;38(8):933-938. doi:10.1038/s41587-020-0636-7

8. Centers for Medicare & Medicaid Services. National Coverage Analysis: Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease. Published online January 11, 2022. https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=Y&NCAId=305

9. Gupta R, Schwartz JL, Ross JS, Kanter G. During COVID-19, FDA's Vaccine Advisory Committee Has Worked To Boost Public Trust – It Can Still Do More. Health Affairs Blog. Published February 26, 2021. Accessed January 26, 2022. https://www.healthaffairs.org/do/10.1377/forefront.20210225.712221/full/

10. Daval CJR, Sarpatwari A, Kesselheim AS. Unwanted Advice? Frequency, Characteristics, And Outcomes Of Negative Advisory Committee Votes For FDA-Approved Drugs. *Health Affairs*. 2022;41(5):713-721. doi:10.1377/hlthaff.2021.01927

11. Califf RM, Zarin DA. Complete, Rapid Reporting of Clinical Trials: A Necessary Component of the Pandemic Response. Medium. Published January 4, 2021. Accessed May 5, 2022. https://califf001.medium.com/complete-rapid-reporting-of-clinical-trials-a-necessary-component-of-the-pandemic-response-aa158eb1a1cb

12. UPDATED: How a pharma company bought 2 accelerated approvals — never ran confirmatory trials — and cashed in until FDA said stop. Endpoints News. Accessed May 5, 2022. https://endpts.com/how-a-pharma-company-bought-2-accelerated-approvals-never-ran-confirmatory-trials-and-cashed-in-until-fda-said-stop/