Alliance FOR AGING RESEARCH
Catalyzing Innovation for Healthy Aging

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August 21, 2020

Commissioner Stephen M. Hahn, MD
Food and Drug Administration
Dockets Management Staff (HFA-305)
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2010-N-0128 for Request for Comments of "Reauthorization of the Prescription Drug User Fee Act; Public Meeting"

Dear Commissioner Hahn,

The Alliance for Aging Research (the "Alliance") is the leading non-profit organization dedicated to accelerating the pace of scientific discoveries and their application to improve the experience of aging and health. The Alliance believes that advances in research help people live longer, happier, more productive lives, and reduce health care costs over the long term. For the past fifteen years, we have worked directly with the U.S. Food and Drug Administration (FDA), patient advocates, researchers, and industry on ways to streamline drug development 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. We had the opportunity to testify before the U.S. Senate and House of Representatives on the sixth reauthorization of the PDUFA, and value the openness of the agency to work with stakeholders and the patient community.

The Prescription Drug User Fee Act (PDUFA) has been a tremendously successful program that decreased the times to review new drugs, improved engagement between the FDA and patient stakeholders, increased the patient-centricity of the agency, and has accelerated the pace at which new treatments are brought to market. We would also be remiss if we need not express our sincere appreciation for the agency's response to the COVID-19 pandemic, such as speeding up guidance development and streamlining the investigational new drug (IND) processes to ensure that potential treatments for the novel coronavirus can be reviewed swiftly. The below recommendations constitute areas that our organizations believe will benefit older adults and patients at large.

Older Adult Disease-Specific Guidance

Earlier this year, the FDA published the draft guidance document, Inclusion of Older Adults in Cancer Clinical Trials. The guidance provided recommendations to improve the representation of adults 65 years and older in clinical trials of drugs for the treatment of cancer, which would better inform the

benefit-risk profile for these respective therapies in this population**. Broadly, the Alliance recommends greater inclusion of older adults in clinical trials to determine reviewed products' safety and efficacy for the aging population.** We were appreciative that the FDA made including more older adults in clinical trials a priority. The draft guidance signaled that researchers and drug sponsors should include more older adults with cancer in their clinical trials.

The Alliance further recommends that in PDUFA VII the agency works to issue similar guidance for drugs meant to treat conditions primarily impacting older adults. The inclusion of older adults in drug trials increases our understanding of a respective drug's benefit-risk profile for older adults and can better inform a drug's use in clinical practice. The inclusion of label information describing a new medical product's use in older adults promotes better prescribing in clinical practice and promotes the safe and effective use of these products. The FDA should model its guidance after the National Institutes of Health Guidelines on the Inclusion of Individuals Across the Lifespan as Participants in Research Involving Human Subjects. For proposed measures, such as geriatric assessment tools, the FDA should consider modeling the European Medicines Agency's Geriatric Medicines Strategy.

Decentralized Clinical Trials

The COVID-19 pandemic has catalyzed novel approaches to digital technologies and decentralized trials. The pandemic further highlighted what has long been known about clinical trials; the lack of geographically diverse clinical trial locations has historically negatively impacted the representativeness of clinical trial participants.[1] Decentralized trials present an opportunity to reduce geographic barriers and make it easier for individuals to participate in clinical trials. Extending clinical trials to a diverse variety of local environments hold the potential to increase enrollment, enhance the diversity and improve retention of trial participants, and expedite trials.

Virtual, or digital, trials hold potential for promoting decentralized trials. The Coronavirus Disease 2019 (COVID-19) pandemic has provided opportunities, by necessity, for testing of virtual trial approaches. The use of remote monitoring and telehealth has allowed some trials to continue during the pandemic; however, some data collection is available only in-person and may require specialized equipment, such as trials requiring high-resolution imaging. Increasing virtual or remote components of clinical trials holds the potential for reducing participant burden (number of in-person visits, etc.), which has additional importance to populations that have impaired mobility. However, we need a greater understanding of the challenges that older adults may face when participating in a remote clinical trial. A limited number of fully virtual trials have been completed, but were focused on established therapies and devices for overactive bladder and diabetes that were previously approved by the FDA.[2] Additional research needs to be performed to determine the circumstances for which virtual trials are appropriate,

[1] Feyman Y, Provenzano F, David FS. Disparities in Clinical Trial Access Across US Urban Areas. JAMA Netw Open. 2020;3(2):e200172. doi:10.1001/jamanetworkopen.2020.0172

[2] National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Sciences Policy; Forum on Drug Discovery, Development, and Translation; Shore C, Khandekar E, Alper J, editors. Virtual Clinical Trials: Challenges and Opportunities: Proceedings of a Workshop. Washington (DC): National Academies Press (US); 2019 Jul 23. Appendix C, Examples of Virtual Clinical Trials Included in the Workshop Handout. Available from: https://www.ncbi.nlm.nih.gov/books/NBK548975/

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, as well as work to establish processes to train trial participants in how to successfully participate and use necessary technologies.

We believe that PDUFA VII will provide an opportunity to further the use of these approaches. **The Alliance encourages the FDA to prioritize the testing, evaluation, and use of decentralized and virtual clinical trials to ensure that older adults and diverse populations affected by a disease are appropriately represented in our clinical trials.** We believe the PDUFA VII should encourage these innovative trial designs that reduce barriers and encourage participation by older adults.

Translation of Real-World Evidence/ Post-Market Requirements

The agency has made great strides in the use of real-world evidence (RWE) in its regulatory decisions. The agency has committed to exploring RWE in evaluating the safety and effectiveness of medicines.

The enhancement of RWE in regulatory decision-making is a key priority for the Alliance for Aging Research. This data can be used to evaluate the post-market safety of products and support drug development approval. Older adults are too often excluded from randomized controlled trials due to exclusion criteria for clinical trials often prohibiting the participation of individuals that have one or more co-morbid conditions. However, 60 percent of US adults have at least one chronic condition.[3] This finding underscores the importance of understanding how treatments may be impacted in real-world conditions, where the majority of adults receiving a therapy will also have another condition.

The Alliance recommends the FDA issue guidance that further clarifies the circumstances where real-world evidence would be accepted and identify the limitations of real-world data. The use of real-world evidence has been critical for 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 that did not have a representative sample of older adults. As sources of real-world data become more varied, and the type of data collected, we will need new methods of analysis to draw insights.

Patient registries have been increasingly used to provide real-world evidence on the effectiveness, quality, and safety of medical interventions. Patient registries can collect clinically meaningful patient data, in a scientifically rigorous manner, to support clinical and health policy decisions. However, the lack of transparency and availability of registry data provides barriers to evaluating outcomes. Many registries do not provide the FDA with access to the data set or regular data summaries. Data from these registries would bolster the availability of RWE and help provide timely response to evidence questions. The Alliance would like to ensure that the FDA has access to the data and oversight over patient registries so that evidence questions can be answered expeditiously. **To support this aim, the FDA should ensure that regular reports (annually, at a minimum) from registries are made available to the agency.**

[3] 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

Additionally, the Alliance supports the collection of data on older adults in the post-market setting, and we recommend that in PDUFA VII the agency should require the publication of post-market studies on older adult patients. Post-market data may enhance clinical guidelines, including information on dosing, side effects, and treatment response; as well as patient decision-making regarding risk-benefit and shared decision-making with providers on treatment choice.

Core Outcome Set

The Alliance commended the FDA when it announced its pilot grant program to develop a set of publicly available core set of clinical outcome assessments (COAs) and their related endpoints. Through our Aging in Motion (AIM) coalition, we had the opportunity to work with the Northwestern University Clinical Outcome Assessment Team (NUCOAT) as it seeks to develop and validate COAs for sarcopenia and other chronic conditions. It is expected that the project will a produce 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.**

Staff Hiring and Retention

The strength of the FDA relies upon its ability to recruit, hire, and retain individuals with specialized skillsets for the review of new medical products. However, despite more funding, hiring authority, and recruitment tools provided to the agency through PDUFA VI and the passage of the 21st Century Cures Act, the agency still faces challenges in recruiting sufficient staff to meet the current demands of the review pipeline. This issue is particularly urgent as almost half of the senior leadership within the agency will be eligible for retirement by the end of FY 2020.[4]

Through PDUFA VI, the agency made new commitments to improve its ability to hire and retain staff who are critical for the review of new drug applications. The agency committed to modernizing its hiring system infrastructure, augmenting its hiring staff capacity and capability, creating a dedicated unit within the Office of Medical Products and Tobacco charged with continuous staffing, and hiring an independent contractor to assess hiring practices for the human drug review program. Despite these commitments, the initial assessment of hiring and retention practices at the agency confirmed well-known problems such as understaffed human resource departments, complicated federal salary schedules, lengthy hiring processes, and conflict of interest rules.[5] A fundamental issue thwarting the efficient and timely hiring of new staff is the multiple recruitment and pay scales that can slow down the hiring process. **The FDA should work toward simplifying its hiring processes in the next reauthorization**

[4] Ogrysko, Nicole. "FDA Developing Alternative Pay System to Resolve Recruitment, Retention Woes." Federal News Network, 6 July 2018, federalnewsnetwork.com/hiring-retention/2018/07/fda-developing-alternative-pay-system-to-resolve-recruitment-retention-woes/

[5] Booz Allen Hamilton, 2020, FDA Interim Hiring and Retention Assessment, www.fda.gov/media/138662/download.

of PDUFA. Potential inefficiencies resulting from its multiple pay scales and hiring authorities should be addressed.

The Alliance believes that for the FDA to operate most effectively, it must be able to compete with the private sector, academia, and other federal agencies for these highly skilled reviewers. Due to the rapid advancements in medicine and science, the agency needs to be able to attract top-tier talent to meet its public health mission. **While a dual focus on recruitment and retention of highly-qualified review staff is necessary to meet growing demand, the FDA should place enhanced emphasis on retention, as it is significantly more expensive to recruit and train new staff than to provide additional compensation or benefits to established employees.**

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 you in the coming years 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 the Alliance for Aging Research's Director of Public Policy, Michael Ward, at mward@agingresearch.org.

Sincerely,

Michael Ward
Director of Public Policy

Ryne Carney
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