

October 28, 2021

Janet Woodcock, M.D.
Acting Commissioner
U.S. Food & Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-0002

RE: Reauthorization of the Prescription Drug User Fee Act; Public Meeting (FDA-2021-N-0891-0001)

Dear Acting Commissioner Woodcock,

The [Alliance for Aging Research](http://www.agingresearch.org) (Alliance) appreciates the opportunity to comment on the performance goals and procedures in the Prescription Drug User Fee Act (PDUFA) VII commitment letter. We look forward to working with the Food & Drug Administration (FDA), Congress, and other stakeholders over the next year to provide the perspectives of older adults on the reauthorization.

The Alliance is the leading nonprofit organization dedicated to accelerating the pace of scientific discoveries and their application to vastly improve the universal human experience of aging and health. For the past fifteen years, we have engaged directly with the FDA, patient advocates, researchers, and industry on the drug development process for Alzheimer's disease and sarcopenia through our leadership of the [Accelerate Cure/Treatments for All Dementias \(ACT-AD\)](#) and [Aging in Motion \(AIM\)](#) coalitions. The Alliance has also continued our active involvement with the [Alliance for a Stronger FDA](#) to ensure annual appropriations that will adequately fund the FDA's essential missions.

Staff Hiring and Retention

The ability of the FDA to fulfill its public health mission relies upon the level of resources and ease of process with which the agency is able to recruit, hire, and retain talented individuals with highly sought-after skill sets. None of the other goals in the commitment letter can be realized unless the agency has adequate staffing to review new medical products. The Alliance is pleased that the commitment letter provides resources for additional staff to support the review of cell and gene therapies and other innovative products. As noted by other stakeholders throughout the negotiation process, reviewing these highly complex products has put a strain on the agency. The additional 132 full-time equivalents (FTE) within the Center for Biologics Evaluation and Research and 77 FTEs hiring targets within the Center for Drug Evaluation and Research (CDER) will significantly help the agency keep pace with the influx of applications for these products.

Furthermore, it has been evident in our conversations with our partners at the FDA that the deluge of complex product reviews combined with the extreme pressures put on the agency by the COVID-19 pandemic has led to burnout of review staff. It is our hope that the agency will be able to hire these additional staff expediently and relieve the tremendous burden placed on agency staff.

RE: Reauthorization of the Prescription Drug User Fee Act; Public Meeting (FDA-2021-N-0891-0001)

In our August 2020 comments on the PDUFA VII agreements, the Alliance noted that a fundamental issue thwarting the efficient and timely hiring of new staff is the agency's multiple recruitment authorities and pay scales that can slow down the hiring process. The PDUFA VII agreement provides funding for an independent contractor with expertise in human resources operations to provide recommendations on how the agency can improve hiring and retention. The Alliance recommends that a key objective of the independent contractor should be to simplify and streamline the hiring process at the agency. The agency competes with the private sector, academia, and other federal agencies for these highly skilled reviewers. Long delays place the agency at a competitive disadvantage in the hiring process, resulting in the potential loss of many capable candidates.

Enhancing Older Adult Clinical Trial Representation and Real-World Evidence

Enhancing real-world evidence (RWE) in regulatory decision-making is a crucial priority for the Alliance. While older adults are the primary users of prescription drugs and other medical products in the United States, they are often underrepresented in randomized clinical trials (RCT). For example, two-thirds of cancer patients in the United States are 65 years old, but 75 percent of cancer RCT enrollees are younger than 65.¹ A key reason for the underrepresentation of older adults in RCTs is strict exclusionary criteria prohibiting the participation of individuals that have one or more co-morbid conditions. However, 60 percent of U.S. adults have at least one chronic condition, and 70 percent of Medicare beneficiaries report two or more.^{2,3} This finding underscores the importance of understanding how treatments may be impacted in real-world conditions, whereas the majority of adults receiving therapy will also have another condition.

We appreciate the ongoing efforts from the FDA to encourage the medical product research communities to recruit and enroll older adults in clinical studies, including numerous draft guidances, public awareness campaigns, fact sheets, personalized consultation with researchers, and more. The March 2020 draft guidance, "[Inclusion of Older Adults in Cancer Clinical Trials](#)," was an important step in addressing the underrepresentation of older adults in cancer clinical trials. It sent a strong message to oncology clinical development programs that they should be deliberate in their recruitment efforts to enlist a group of older adults that reflects the intended population for the treatment being studied and evaluated. As the FDA itself states, "To make sure that the FDA has a full picture of the risk or benefit of a medical product, patients enrolled in a trial should be representative of the types of patients who are likely to use the medical product if it is approved or cleared by the FDA."⁴ The guidance also recognizes that effective solutions to underrepresentation must also include a strategy to include older adults throughout the trial process—from early clinical development to post-market data collection. The Alliance strongly supports this broad vision for inclusion. **The Alliance urges the FDA to formalize this**

¹ Lewis JH, Kilgore ML, Goldman DP, et al. Participation of patients 65 years of age or older in cancer clinical trials. *J Clin Oncol*. 2003;21(7):1383–1389

² Centers for Disease Control and Prevention. Chronic Diseases in America. 23 Oct 2019. Accessed 13 Aug 2020. <https://www.cdc.gov/chronicdisease/resources/infographic/chronic-diseases.htm>

³ Chronic Conditions Charts: 2015. Baltimore, MD: Centers for Medicare & Medicaid Services. Found on the internet at https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/ChronicConditions/Chartbook_Charts.htm

⁴ U.S. Food and Drug Administration. FDA Encourages More Participation, Diversity in Clinical Trials. Available at <https://www.fda.gov/consumers/consumer-updates/fda-encourages-more-participation-diversity-clinical-trials>. Last updated on 1/16/18.

RE: Reauthorization of the Prescription Drug User Fee Act; Public Meeting (FDA-2021-N-0891-0001)

guidance and issue similar agency-wide guidance for all medical products meant to treat conditions that primarily impact older adults.⁵

The FDA's own 2020 guidance, "[Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry](#)," urges industry to design trials in a manner that reduces the barriers to entry and overall burden on participants, including older adults, therefore encouraging diversity in enrollment and study. This includes broadening eligibility requirements to include older adults, which "...maximizes the generalizability of trial results and the ability to understand the therapy's benefit-risk profile across the patient population likely to use the drug in clinical practice, without jeopardizing patient safety."⁶ This also includes designing trials so that the criteria for various phases can be modified to reduce limitations on specific participants. The FDA's PFUFA VII clinical trial diversity plans should include and encourage the full range of research designs outlined in the FDA's broader "Enhancing the Diversity of Clinical Trial Populations" guidance.

The Alliance praises the FDA for its March 2021 workshop, "Roadmap to 2030 for New Drug Evaluation in Older Adults," that brought together stakeholders from academia, industry, and regulatory agencies in a virtual setting to discuss the status of inclusion of older adults in clinical trials and strategies to ensure the safe and effective use of drugs in this population. As part of the presentations, [former FDA Commissioner Robert Califf](#) called for "Bottom Line" recommendations that included the formation of an FDA Office on Older Adults, as well as:

- Require pharmacokinetic/pharmacodynamic (pK/pD) and human factors studies if intended use includes older adults
- Require specific consideration of including a representative sample of older adults in registration trials
- Require specific RWE in the post-market driven by specific likely uses of the medication
- Work with multiple sectors to advance the framework, so the whole becomes much greater than the sum of the parts.

It is critical that we understand potential age-related differences in pharmacologic properties, toxicities, and efficacy of new treatments. However, this can often not be done due to the underrepresentation of older adults in RCTs. While we need to build out our evidence base on novel medicines by including more older adults in RCTs, we can also build our evidence base using RWE in this population. RWE has been essential in increasing our understanding of how new treatments are working in older adults. This data can complement data from randomized clinical trials by filling in our data gaps for trials with a representative sample of older adults. As real-world data sources become more varied and the type of data collected, we will need new analysis methods to draw insights. With sufficiently robust datasets, there is the potential to draw meaningful understandings on the safety and efficacy of novel medicines in subsets of older adults by comorbidity, cognitive function, and frailty status.

The Alliance applauds the FDA for its efforts to advance the use of RWE in regulatory decision-making in the PDUFA VII commitment letter. The Advancing RWE Program pathway has the potential to advance the field of RWE and broadly inform FDA and industry practices through its regular reporting

⁵ <https://www.agingresearch.org/alliance-submits-comments-to-u-s-food-drug-administration-regarding-the-inclusion-of-older-adults-in-cancer-clinical-trials/>.

⁶ Center for Drug Evaluation and Research. June 2019. Guidance Document: Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry. Rockville, MD: U.S. Food & Drug Administration.

RE: Reauthorization of the Prescription Drug User Fee Act; Public Meeting (FDA-2021-N-0891-0001)

requirements. The use of RWE is evolving, and we appreciate the flexibility that agency has introduced into the process. We are learning as a research community how best to use this data. We also want to emphasize the importance of updating RWE guidance and holding public workshops on how RWE can meet regulatory requirements supporting labeling effectiveness and post-approval study requirements. Due to the significance of RWE programs for older adults, we ask that the agency consider accelerating its timeline to implement these commitments.

As mandated by 21st Century Cures, we believe that the agency should continue to explore the use of RWE in fulfilling post-marketing study requirements. A key consideration that the agency should explore as it develops its thinking on RWE is when and how RWE could be accepted in Phase IV studies for drugs receiving [accelerated approval](#).

Patient-Focused Drug Development

Since the PDUFA V negotiations, the Alliance has strongly advocated for the FDA's Patient-Focused Drug Development (PFDD) Initiative. We believe incorporating the patient voice into regulatory decision-making is a vital component of the process. We have seen firsthand the value of the agency's PFDD initiatives. At the urging of the Alliance-led AIM coalition, sarcopenia was selected as a condition of interest for an FDA-led PFDD meeting. The meeting brought together patients, advocates, researchers, and review division staff for the agency to learn about the experiences and preferences of patients living with the condition. This was the first time that many within the review division were able to hear the perspectives of people living with sarcopenia on how they live with the condition and their treatment and outcome preferences.

In the PDUFA VII commitment letter, the agency will dedicate resources to train staff to integrate PFDD methods into regulatory decision-making, issue an RFI on PFDD methodological considerations, and issue draft guidance on using and submitting patient preference information. We applaud these proposed activities.

Furthermore, through the AIM coalition, we were invited to work with the [Northwestern University Clinical Outcome Assessment Team \(NUCOAT\)](#) on a CDER pilot program as it seeks to develop and validate COAs for sarcopenia and other chronic conditions. It is expected that the project will produce a core set of physical function outcome sets that measure a range of physical function severity that could be generalizable across multiple conditions. This work has tremendous potential to increase the science of developing COAs and foster a new era of patient-focused drug development. Additionally, these COAs provide clarity and transparency to drug development and the research communities that can promote investment in neglected therapeutic areas, such as sarcopenia. The Alliance recommends that the agency expand investment and resources available to develop publicly available and FDA-validated COAs. We appreciate that the agency has committed to creating a virtual catalog of standard core sets and will use non-user fee funding for further work to develop standard core sets.

Digital Health Technologies/Decentralized Trials

The Alliance is encouraged by the FDA's plans to expand the role of digital health technologies in drug development and review while devoting resources to expanding digital health expertise. If properly designed, digital health technologies and decentralized trials can increase older adult participation in clinical research. There is tremendous diversity among older adults based on health status, lifestyle, and interactions with the healthcare system. Digital health technologies have the

RE: Reauthorization of the Prescription Drug User Fee Act; Public Meeting (FDA-2021-N-0891-0001)

potential to increase enrollment and improve retention of older adults, particularly among those residing in rural areas and with mobility issues. Furthermore, by bringing clinical research tools directly to patients, sponsors will be able to select from a much broader range of candidates. We are supportive of the steps the agency will take to strengthen the use of digital health technology to support new drug registration, label expansion, and safety monitoring.

While digital health technologies have many potential benefits, we need to ensure we are using such technologies appropriately. As the agency builds capacity and develops final guidance on regulatory considerations for data generated from digital technologies, we urge the agency to consider the challenges that older adults may face using digital health technologies. Research has shown that there is a deep "digital divide" between different subgroups of older adults based on socioeconomic factors, educational levels, and ethnicity.⁷ These are the same demographic groups underrepresented in traditional clinical trials, and we need to ensure that they are not left behind as clinical research evolves into the digital age. The FDA and stakeholders need to carefully consider overcoming this digital divide and making our trial populations more representative rather than reinforcing current patterns.

Furthermore, while not included in the agreement letter, we urge the agency to publish guidance on decentralized trials. Additional research needs to be performed to determine the circumstances for which virtual trials are appropriate and others where a hybrid (partially virtual/partially in-person) approach or a traditional in-person mode is required. The FDA also needs to evaluate best practices for promoting retention in trials utilizing virtual components and establish processes to train trial participants to participate and use necessary technologies successfully.

Conclusion

Thank you again for the opportunity to provide comments on our organization's priorities for the reauthorization of the PDUFA program. We look forward to working with the Agency and Congress on this important program and hope to serve as a resource to the agency on issues impacting older adults. If you have any questions, please do not hesitate to contact us. Inquiries can be directed to Michael Ward, mward@agingresearch.org, and Ryne Carney, rcarney@agingresearch.org.

Sincerely,



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⁷ Tappen, Ruth M., et al. "Digital Health Information Disparities in Older Adults: A Mixed Methods Study." *Journal of Racial and Ethnic Health Disparities*, 2021, <https://doi.org/10.1007/s40615-020-00931-3>.