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Hearing on “FDA User Fee Reauthorization: Ensuring Safe and Effective Drugs and Biologics”

Subcommittee on Health

U.S. House of Representatives Committee on Energy and Commerce

February 3, 2022

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 researcher and a fellow in the National Clinician Scholars Program at Yale School of Medicine. I also serve our nation’s veterans as a primary care physician at the West Haven Veterans Affairs Medical Center. 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. 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.

The past two years of living in continued uncertainty amid an ongoing pandemic has reinforced the critical role of the FDA in protecting patients and public health. The agency has not only enabled the market entry of multiple proven vaccines, drugs, and diagnostics, but has continuously evaluated rapidly emerging evidence related to these health technologies to make scientifically driven regulatory decisions to ensure their appropriate use. While COVID-19 has certainly highlighted the need for and the strengths of the FDA, other recent events have also confirmed the need for urgent reforms.¹

As this committee is well aware, the FDA recently and controversially granted accelerated approval to aducanumab, a costly treatment approved for early-stage Alzheimer’s disease based on an unvalidated surrogate endpoint.² The FDA proceeded forward with this approval despite concerns raised by multiple experts including those on the agency’s own independent advisory committee around its significant safety risks. While this unusual approval is concerning enough by itself, it has also exposed other longstanding, problematic practices at the FDA that must be addressed if the agency is to fulfill its mission of “protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological medicines, and medical devices.”³

In this written testimony, I will outline the importance of maintaining a strong FDA, specific aspects of the proposed user fee agreements that are essential for improving the health of

¹ Gonsalves G, Morten C, Ramachandran R, Ross JS. Opinion | The FDA is in desperate need of some soul-searching. *Washington Post*. <https://www.washingtonpost.com/opinions/2021/06/17/fda-aducanumab-alzheimers-drug-approval-erodes-confidence/>. Published June 17, 2021.

² Ramachandran R, Ross JS. New Alzheimer’s drug sets dangerous precedent. *CNN Opinion*. Published online June 17, 2021. <https://www.cnn.com/2021/06/17/opinions/biogen-alzheimers-drug-opinion-ramachandra-ross/index.html>

³ Food and Drug Administration. What We Do. *FDA*. Published June 28, 2021. Accessed January 31, 2022. <https://www.fda.gov/about-fda/what-we-do>

patients, and opportunities for Congress to consider additional safeguards as part of these agreements in order to uphold and support an agency vital to our nation's public health.

The FDA's regulatory decision-making process is essential for my patients and for my clinical practice.

For clinicians like me, FDA approval of a drug or biologic medicine signals that the approved medical product is safe and effective to be prescribed to patients. With FDA approval comes the understanding that the agency has required and reviewed data collected from well-designed clinical trials testing the drug in patients like mine before determining that these new treatments are indeed, safe and effective. It also gives reassurance that the FDA has done its due diligence in certifying that the manufacturing processes for these medications are safe and of high quality.

The FDA also contributes to creating an enabling environment for robust health technology development. The agency routinely provides guidance to drug developers and manufacturers regarding regulatory standards for medical product approval and works closely with sponsors throughout the submission and application review process. Moreover, the agency also awards several incentives to drug manufacturers to motivate the research and development of novel products for unmet medical needs. This can include designations for special regulatory programs⁴ that expedite the regulatory review process or that allocate FDA resources including staff to shorten clinical development times as well as intellectual property protections in the form of exclusivity periods upon approval.⁵

The FDA also plays an oversight role during the regulatory review process in analyzing the data generated from clinical trials. The agency has the authority to issue holds on studies if the drug being tested is suspected to cause potential adverse effects or if standards for good clinical trial conduct are not being upheld. Even after the drug has been allowed onto the market, the FDA continues to monitor safety and efficacy of treatments. Such ongoing surveillance is especially critical for protecting patients as the FDA increasingly approves new drugs and biological medicines based on less robust evidence in exchange for earlier access to these treatments.^{6,7} This continuous monitoring has led the agency to make rapid, evidence-based

⁴ Food and Drug Administration. Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review. *FDA*. Published June 15, 2019. Accessed January 31, 2022. <https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review>

⁵ Food and Drug Administration. Frequently Asked Questions on Patents and Exclusivity. *FDA*. Published online February 5, 2020. Accessed January 31, 2022. <https://www.fda.gov/drugs/development-approval-process-drugs/frequently-asked-questions-patents-and-exclusivity>

⁶ Medicine I of. *The Future of Drug Safety: Promoting and Protecting the Health of the Public*. (Baciu A, Stratton K, Burke SP, eds.). The National Academies Press; 2007. doi:[10.17226/11750](https://doi.org/10.17226/11750)

⁷ 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](https://doi.org/10.1001/jamanetworkopen.2020.3284)

decisions in the form of warning letters or withdrawals of marketed medical products to protect patients from further harm.

The FDA also translates the underlying rationale behind their complex regulatory decisions to both patients and clinicians through several different avenues. This includes public hearings with independent experts, regulatory review summary documents, publications in medical journals, public testimony to elected officials, educational briefings, prescriber alerts, public newsletters, and press releases. The agency also uses social media and other traditional media avenues to broadly communicate their activities and decisions.

At the start of the pandemic, the FDA quickly pivoted to address the ongoing public health emergency of COVID-19, redirecting resources and personnel, and engaging independent experts to hasten the robust development and availability of COVID-19 diagnostics, vaccines, and therapeutics. The agency established the Coronavirus Treatment Acceleration Program (CTAP) to support clinical trials testing new treatments and vaccines for COVID-19.⁸ They also partnered closely with other agencies including the National Institutes of Health (NIH) as part of the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) partnership, providing expertise around clinical trial design and conduct as well as regulatory standards for authorization and approval. The FDA has also made strides during the ongoing pandemic to increase transparency around their emergency use authorization recommendations and regulatory decisions related to COVID-19. This has helped promote public confidence in their scientific review process and to ensure that clinicians and patients are made aware of how to appropriately use COVID-19 health technologies.

Like many of my colleagues, I have concerns that the increasing reliance on user fees from the very industry that the FDA regulates has unduly impacted regulatory standards creating further unnecessary flexibility for manufacturers in the regulatory review and approval process.⁹ Increasingly, the agency has expedited the approval of drugs and biological medicines, which has been found to be associated with less robust clinical trial evidence and more uncertainty of these treatments' clinical benefit. I firmly believe that in order for the FDA to maintain its independence as a national regulatory authority tasked with protecting public health that Congress should be appropriating further funding to the agency, thereby reducing its dependence on industry actors and mitigating undue influence that fails to prioritize patients. Nevertheless, in the absence of sufficient funding for the FDA to maintain its current operations as well as to address its growing footprint on our healthcare system, Congress should intervene to ensure that these user fee agreements include safeguards to protect patients and public health.

⁸ Food and Drug Administration. Coronavirus Treatment Acceleration Program (CTAP). *FDA*. Published January 7, 2022. Accessed January 31, 2022. <https://www.fda.gov/drugs/coronavirus-covid-19-drugs/coronavirus-treatment-acceleration-program-ctap>

⁹ Darrow JJ, Avorn J, Kesselheim AS. Speed, Safety, and Industry Funding — From PDUFA I to PDUFA VI. *New England Journal of Medicine*. 2017;377(23):2278-2286. doi:[10.1056/NEJMhle1710706](https://doi.org/10.1056/NEJMhle1710706)

The Prescription Drug User Fee Authorization (PDUFA),¹⁰ Generic Drug User Fee Authorization (GDUFA),¹¹ and Biosimilar User Fee Authorization (BsUFA)¹² Acts funds important operations at the FDA as well as other urgently needed priorities.

The creation of new and unexpected workstreams dedicated to COVID-19 has required the use of further resources and funding for the hiring of additional staff to ensure timely review of urgently needed diagnostics, vaccines, and therapeutics. Moreover, as shown within the annual PDUFA Performance reports, sponsors have been submitting an increasing number of new drug approval (NDA) and biologics license approval (BLA) applications.¹³ Most of these submissions were also for new drugs and biologics that received expedited review pathway designations including priority review, which requires the FDA to complete their review process in six months rather than the standard 10 months. In 2020, the FDA received 56% more submissions for original priority NDAs and BLAs compared to the 5-year average of the number of such submissions received between 2015 and 2019.¹⁴

For the FDA to be able to rigorously review a growing number of NDAs and BLAs, user fees have been proposed to pay for hiring additional staff support as well as to retain current staff. Ensuring that the FDA has sufficient staff to continue its critical role in assessing medication efficacy and safety will also allow the agency to be nimble, particularly when faced with unanticipated public health threats. Additionally, the FDA has committed to further streamlining the process for generic and biosimilar drug review, which may allow for more timely patient access to more affordable generic and biosimilar alternatives to costly brand-name drugs and biologics.

The FDA has also committed to taking a stepwise, thoughtful approach in the adoption of novel evidence generation through real-world evidence (RWE) studies and other complex clinical trial designs. Such careful evaluation will be necessary to determine whether such methods are not just more efficient, but also sufficient in making regulatory decisions. Finally, the FDA has also pledged to strengthen safety surveillance efforts including the Sentinel Initiative, increase its public availability, and enhance its capability to conduct analyses of specific safety issues. This will help to advance safety signal evaluations so that the agency can take more timely action and prevent drug-related adverse events.

¹⁰ *Prescription Drug User Fee Amendments of 2022.*; 2022. Accessed January 31, 2022.

https://energycommerce.house.gov/sites/democrats.energycommerce.house.gov/files/documents/PDUFA-title_01_xml_1.pdf

¹¹ *Generic Drug User Fee Amendments of 2022.*; 2022. Accessed January 31, 2022.

https://energycommerce.house.gov/sites/democrats.energycommerce.house.gov/files/documents/GDUFA-title_01_xml_1.pdf

¹² *Biosimilar User Fee Amendments of 2022.* Accessed January 31, 2022.

https://energycommerce.house.gov/sites/democrats.energycommerce.house.gov/files/documents/BsUFA-title_01_xml_1.pdf

¹³ Food and Drug Administration. FY 2020: Performance Report to Congress for the Prescription Drug User Fee Act. Published online 2020. <https://www.fda.gov/media/151602/download>

¹⁴ *Id*

The user fee agreements offer several opportunities for Congress to further strengthen the FDA regulatory review process and make it more patient-centered in order to ensure timely access to drugs and biologic medicines proven to be truly effective and safe.

Reforms to that end include:

Including More Clinically Meaningful, Patient-Centered Measures of FDA’s Performance

As part of the user fee agreements, the FDA has put forward a number of performance goals and metrics related to timely agency review of and action on drug and biologic medicines submissions. While laudable that FDA is making efforts to increase its efficiency in reviewing applications, the agency should also measure more clinically meaningful and patient-centered measures of its performance.¹⁵ Examples of such measures include:

- the percentage of NDAs and BLAs approved for which prespecified primary endpoints within pivotal trials were missed (our research examining this frequency in a subset of drugs and biologic medicines showed that primary endpoints were missed in approximately one in 10 FDA approved drugs¹⁶; for aducanumab, in only one of two pivotal clinical trials, which were halted due to futility, was the prespecified endpoint met by a very small, clinically irrelevant margin¹⁷);
- the percentage of NDAs and BLAs for which FDA approval decisions were concordant with the recommendations of the agency’s independent advisory committees (prior studies have found that 22% of FDA’s approval decisions were discordant with recommendations from its advisory committees with the agency making more restrictive decisions in a majority of these instances than what had been recommended by the advisory committee¹⁸);
- the percentage of NDAs and BLAs approved with postmarketing requirements where those mandatory studies have been fulfilled and have demonstrated positive results in confirming the drugs’ efficacy and safety (prior research has found that even five or six years after approval, a significant proportion of studies remain uncompleted or have yet to be initiated¹⁹); and
- the percentage of NDAs and BLAs approved for which the FDA later withdrew or issued warnings based on completed postmarketing studies (an earlier study of therapies approved by the FDA between 2001 and 2010 found that nearly a third were affected by a

¹⁵ Abrams M. Comments Regarding the Reauthorization of the Prescription Drug User Fee Act; Public Meeting; Request for Comments; Docket No. FDA-2021-N-0891. Published online October 28, 2021. Accessed January 31, 2022. <https://www.citizen.org/wp-content/uploads/2606.pdf> (Public Citizen has been proposing such measures as public stakeholders to the FDA PDUFA VII Reauthorization Meetings)

¹⁶ *Ongoing work*

¹⁷ Alexander GC, Knopman DS, Emerson SS, et al. Revisiting FDA Approval of Aducanumab. *New England Journal of Medicine*. 2021;385(9):769-771. doi:[10.1056/NEJMp2110468](https://doi.org/10.1056/NEJMp2110468)

¹⁸ Zhang AD, Schwartz JL, Ross JS. Association Between Food and Drug Administration Advisory Committee Recommendations and Agency Actions, 2008–2015. *The Milbank Quarterly*. 2019;97(3):796-819. doi:[10.1111/1468-0009.12403](https://doi.org/10.1111/1468-0009.12403)

¹⁹ Woloshin S, Schwartz LM, White B, Moore TJ. The Fate of FDA Postapproval Studies. *New England Journal of Medicine*. 2017;377(12):1114-1117. doi:[10.1056/NEJMp1705800](https://doi.org/10.1056/NEJMp1705800)

postmarket safety event – either withdrawal, FDA issuance of boxed warnings, or FDA issuance of safety communications²⁰).

Furthermore, ensuring evaluation of more patient-centered, clinically meaningful metrics could prompt the FDA to make commitments around their regulatory review processes that benefit patients, not just industry sponsors. Without such measurement, the FDA will focus its efforts and resources to reaching benchmarks primarily toward hastening regulatory review of health technologies without ample consideration of whether its stated mission of also ensuring that these medical products are also “more effective, safer, and more affordable”²¹ is being achieved.

Revisiting Evidentiary Standards for Drugs and Biologics Approved Through Expedited Review Pathways

While expedited review pathways such as the accelerated approval pathway have allowed for patients to access drugs earlier based on surrogate endpoints instead of clinical endpoints, it has come with the tradeoff of continued uncertainty of their clinical benefit. Under accelerated approval, the FDA mandates the completion of additional studies after approval to confirm the drugs’ and biologics’ hypothesized clinical benefit within a certain time period. Contingent on the coverage decision made by payors, the accelerated approval therapeutic can be prescribed by clinicians and made available to patients for use upon approval and before the completion of these confirmatory trials. When these studies are completed, the FDA reviews the confirmatory trial data to determine whether these drugs would be eligible for standard approval.

An analysis by *The BMJ* of 253 drugs approved through the accelerated approval pathway between 1992 and 2020 found that nearly half of the drugs (n=112) have not been confirmed to be clinically effective.²² Of these drugs without confirmatory evidence of their clinical benefit, 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.

In the case of aducanumab, the FDA has given Biogen a gratuitous nine years to complete their confirmatory trials, which is much longer than the median postapproval trial duration or results reporting deadline for other accelerated approval drugs.²³ However, for other

²⁰ Downing NS, Shah ND, Aminawung JA, et al. Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010. *JAMA*. 2017;317(18):1854-1863. doi:[10.1001/jama.2017.5150](https://doi.org/10.1001/jama.2017.5150)

²¹ Food and Drug Administration. What We Do. About FDA. Published June 28, 2021. Accessed January 31, 2022. <https://www.fda.gov/about-fda/what-we-do>

²² Mahase E. FDA allows drugs without proven clinical benefit to languish for years on accelerated pathway. *BMJ*. 2021;374:n1898. doi:[10.1136/bmj.n1898](https://doi.org/10.1136/bmj.n1898)

²³ Wallach JD, Ramachandran R, Bruckner T, Ross JS. Comparison of Duration of Postapproval vs Pivotal Trials for Therapeutic Agents Granted US Food and Drug Administration Accelerated Approval, 2009-2018. *JAMA Network Open*. 2021;4(11):e2133601. doi:[10.1001/jamanetworkopen.2021.33601](https://doi.org/10.1001/jamanetworkopen.2021.33601)

accelerated approval drugs, long delays in completing required confirmatory trials have also been described.²⁴ The FDA has also waived postapproval trial requirements for some drugs despite accelerated approval being conditioned on completion of further studies to demonstrate clinical benefit.²⁵

Even when these required confirmatory trials are conducted and show negative results, the FDA has failed to withdraw indication approvals. In April 2021, FDA’s Oncologic Drugs Advisory Committee (ODAC) reviewed confirmatory evidence for six oncology indications that had earlier received accelerated approval.²⁶ Despite some of these drugs failing to confirm clinical benefit in their postmarket studies, ODAC voted to maintain their approval. While the FDA could make a regulatory decision that differs from the recommendations of advisory committees, this rarely occurs.²⁷

Finally, postmarket confirmatory clinical trials required for accelerated approval drugs 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. In one study looking at cancer drugs approved by the FDA between 1992 and 2017 through the accelerated approval pathway, 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.²⁸ Additionally, postmarket confirmatory studies for accelerated approval drugs are also small and short, with many lacking randomization, blinding, or concurrent controls²⁹ – key characteristics of well-designed clinical trials.

As part of these user fee agreements, the FDA should commit to revisiting evidentiary standards for approval through expedited pathways such as accelerated approval. First, the FDA should not allow for accelerated approvals to continue forward in perpetuity. The FDA could withdraw accelerated approval indications if postapproval confirmatory trials are significantly delayed or fail to show clinical benefit,³⁰ but this can a lengthy process involving a public

²⁴ Naci H, Smalley KR, Kesselheim AS. Characteristics of Preapproval and Postapproval Studies for Drugs Granted Accelerated Approval by the US Food and Drug Administration. *JAMA*. 2017;318(7):626-636. doi:[10.1001/jama.2017.9415](https://doi.org/10.1001/jama.2017.9415)

²⁵ Gyawali B, Ross JS, Kesselheim AS. Fulfilling the Mandate of the US Food and Drug Administration’s Accelerated Approval Pathway: The Need for Reforms. *JAMA Internal Medicine*. 2021;181(10):1275-1276. doi:[10.1001/jamainternmed.2021.4604](https://doi.org/10.1001/jamainternmed.2021.4604)

²⁶ Powell K, Lythgoe MP, Prasad V. The Oncologic Drugs Advisory Committee Votes of April 2021—Implications for the Fate of Accelerated Approval. *JAMA Oncology*. 2021;7(11):1607-1609. doi:[10.1001/jamaoncol.2021.3046](https://doi.org/10.1001/jamaoncol.2021.3046)

²⁷ Zhang AD, Schwartz JL, Ross JS. Association Between Food and Drug Administration Advisory Committee Recommendations and Agency Actions, 2008–2015. *The Milbank Quarterly*. 2019;97(3):796-819. doi:[10.1111/1468-0009.12403](https://doi.org/10.1111/1468-0009.12403)

²⁸ Gyawali B, Hey SP, Kesselheim AS. Assessment of the Clinical Benefit of Cancer Drugs Receiving Accelerated Approval. *JAMA Internal Medicine*. 2019;179(7):906-913. doi:[10.1001/jamainternmed.2019.0462](https://doi.org/10.1001/jamainternmed.2019.0462)

²⁹ Naci H, Smalley KR, Kesselheim AS. Characteristics of Preapproval and Postapproval Studies for Drugs Granted Accelerated Approval by the US Food and Drug Administration.

³⁰ Beaver JA, Pazdur R. “Dangling” Accelerated Approvals in Oncology. *New England Journal of Medicine*. 2021;384(18):e68. doi:[10.1056/NEJMp2104846](https://doi.org/10.1056/NEJMp2104846)

hearing should the sponsor not voluntarily withdraw the indication.³¹ During this time, the drug remains available for patients despite continued uncertainty of its clinical benefit or even when postapproval trials show negative results, as with the six indications considered by the FDA's ODAC in late April 2021.

Regulatory authorities in other countries including the United Kingdom, Australia, and Europe who award similar such approvals allow them to expire and require renewal of these conditional approvals every one to two years.³² As part of the renewal process, sponsors must submit an interim report on any outstanding obligations including timelines for completion of confirmatory trials. The FDA should adopt a similar approach to ensure more timely completion of confirmatory clinical trials, which could thereby mitigate potential clinical and financial harms for patients should the drug fail to demonstrate meaningful benefit. Regardless, should the confirmatory trials demonstrate negative results, the FDA should also automatically withdraw accelerated approval instead of waiting to convene advisory committee members for further discussion or relying on manufacturers to voluntarily withdraw these indications.³³

Coupled with these steps, the FDA should adopt similar practices from its COVID-19 initiatives in investing in educational efforts to inform patients and clinicians when accelerated approval is granted for a new drug and that it may be possible for the drug could be withdrawn should confirmatory trials fail to show clinical benefit for patients. Clear and ongoing communication about the regulatory review process will help mitigate any possible treatment disruptions if the indication is removed.

Moreover, the FDA should require that confirmatory trials for accelerated approval drugs use clinical endpoints, not surrogate endpoints, especially when the surrogate endpoints used in the preapproval clinical trials are unvalidated and without a proven association with clinical outcomes. Finally, the FDA should also mandate that for sponsors to receive accelerated approval that confirmatory trial protocols must be discussed and finalized with agency officials in order to verify that the trials are well-designed and for the sponsors to begin enrollment as soon as the drug is approved, thereby preventing against any delays in initiating such trials. These reforms will ensure that the FDA achieves the intent of the accelerated approval pathway of ensuring patients timely access to treatments are truly promising, not just wishful thinking.³⁴

³¹ *Food and Drug Administration Safety and Innovation Act*. Vol 301.; 2012.

<https://www.congress.gov/112/plaws/publ144/PLAW-112publ144.pdf>

³² Mehta GU, de Claro RA, Pazdur R. Accelerated Approval Is Not Conditional Approval: Insights From International Expedited Approval Programs. *JAMA Oncology*. Published online January 20, 2022. doi:[10.1001/jamaoncol.2021.6854](https://doi.org/10.1001/jamaoncol.2021.6854)

³³ Gyawali B, Ross JS, Kesselheim AS. Fulfilling the Mandate of the US Food and Drug Administration's Accelerated Approval Pathway: The Need for Reforms. *JAMA Internal Medicine*. 2021;181(10):1275-1276. doi:[10.1001/jamainternmed.2021.4604](https://doi.org/10.1001/jamainternmed.2021.4604)

³⁴ *Id*

Using Real-World Evidence Appropriately and Transparently for Regulatory Decision-making

Increasingly, the FDA has been examining the quality and acceptability of real-world evidence (RWE) for regulatory decision-making as mandated under the 21st Century Cures Act, particularly for supporting new indication approvals of approved drugs or satisfying postapproval study requirements. Legislative proposals have also emerged to allow the use of real-world data (RWD) including patient registries, electronic health records, medical claims, and digital health technologies to fulfill postapproval confirmatory trial study requirements for accelerated approval drugs.³⁵ Within the proposed user free agreements, the FDA has committed to initiating the Advanced Real-World Evidence Pilot Program where the agency will work closely with a small group of sponsors in designing a RWE study using RWD in support of a proposed regulatory decision.

Recent research has raised questions on the feasibility of using RWD 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 RWD sources of administrative claims or electronic health records data.³⁶ Another study examined whether it would be feasible to use such data to emulate FDA-required postapproval confirmatory trials for all new drugs that received accelerated approval between 2009 and 2018.³⁷ Of the 50 confirmatory trials required by the FDA for these drugs, none could be feasibly emulated using currently available RWD in terms of medical claims or structured electronic health record data. This suggests that currently available RWD and observational methods are unlikely to replace postapproval confirmatory trial requirements as has been proposed.

When RWD 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.³⁸ 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 RWD 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 RWD as well as appropriate statistical analyses as such data is not as well controlled as in traditional clinical trials.

³⁵ DeGette D, Upton F. *Discussion Draft: Cures 2.0 Act.*; 2021:127.

https://degette.house.gov/sites/degette.house.gov/files/Cures%202.0_DISCUSSION%20DRAFT.pdf

³⁶ Bartlett VL, Dhruva SS, Shah ND, Ryan P, Ross JS. Feasibility of Using Real-World Data to Replicate Clinical Trial Evidence. *JAMA Network Open*. 2019;2(10):e1912869. doi:[10.1001/jamanetworkopen.2019.12869](https://doi.org/10.1001/jamanetworkopen.2019.12869)

³⁷ 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](https://doi.org/10.1001/jamanetworkopen.2021.33667)

³⁸ Wallach JD, Deng Y, McCoy RG, et al. Real-world Cardiovascular Outcomes Associated With Degarelix vs Leuprolide for Prostate Cancer Treatment. *JAMA Network Open*. 2021;4(10):e2130587. doi:[10.1001/jamanetworkopen.2021.30587](https://doi.org/10.1001/jamanetworkopen.2021.30587)

Although the FDA is taking steps to carefully understand these complexities to identify appropriate study designs and characteristics for using RWD, the agency should invest in further research with public stakeholder engagement to clearly outline appropriate use conditions for RWD 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,³⁹ sponsors of RWE studies should also do the same. This practice of transparency should be initiated as part of the Advancing RWE Pilot Program to allow for further independent expertise in determining appropriate use of such studies toward regulatory decision-making.

Ensuring Timely Completion and Integrity of Postmarketing Studies

Increasingly, the FDA is approving drugs and biologic medicines through expedited review pathways supported by fewer pivotal clinical trials that are smaller, shorter, and more often evaluating surrogate endpoints compared to those approved through standard pathways.⁴⁰ With treatments being approved based on trials with less rigorous study design, it has become increasingly important for the FDA to require postmarket studies to continue to evaluate their safety and efficacy after approval. However, studies have found that many sponsors either fail to complete or even initiate required postmarketing studies. One study found that of the postmarketing requirements and commitments issued by the FDA in 2009 and 2010, nearly 20% have not even been started, 25% were delayed or ongoing, and just over 50% had been completed five to six years after approval.⁴¹ Such delays have also been seen for accelerated approval drugs where approval is conditioned on the completion of required postapproval confirmatory studies; in a study of drugs granted accelerated approval by the FDA between 2009 and 2013, only approximately two-fifths of these drugs were found to have confirmatory evidence of efficacy in postmarket trials within 3 years of approval.⁴²

Additional studies examining required postmarketing studies found that the median times allowed by the FDA for sponsors to submit protocols for clinical trials ranged widely between

³⁹ National Institutes of Health, Department of Health and Human Services. *PART 11—CLINICAL TRIALS REGISTRATION AND RESULTS INFORMATION SUBMISSION.*; 2017. Accessed August 17, 2021. <https://www.ecfr.gov/>

⁴⁰ 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](https://doi.org/10.1001/jamanetworkopen.2020.3284)

⁴¹ Woloshin S, Schwartz LM, White B, Moore TJ. The Fate of FDA Postapproval Studies. *New England Journal of Medicine.* 2017;377(12):1114-1117. doi:[10.1056/NEJMp1705800](https://doi.org/10.1056/NEJMp1705800)

⁴² Naci H, Smalley KR, Kesselheim AS. Characteristics of Preapproval and Postapproval Studies for Drugs Granted Accelerated Approval by the US Food and Drug Administration. *JAMA.* 2017;318(7):626-636. doi:[10.1001/jama.2017.9415](https://doi.org/10.1001/jama.2017.9415)

three and 15 months.⁴³ Moreover, the authors also found that the median times permitted for the sponsor to complete the required study following protocol submission were two to 13 times longer than the time required for primary outcome ascertainment; accelerated approval drugs were also noted to have approximately two years longer than the time required for primary outcome ascertainment. These findings suggest that the FDA should shorten the time allotted for required postmarket study protocol submission, study initiation, and trial completion in addition to the stated agency goals within the proposed user fee agreements of identifying and communicating anticipated postmarketing requirements to sponsors ahead of approval.

Maintaining Rigorous Standards for Approval for Therapeutics for Diseases of Unmet Need Cell and Gene Therapies

Within the proposed user fee agreements, the FDA has committed to enhancing the Cell and Gene Therapy Program to facilitate more timely development and availability of novel cell and gene therapies. The agency has stated that it will further expand this program through increased staff support and continued engagement with stakeholders around novel development approaches as well as the use of real-world evidence as confirmatory evidence of clinical benefit.

In a recent study, we examined the five novel gene therapies that have received FDA approval as of December 31, 2020.⁴⁴ We found that through the regenerative medicine advance therapy (RMAT) designation, the FDA has been able to successfully expedite the development and market entry of these products. In fact, their median clinical development period was substantially faster than that of traditional pharmaceutical products, but similar in length to breakthrough therapy approvals at less than five years. However, this expediency also seems to have come with tradeoff of more limited premarket evidence. Most approvals for these gene therapies were based on one small, single-arm, open-label trial using a surrogate marker as the primary efficacy endpoint. Such evidence is even more limited than that of drugs receiving orphan drug or breakthrough therapy designations. Despite the need for postmarketing studies in the absence of robust evidence supporting the approval of these gene therapies, only for three of the five treatments did the FDA require postmarketing studies.

To mitigate the ramifications of such limited evidence on patients and clinicians, the FDA should require both traditional postmarketing studies as well as continued collection of RWD through the establishment of patient registries to follow patients for longer durations after treatment administration and ensure that this data is made publicly available for patients, clinicians, and researchers to learn from. The FDA should also consider awarding approvals to

⁴³ Wallach JD, Egilman AC, Ross JS, Woloshin S, Schwartz LM. Timeliness of Postmarket Studies for New Pharmaceuticals Approved Between 2009 and 2012: a Cross-Sectional Analysis. *J Gen Intern Med.* 2019;34(4):492-495. doi:[10.1007/s11606-018-4779-x](https://doi.org/10.1007/s11606-018-4779-x)

⁴⁴ 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](https://doi.org/10.1136/bmjebm-2021-111720)

gene therapies with limited premarket evidence conditioned on the timely completion of mandatory and well-designed confirmatory trials.

Antibiotics and Antifungals

Legislators are currently considering additional financial incentives^{45,46} for novel antibiotics and antifungals including those that receive the qualified infectious disease product (QIDP) designation from the FDA. In 2019, the Centers for Medicare and Medicaid Services implemented such an incentive in the form of increased new technology add-on payments and the removal of “substantial clinical improvement” criteria for this additional reimbursement.⁴⁷ While the intent of this rule change was to incentivize manufacturers to pursue antimicrobial drug development given the limited product pipeline amid the growing global threat of antimicrobial resistance,⁴⁸ it fails to address the quality of products receiving this incentive. Prior characterization of pivotal clinical trials for FDA-approved antimicrobials (including a small number awarded the 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.⁴⁹

In our recent research examining the evidentiary basis for approval of these QIDP indications, we found that over 20% were approved based on in vitro studies and a majority were tested in non-inferiority pivotal trials,⁵⁰ which allow for intervention drugs to be less effective compared with older, effective antimicrobials by a prespecified margin.⁵¹ 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 these financial incentives may be misaligned, rewarding manufacturers of QIDPs with unclear effectiveness against resistant pathogens, despite receiving this special designation intended for this purpose. Instead of awarding costly financial incentives to unproven treatments, the FDA should have

⁴⁵ Davis DK. *DISARM Act of 2021.*; 2021. Accessed November 2, 2021. <https://www.congress.gov/bill/117th-congress/house-bill/4127>

⁴⁶ Bennet MF. *PASTEUR Act of 2021.*; 2021. Accessed November 2, 2021. <https://www.congress.gov/bill/117th-congress/senate-bill/2076/text>

⁴⁷ *Medicare Program; Hospital Inpatient Prospective Payment Systems for Acute Care Hospitals and the Long-Term Care Hospital Prospective Payment System and Policy Changes and Fiscal Year 2020 Rates; Quality Reporting Requirements for Specific Providers; Medicare and Medicaid Promoting Interoperability Programs Requirements for Eligible Hospitals and Critical Access Hospitals.* Centers for Medicare and Medicaid Services; 2019. <https://www.federalregister.gov/documents/2019/08/16/2019-16762/medicare-program-hospital-inpatient-prospective-payment-systems-for-acute-care-hospitals-and-the>

⁴⁸ Murray CJ, Ikuta KS, Sharara F, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet.* 2022;0(0). doi:[10.1016/S0140-6736\(21\)02724-0](https://doi.org/10.1016/S0140-6736(21)02724-0)

⁴⁹ Deak D, Outterson K, Powers JH, Kesselheim AS. Progress in the Fight Against Multidrug-Resistant Bacteria? A Review of U.S. Food and Drug Administration–Approved Antibiotics, 2010–2015. *Ann Intern Med.* 2016;165(5):363. doi:[10.7326/M16-0291](https://doi.org/10.7326/M16-0291)

⁵⁰ *Ongoing work*

⁵¹ Food and Drug Administration. Non-Inferiority Clinical Trials to Establish Effectiveness: Guidance for Industry. Published online November 2016. <https://www.fda.gov/media/78504/download>

further discretion in granting the QIDP designation and 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.

Maintaining On-Site Manufacturing Facility Inspection Requirements

Just recently, the FDA announced that it has again halted any non-mission critical inspections in the United States due to the spread of the Omicron variant of COVID-19.⁵² The agency also announced that it would delay moving forward with key surveillance foreign inspections that were scheduled to restart this month. Moreover, compared to 2019, the FDA completed 1,500 fewer inspections in 2020. As a result, less than half of the 2020 inspections ended with an Official Action Indicated determination compared with 2019 inspections. While the agency has pivoted to more remote forms of evaluation of manufacturing facilities, this does not fulfill surveillance inspection requirements of being conducted in-person and on-site. Such inspections are critical to ensuring safe, high quality, and effective medical products for patients. Instead of halting these important checks, the FDA should allocate further resources towards safely continuing these essential in-person, on-site inspections instead of substituting these with remote, paper-based alternatives.

Upholding FDA's Legally Mandated Responsibility to Enforce Reporting of Clinical Trials Results Information

Under the Food and Drug Administration Act of 2007, clinical trial sponsors are mandated to register and then later, submit results information to ClinicalTrials.gov, generally within 12 months of the trial's primary completion date.⁵³ Transparency of such results information is important as it informs clinical care decisions and accelerates future research endeavors. Although sponsors have largely met the requirement to register and submit their trial protocols, reporting of results information remains limited despite this legal mandate and further guidance from the NIH and FDA.^{54,55} As of January 18, 2021, nearly 60% of trials failed to report their results on time and more than 30% (almost 3000 clinical trials with primary completion dates on or after January 18, 2017) had not yet reported results.⁵⁶ The FDA and NIH

⁵² Food and Drug Administration. Non-Inferiority Clinical Trials to Establish Effectiveness: Guidance for Industry. Published online November 2016. <https://www.fda.gov/media/78504/download>

⁵³ National Institutes of Health, Department of Health and Human Services. *PART 11—CLINICAL TRIALS REGISTRATION AND RESULTS INFORMATION SUBMISSION*.; 2017. Accessed August 17, 2021. <https://www.ecfr.gov/>

⁵⁴ *Id*

⁵⁵ 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>

⁵⁶ DeVito NJ, Goldacre B. Evaluation of Compliance With Legal Requirements Under the FDA Amendments Act of 2007 for Timely Registration of Clinical Trials, Data Verification, Delayed Reporting, and Trial Document Submission. *JAMA Internal Medicine*. Published online May 24, 2021. doi:[10.1001/jamainternmed.2021.2036](https://doi.org/10.1001/jamainternmed.2021.2036)

share responsibility for enforcing FDAAA although the NIH has historically declined to take any enforcement action on its own, instead waiting for the FDA to do so.

Through an ongoing Freedom of Information Act-based investigation, we obtained all enforcement actions that the FDA has taken regarding FDAAA noncompliance as of late April 2021.⁵⁷ These were all in the form of Preliminary Notices of Noncompliance (or Pre-Notices), of which FDA had issued only 58 in total to trial sponsors; of these, fifty-seven were issued for potential missing clinical trial results information. None of these Pre-Notices were issued to federal agencies, including the NIH despite the NIH being the sponsor for many trials that have failed to submit their results information to ClinicalTrials.gov as required.⁵⁸ We also found that these Pre-Notices were extremely effective at improving compliance – as of mid-August of last year, more than 90% of the recipients had reported missing information to ClinicalTrials.gov within a median time of three weeks.

The FDA has since issued three Notices of Noncompliance to those recipients of Pre-Notices who had still failed to submit their missing trial results information.⁵⁹ With these Notices come the warning of costly, daily civil penalties and possible criminal prosecution should the sponsor fail to act. Upon receiving these Notices, all three sponsors swiftly reported their missing trial results information to ClinicalTrials.gov. It is clear, however, that the FDA could and should send more Pre-Notices and Notices and make these enforcement efforts publicly know, including through ClinicalTrials.gov. Such transparency would improve public accountability and encourage more prompt submission of missing results information. Funding through user fees or through Congressional appropriation should also be directed to support the FDA in their legal enforcement obligations to further improve the submission of clinical trials results information.

Increasing Overall Transparency of Regulatory Decision-making Processes

Within the user fee agreements, the FDA has committed to further increasing their communication efforts with industry throughout the initial review process. They have also proposed various pilot programs (e.g. Split Real Time Application, Rare Disease Endpoint Advancement, Advancing Real World Evidence) and enhancements to established programs around expedited review pathways where the agency plans to work closely with industry partners to more efficiently review candidate drugs and biologic medicines. While the FDA has noted instances where they would host public workshops that would be made available to stakeholders outside of industry, further commitments from the agency to solicit and ensure participation from independent stakeholders are necessary.

⁵⁷ Ramachandran R, Morten CJ, Ross JS. Strengthening the FDA’s Enforcement of ClinicalTrials.gov Reporting Requirements. *JAMA*. Published online November 12, 2021. doi:[10.1001/jama.2021.19773](https://doi.org/10.1001/jama.2021.19773)

⁵⁸ FDAAA TrialsTracker. Accessed January 31, 2022. <http://fdaaa.trialstracker.net/>

⁵⁹ Food and Drug Administration. ClinicalTrials.gov - Notices of Noncompliance and Civil Money Penalty Actions. FDA.gov. Published September 1, 2021. Accessed October 8, 2021. <https://www.fda.gov/science-research/fdas-role-clinicaltrialsgov-information/clinicaltrialsgov-notices-noncompliance-and-civil-money-penalty-actions>

In the case of aducanumab, the FDA was reported to have engaged in an unusually close collaboration with the manufacturer, Biogen during the regulatory review process.⁶⁰ Despite FDA's own independent advisory committee nearly unanimously voting to not approve this drug,⁶¹ the agency proceeded to continue to work with Biogen behind closed doors on its application. This led to the controversial decision to approve the drug through the accelerated approval pathway based on an unproven surrogate marker;⁶² just months before, FDA officials had assured the advisory committee that they would not be using this biomarker “as a surrogate for efficacy.”⁶³ Learning from this experience, the FDA should institute a firewall between staff engaged in assisting manufacturers in their submission and those that conduct the review. By doing so, patients and clinicians will be more assured that the agency is maintaining its own independence without undue influence from drug sponsors in making regulatory decisions.

When the FDA does adopt a more transparent approach, it has had success in instilling public trust in its regulatory decision-making process. With COVID-19 vaccines and therapeutics, the FDA has hosted an unprecedented number of public advisory committee meetings where anyone can view discussions between this group of independent experts and FDA officials.⁶⁴ Moreover, the FDA has made available review summaries for COVID-19 vaccines and drugs ahead of these meetings and upon emergency use authorization despite there not being a statutory mandate to do so as with approvals.⁶⁵ This has allowed other independent experts, clinicians, and patients to review the submitted evidence themselves and better understand the FDA's rationale in making regulatory decisions. As a minimum, the FDA should employ such practices when making regulatory decisions for other disease areas.

Adopting more transparent approaches to instill public trust in FDA's decision-making process should not be “one-size-fits-all”, but rather adapted to the complexity of the regulatory decision and public health need. Although the FDA did convene an advisory committee for aducanumab in November 2020, the drug's approval became predicated on a separate review pathway that was never discussed with this group of independent experts.⁶⁶ Thus, when the FDA decided to approve aducanumab, this surprised its own advisory committee, prompting the

⁶⁰ Feuerstein A, Herper M, Garde D. Inside “Project Onyx”: How Biogen used an FDA back channel to win approval of its polarizing Alzheimer's drug. *STAT News*. Published June 29, 2021. Accessed January 31, 2022. <https://www.statnews.com/2021/06/29/biogen-fda-alzheimers-drug-approval-aduhelm-project-onyx/>

⁶¹ Food and Drug Administration. Peripheral and Center Nervous System Drugs Advisory Committee Meeting. Published online November 6, 2020. Accessed January 29, 2022. <https://www.fda.gov/media/145691/download>

⁶² Panza F, Lozupone M, Logroscino G, Imbimbo BP. A critical appraisal of amyloid- β -targeting therapies for Alzheimer disease. *Nat Rev Neurol*. 2019;15(2):73-88. doi:[10.1038/s41582-018-0116-6](https://doi.org/10.1038/s41582-018-0116-6)

⁶³ Food and Drug Administration. Peripheral and Center Nervous System Drugs Advisory Committee Meeting.

⁶⁴ 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/doi/10.1377/forefront.20210225.712221/full/>

⁶⁵ Food and Drug Administration. Emergency Use Authorization. FDA. Published January 31, 2022. Accessed January 31, 2022. <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization>

⁶⁶ Alexander GC, Knopman DS, Emerson SS, et al. Revisiting FDA Approval of Aducanumab. *New England Journal of Medicine*. 2021;385(9):769-771. doi:[10.1056/NEJMp2110468](https://doi.org/10.1056/NEJMp2110468)

subsequent resignation of three members.⁶⁷ Instead, the FDA could have convened the advisory committee once again to discuss the possibility of this alternative pathway for approval and maintained continued communication with members throughout the approval process.

Finally, further transparency and reforms are needed in FDA's process for engagement of stakeholders in shaping user fee agreements. Currently, the FDA convenes industry stakeholders separately from other public stakeholders for their discussions on what should be included within user fee agreements.⁶⁸ While the FDA posts summaries of these meetings online, these are quite brief with little to no detail on what specific proposals were discussed nor the considerations posed by the stakeholders who participated. As these discussions around user fee agreements are not specific to individual drugs or biologic medicines, it is unclear why this separation in FDA's interactions with industry and public stakeholders exists or why such information would need to be kept confidential. Should truly commercially confidential information need to be considered as part of these negotiations, the FDA could convene relevant stakeholders separately for that purpose.

In reviewing the PDUFA VII Commitment Letter put forward by the FDA in late September of last year and recently released draft legislation, the provisions seem to be almost identical despite public comments from independent patient and consumer advocacy organizations calling for specific revisions to the proposed agreement. The FDA in their response to these public comments stated that they have “not made changes to those recommendations for the reauthorization of PDUFA” with the rationale that there is “general support for the PDUFA VII agreement.”⁶⁹ Coupled with the FDA's current policy of having separate, non-transparent negotiations with biopharmaceutical companies and trade associations, the agency has seemingly put more weight on industry recommendations rather than those organizations who independently represent the public's interest. Convening all stakeholders together for future user fee agreement negotiations would be a first step towards restoring balance to an asymmetry of influence on FDA's process in drafting its user fee commitment letters and legislation.

As clinicians, we often have discussions with our patients about potential treatment options. In those discussions, we consider both the potential benefits as well as the potential risks in making specific clinical care recommendations. Ultimately, we work in partnership with our patients in developing a treatment plan that centers their health and well-being above all else and where the benefits outweigh the risks as much as possible. With these user fee agreements, Congress and the FDA must take a similar approach, considering both the benefits and the risks, both short-

⁶⁷ Mahase E. Three FDA advisory panel members resign over approval of Alzheimer's drug. *BMJ*. 2021;373:n1503. doi:[10.1136/bmj.n1503](https://doi.org/10.1136/bmj.n1503)

⁶⁸ Food and Drug Administration. PDUFA VII: Fiscal Years 2023 – 2027. *FDA*. Published August 23, 2021. Accessed January 31, 2022. <https://www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-vii-fiscal-years-2023-2027>

⁶⁹ Food and Drug Administration. Summary of views and comments received to Docket No. FDA-2021-N-0891 regarding proposed recommendations for PDUFA VII. Accessed January 31, 2022. <https://www.fda.gov/media/155023/download>

and long-term, of the included proposals. It is clear to me that overall, the benefits of having an adequately funded FDA outweigh any potential risks. However, further reforms must be made to ensure that the FDA is fulfilling its mandate and promise of protecting and improving our patients' and our nation's health.