MILKEN INSTITUTE
FasterCures

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October 28, 2021

The Honorable Janet Woodcock, M.D.
Acting Commissioner
Food and Drug Administration
Dockets Management Staff (HFA-305)
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: FDA-2021-N-0891 for "Reauthorization of the Prescription Drug User Fee Act; Public Meeting; Request for Comments."

Dear Commissioner Woodcock,

FasterCures appreciates the opportunity to provide comments to the Food and Drug Administration's (FDA's) request for comments on the reauthorization of the Prescription Drug User Fee Act (PDUFA). We applaud FDA's efforts to build on the strengths of previous PDUFA commitments, such as incorporating the patient's voice in the regulatory process and introducing commitments that leverage lessons learned from the COVID-19 pandemic to strengthen and modernize the biomedical research system. We look forward to contributing our comments on these activities that are aimed at fostering an innovative and patient-centric R&D system and ensuring that new treatments are delivered to those who need them the most in a timely manner.

FasterCures, a center of the Milken Institute, is driven by a singular goal: to save lives by speeding scientific advancements to all patients. With an independent voice, FasterCures is working to build a system that is effective, efficient, and driven by a clear vision: collaborating with our partners to build a patient-centric system where science is accelerated, unnecessary barriers are overcome, and lifesaving and life-enhancing treatments get to those who need them as rapidly and as safely as possible.

FasterCures' comments on the PDUFA VII commitments focus on the following priority areas that align with the Center's mission and workstream:

- Augmenting the patient's voice in the drug development and review process
- Investing in the development and review of cell and gene therapies
- Accelerating medical product development
- Collection and use of real-world data and evidence
- Expanding capacity to review innovative clinical trials design and methodology
- Increasing diversity in clinical trials and patient engagement

Augmenting the Patient's Voice in the Drug Development and Review Process

FasterCures is a proponent of representing the patient's voice throughout the biomedical ecosystem and applauds the FDA for detailing activities in the PDUFA VII commitment letter that build on and enhance existing agency efforts. We were supportive of the introduction of the patient-focused drug development (PFDD) initiative as part of PDUFA V reauthorization and its continuation in PDUFA VI. We have continued to support these activities by creating a set of tools for patient advocacy organizations that are

interested in hosting an externally led PFDD meeting, including a report on "Smart Practices from Community Leaders," a PFDD Readiness Assessment, Meeting Tracker, and Community Toolbox.[1] We are pleased with FDA's commitment to advancing PFDD activities in PDUFA VII by strengthening capacity to facilitate the development and use of patient-focused methods to inform drug development and regulatory decisions. The experts identified internally at the FDA and outside of the agency, through the Intergovernmental Personnel Act's sole focus on methodological considerations for enhancing patient-centricity in the drug development and review process, is the logical next step in FDA's efforts in this area. We also applaud the FDA for expanding PFDD activities in the Center for Biologics Evaluation and Research (CBER) by proposing to convene a public meeting to better understand patient perspectives on gene therapy products.

FasterCures is also supportive of the FDA's commitment to solicit the public's input on methodological issues for the submission and use of patient data for benefit-risk assessment, product labeling, and other issues. As this work progresses, it is essential that the agency endeavors to engage patients and patient advocacy groups for their perspectives, as they are best positioned to elucidate areas of pressing patient needs for information for FDA's consideration.

The PDUFA VII commitment letter highlights the FDA's pledge to continue developing standard core sets of Clinical Outcome Assessments (COAs) and Related Endpoints. These efforts include soliciting public input to allow FDA to understand stakeholders' perspectives on diseases and domains of greatest need or highest priority for development of Standard Core COAs and Endpoints and where patient-preference information can inform regulatory decision-making. The PDUFA VII commitment letter currently has no specifics about the timeline for these activities. We believe this is an important area for engaging patients in setting priorities and look forward to further details from the FDA.

Investing in the Development and Review of Cell and Gene Therapies

We are encouraged by FDA's commitment to expanding staff capacity and expertise to meet the burgeoning demand on the agency precipitated by the robust pipeline of biological products, such as cell and gene therapies (CGT). These technologies represent the frontier of treating some of the most complex and incurable diseases that currently exist. As such, it is important to eliminate any potential barriers to efficient development and approval of these products to ensure that they get to patients that need them.

The FDA has been vocal about the lack of staff capacity and capability to address the complexities inherent in reviewing cell and gene therapies. We recognize the additional constraints on staff at FDA CBER in the last 18 months as it pivoted its efforts to support product sponsors in the development and manufacturing of preventive vaccines and therapeutic products for COVID-19. The proposed phased-in hiring of additional staff at CBER detailed in PDUFA VII will go a long way in relieving the time and resource constraints that the center is facing in reviewing CGT products and in preparation for the anticipated influx of these products.

FasterCures has long championed incorporating the patient's voice and preference in the research and development process and is incredibly supportive of the proposed patient-focused drug development activities in PDUFA VII with relevant stakeholders to understand patient perspectives on gene therapy products. Through our programs on CGT, FasterCures has developed resources, including a patient and caregiver journey map in consultation with our community, that consider many of the questions that arise for patients and caregivers when confronted with an option of a cell or gene therapy.[2] The journey map

[1] Milken Institute, "Patient-Focused Drug Development Meetings: Smart Practices from Community Leaders," 2019, accessed October 12, 2021, https://milkeninstitute.org/report/patient-focused-drug-development-meetings-smart-practices-community-leaders.
[2] Milken Institute, "Mapping the Patient and Caregiver Journey for Cell and Gene Therapies," July 30, 2021, accessed October 12, 2021, https://milkeninstitute.org/report/patient-focused-drug-development-meetings-smart-practices-community-leaders.

can be an important resource to the agency as it carries out the stakeholder engagement activities in PDUFA VII and develops draft guidance and Question and Answer documents to inform CGT sponsors.

Finally, we appreciate FDA's commitment to increase interactions with sponsors during product development to overcome challenges related to Chemistry, Manufacturing, and Controls (CMC) activities. Through the course of our work, FasterCures identified a need for more opportunities for timely and iterative interactions between FDA and product sponsors on a sponsor's CMC evidence generation plans. Sponsors of products that receive an expedited drug development designation need to pursue a more rapid manufacturing development program to accommodate the accelerated pace of the clinical program; however, no such standalone program to accelerate CMC development exists. We support FDA's intention to conduct a CMC Development and Readiness Pilot (CDRP) that would allow sponsors additional CMC-focused meetings and discussions based on key milestones. We encourage FDA to share the lessons learned from the Pilot in a public workshop, to the extent feasible.

Accelerating Medical Product Development

The FDA and its staff have been widely praised for the speed and flexibility with which the agency responded to the demands and additional responsibilities introduced by the COVID pandemic and worked with sponsors to develop diagnostics and therapies. As discussed in FasterCures' publication on silver linings from COVID-19[3], we believe that lessons from the pandemic offer valuable insights for improving and accelerating R&D in the future. We are therefore supportive of activities identified as part of PDUFA VII that aim at reducing delays in the drug development cycle and accelerating the process to get therapeutic products to patients. These activities include enhancements to FDA meeting management goals with the introduction of the Type D meeting – which will allow for quicker FDA feedback on obstacles that the sponsor faces on a focused set of issues – and the INTERACT meeting – which will allow sponsors to address novel issues at the pre-IND phase with the FDA that would otherwise cause delays in getting the product to clinical trial. Another direct and important implication of the pandemic is the FDA's amendment of face-to-face meetings to include both in-person meetings and virtual meetings on technology platforms that allow for both audio and visual communication.

FasterCures applauds the FDA's inclusion of the Split Real Time Application Review (STAR) pilot program which aims to accelerate the review process "to allow earlier patient access to therapies that address an unmet medical need."[4] The Real-Time Oncology Review (RTOR) pilot program, which serves as the precedent for the STAR program, has demonstrated success by shaving 3-4 months off the time to FDA approval (compared to PDUFA goal date) for a handful of applications.[5] The STAR pilot program will initially apply to efficacy supplements across all therapeutic areas and will seek to expedite patient access to novel uses for existing therapies. While this is an important first step, the FDA should continue to evaluate lessons and best practices from RTOR and STAR for opportunities to apply the expedited multi-step review process in other instances of product development and review. The Coronavirus Treatment Acceleration Program (CTAP), created during the pandemic to accelerate the review of new treatments for patients as safely as possible, proved that it was possible to create and implement a special program for new product review in an emergency situation. The next step will be to adopt lessons across these programs into the FDA processes.

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[3] Esther Krofah and Kristin Schneeman, "Lessons Learned from COVID-19: Are There Silver Linings for Biomedical Innovation?," January 25, 2021, accessed October 12, 2021, https://milkeninstitute.org/sites/default/files/reports-pdf/MI_SilverLining_012521.pdf.

[4] FDA, "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 through 2027," August 2021, last accessed October 25, 2021, https://www.fda.gov/media/151712/download.

[5] Catherine Feng, Riddhi Virparia, and Eric T-K Mui, "Analysis of the Real-Time Oncology Review (RTOR) Pilot Program for Approvals of New Molecular Entities," *Therapeutic Innovation & Regulatory Science* 55, no. 4 (July 2021) :881-888, doi: 10.1007/s43441-021-00296-7

Other proposals in the PDUFA VII commitment letter, such as FDA's continued investment in the breakthrough therapy program, early consultation on the use of new surrogate endpoints, and efforts to advance development of drugs for rare diseases are all welcome goals that we believe will not only accelerate product development but will also facilitate greater innovation in the design and conduct of trials.

Collection and Use of Real-World Data and Evidence

The pandemic underscored the immense potential of real-world data and evidence (RWD/RWE) in filling knowledge gaps and providing information as quickly as possible about diseases and treatments in real-world situations. We are pleased that FDA included provisions in PDUFA VII that continue its efforts to leverage RWD/RWE in regulatory activities. While randomized controlled trials (RCTs) will remain the "gold standard" in evidence generation for new product review and approval, they have several inherent limitations related to their inability to fully capture the effect of products in real-world situations and in diverse population groups, especially those that are often underrepresented in clinical trials. The focus on augmenting FDA's use of RWD/RWE for post-market surveillance through the Sentinel Initiative to include exploring the potential for its use in support of new labeling claims, including approval of new indications of approved medical products or for satisfying post-marketing study requirements, could have significant implications for sponsors by providing them with a viable alternative for often costly and time-consuming approaches for collecting data to document the efficacy of their products post-approval.

As the FDA advances its efforts to leverage RWD/RWE as part of the review process, we want to highlight the importance of reviewing initiatives that emerged during the pandemic for best practices. One notable example is the Reagan-Udall Foundation's COVID-19 Evidence Accelerator, which provided a forum for participants from across the health research and care ecosystem to convene weekly to agree on a common set of core data elements, prioritize COVID-related research queries of their data, conduct parallel analyses, share and compare results, and improve methods. While this platform did not have the expressed purpose of aggregating data, it brought together data and technology companies as active partners in troubleshooting and responding to evidence generation needs. We hope the FDA will leverage the forum as a "think tank" to troubleshoot and identify solutions to using RWD/RWE in the context specified in the PDUFA VII commitment letter.

Expanding Capacity to Review Innovative Clinical Trials Design and Methodology

FasterCures is pleased with FDA's commitment to invest in expanding staff capacity to review innovative clinical trials design and methodology, specifically for advancing model-informed drug development and reviewing complex innovative designs. These models and innovative trials design hold the potential for addressing some of the persistent shortfalls in traditional clinical trials, including the cost and burden of carrying them out. Innovative trial designs such as master protocol trials – including REMAP-CAP, I-SPY COVID, SOLIDARITY, AGILE-ACCORD, and ACTIV's suite of master protocols[6] deployed during the COVID-19 pandemic – demonstrated what was possible for the future of the clinical trials ecosystem. Just as existing master protocols such as REMAP-CAP for pneumonia and I-SPY for breast cancer were adapted to studying treatments for COVID, we encourage the FDA to evaluate the utility of adapting the master protocols deployed during the pandemic for addressing areas of unmet medical needs. The FDA's focus on strengthening staff capacity to facilitate the appropriate use of these methods is a step in the right direction for modernizing drug development and review.

[6] Esther Krofah and Kristin Schneeman, "Lessons Learned from COVID-19: Are There Silver Linings for Biomedical Innovation?," January 25, 2021, accessed October 12, 2021, https://milkeninstitute.org/sites/default/files/reports-pdf/MI_SilverLining_012521.pdf.

Increasing Diversity in Clinical Trials and Patient Engagement

Notably missing from the PDUFA VII commitments are activities explicitly geared at increasing diversity and inclusion in clinical trials and patient engagement, despite being a topic for discussion in the January 15, 2021, FDA-stakeholder meeting held to discuss the PDUFA VII reauthorization. The COVID-19 pandemic offered valuable lessons and best practices for enhancing diversity in clinical trials. The next five years of PDUFA VII can be an important vehicle for building on those lessons to ensure better representation of diverse patient groups in the R&D process in general, and specifically in clinical trials.

Communities of color have been historically underrepresented in FDA trials. Despite making up 13 percent of the U.S. population, African Americans accounted for 8 percent of the population enrolled in clinical trials for new molecular entities and therapeutic biologics approved by FDA in 2020; Latinos make up 18 percent of the population, but only 11 percent of participants.[7,8] These proportions have remained largely unchanged in the last five years. Appropriate representativeness of diverse patient groups in clinical trials not only assures the safety, acceptability, and efficacy of the product for all members of the population but also promotes equitable access to care by ensuring that patient groups that bear the greatest burden of the disease have access to cutting-edge products through clinical trials.

FasterCures recognizes the imperative for increasing enrollment of underrepresented populations, including racial and ethnic minorities, in clinical trials and has a dedicated workstream focused on advancing this effort by:

- identifying and promoting actionable strategies for increasing diversity in the planning, design, recruitment, enrollment, and execution of clinical trials; and
- addressing diversity and inclusion in the health research workforce.

We appreciate the FDA's recent efforts to improve diversity in clinical trials, including the release of final guidance on "Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry".[9] The guidance document includes recommendations on designing and executing clinical trials of drugs and biologics that include people with different demographic characteristics (e.g., sex, race, ethnicity, age, location of residency) and non-demographic characteristics (e.g., patients with organ dysfunction, comorbid conditions, and disabilities; those at weight range extremes; and populations with diseases or conditions with low prevalence) and represents an important step in addressing lack of representation in clinical trials. Lessons learned from conducting medical research during the COVID-19 pandemic, including efforts by vaccine manufacturers to improve representation in their clinical trials, should be harnessed and normalized as part of biomedical research.

Specifically, the FDA should standardize the practice of accurate and complete documentation of minority representation in clinical trials by sponsors. Documentation should address barriers that researchers and drug sponsors face in recruiting diverse populations for their studies and patient and community-engaged strategies to address those barriers. The activities in PDUFA VII geared at advancing the use of real-world evidence in regulatory decision-making is a great opportunity for the FDA to supplement available information to understand the clinical and safety impact of therapeutic products that may have had an underrepresentation of relevant patient groups in the original clinical trial. In communicating and implementing the pilot Advancing RWE program in PDUFA VII, the FDA should consider emphasizing the

[7] United States Census Bureau, "Quick Facts: United States," accessed October 20, 2021, https://www.census.gov/quickfacts/fact/table/US/PST045219.

[8] FDA, "2020 Drug Trials Snapshots: Summary Report," February 2021, accessed October 20, 2021, https://www.fda.gov/media/145718/download.

[9] FDA, "Guidance Document: Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry," November 2020, accessed October 20, 2021, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enhancing-diversity-clinical-trial-populations-eligibility-criteria-enrollment-practices-and-trial.

importance of accurate documentation and reporting on relevant patient subgroups to facilitate analyses that can provide insights into differential impact as well as preference for therapies by different patient groups.

Opportunities for early sponsor consultation with the FDA, such as the new meeting Type D proposed in the PDUFA VII commitment letter and other strategies for enhancing communication between the FDA and medical product sponsors, offer great avenues for discussing sponsor strategies and barriers to enhancing diversity in their clinical trials. The proposed enhancements to the post-marketing required (PMR) studies in PDUFA VII, which requires the FDA to communicate details about anticipated PMRs earlier in the review process, present an opportunity for the agency to emphasize the importance of and define goals for diversity and inclusion in patient populations included in post-approval studies.

Finally, commitments in PDUFA VII that are focused on enhancing drug development and review such as patient engagement activities, including efforts to build on FDA's PFDD accomplishments and activities around the use of patient experience data for benefit-risk assessment and product labeling, should be leveraged to improve diversity and inclusion in the regulatory process.

We appreciate the FDA's consideration of these suggestions and look forward to working with the agency throughout this PDUFA reauthorization and subsequent implementation of key goals.

Sincerely,

Esther Krofah
Executive Director, FasterCures