Alliance
FOR AGING RESEARCH

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August 22, 2016

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

RE: FDA-2016-N-1895-0009 Prescription Drug User Fee Act; Request for Comment

Dear Dr. Woodcock:

The Alliance for Aging Research 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 ten 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 Alzheimer's Disease (ACT-AD) and Aging in Motion (AIM) coalitions. Because of this experience in the regulatory space we recognize the critical role that the Prescription Drug User Fee Act (PDUFA) plays in maintaining processes across the human drug review program that allow patients timely access to safe and innovative treatments, particularly in areas of unmet need like Alzheimer's disease and sarcopenia.

We were grateful to have access to senior representatives from the FDA during monthly stakeholder consultation meetings held throughout the PDUFA VI negotiations. We also were honored to have the opportunity to provide patient perspectives on panels during the public meeting held to kick off the reauthorization process in July of 2015 and on the PDUFA VI Commitment Letter in August of 2016. In addition to the feedback we provided during these meetings, we would like to provide further comments on several provisions that we support as part of PDUFA VI.

Pre-Market Review

Early and ongoing communication with the FDA is essential to expediting drug development. We believe that PDUFA VI makes critical changes to the FDA's internal communications and communications with sponsors that will help to shape more successful clinical programs.

First and foremost, we support the utilization of user fees under Section I, number 1 of the Commitment Letter, to maintain dedicated staff within the Center for Biologics Evaluation and

Research (CBER) and the Center for Drug Evaluation and Research (CDER) focused on improved communication between the FDA and sponsors during drug development. We were encouraged to learn that these staff will provide ongoing training to the medical product review divisions on best practices for communicating with sponsors, while at the same time working to better facilitate responses to general questions from sponsors on drug development and ensure timely resolution of issues with specific INDs. We also support the use of fees for an independent assessment of current communications practices and a planned public workshop to examine the results of this assessment with an eye toward issuing updated guidance on FDA-Sponsor Communications, if it is necessary.

The second provision we support under Section I is number 3, early consultation on the use of new surrogate endpoints. The meetings described in this section will allow companies to engage with FDA's senior leadership on the feasibility of using a surrogate endpoint that has not previously been used as the basis for an approval and address any knowledge gaps that require attention. While we do not yet have a qualified biomarker for use as a surrogate in sarcopenia or Alzheimer's disease, we know that clinical trials utilizing surrogate endpoints will be increasingly important as drug development moves toward intervention earlier in the course of these diseases. Establishing this dedicated process for meetings on surrogates that can occur as early as end of Phase 1 is a priority for us.

The third provision that is important to the Alliance is Section I, number 5, advancing the development of combination products. It is expected that the number of products in development that are combination products will increase to almost 40 percent in the future. Because of this significant increase, it is important that FDA is able to ensure that drug-device and biologic-device combinations do not face unexpected delays in the review process. We are pleased that PDUFA VI will provide funding for capacity building, staff training, and performance goals for CDER-led and CBER-led combination product activities.

During the kick-off meeting for the PDUFA VI reauthorization process, we highlighted the strain the creation of the Breakthrough Therapy Program placed on the Agency because it is resource-intensive and did not come with additional funding under PDUFA V. We support the addition of user fees in PDUFA VI that allows for 36 FTEs out of general PDUFA funds to assist with this expedited approval pathway. The Breakthrough Therapy Program has been incredibly successful in delivering truly innovative products for serious and life-threatening conditions. We will be glad to see it continue and hope it will be a viable pathway for Alzheimer's disease and sarcopenia treatments in the near future.

The final provision we support in Section I is number 6, enhancing the use of real-world evidence in regulatory decision making. Data on medical products generated as part of the practice of medicine is already being successfully utilized for the purposes of assessing a product's safety in populations that are underrepresented in randomized controlled trials (RCTs). Older adults are often excluded from RCTs due to advanced age or presence of comorbidities. Real-world evidence has been critical in understanding how new treatments are performing in this population when they enter the post-market space. We support FDA's efforts under PDUFA VI to go beyond the current use of real-world evidence for assessing safety post-market and to explore how this valuable information can be used in assessing a product's efficacy. The

proposed multi-stakeholder public workshops, methodology-development pilot programs, and regulatory guidance represent a sound, comprehensive approach to harnessing the potential of real-world evidence for patients, product sponsors, and the Agency.

Regulatory Decision Tools

The Alliance for Aging Research has been a strong advocate for the Patient Focused Drug Development (PFDD) Initiative since the PDUFA V negotiations. We were fortunate that, at the urging of our AIM Coalition, sarcopenia was selected for an FDA-led PFFD meeting in 2017. Prior to this meeting, we have already experienced the power that a full understanding of the patient's experience can have on FDA medical reviewers. We supported the continuation of FDA-led PFDD meetings as part of PDUFA VI and are pleased that FDA will have the flexibility under Section J of the Commitment Letter to utilize user fee funds for disease-specific meetings, if they determine them to be useful. We are also encouraged that PDUFA VI provides resources for 230 FTEs with expertise in patient-focused methods to be embedded into the review divisions. It is anticipated that these new staff will provide clinical, statistical, psychometric and health outcomes skills to enhance FDA's capacity to guide the incorporation of patient-reported outcomes and other patient-focused clinical outcome assessments into drug development programs.

To compliment the internal changes at FDA in the area of PFDD, Section J, number 1b. of the Commitment Letter lays out a clear process for developing sequential guidance with full participation from the patient advocacy community, industry and FDA on the collection of patient input leading to the development of patient-centered measures. We strongly support FDA's leadership in PFDD, because there is no one patient advocacy organization or company that can or should speak for all patients, and because the process is ultimately meant to inform improved medical product development within the FDA's review divisions. The proposed outlined process maintains and clarifies FDA's role, while providing much-needed user fee funding for external capacity building. The Alliance looks forward to participating in the public process between FY 2018 and FY 2021 to represent the unique needs of older adults. We further support FDA's commitment to creating and maintaining a repository of clinical outcome assessment tools, patient-focused meeting resources, and other patient-focused efforts. This repository will help ensure that there is efficient use of patient group and industry resources when pursing the development of novel PFDD tools.

Since PDUFA V, we have supported the dedication of user fees to develop a transparent and structured benefit-risk framework at the FDA. Understanding the components of FDA's benefit-risk assessment and how these components are applied in the context of regulatory decision-making is of keen interest to industry and the patient advocacy community. The updated benefit-risk implementation plan, planned public meeting and proposed draft guidance under Section J, number 2 of PDUFA VI will enable more productive activities in the stakeholder community to capture patient experiences and communicate those findings to the FDA throughout the drug development process and at the time of product review.

Section J, numbers 3 and 4 of the Commitment Letter greatly enhance FDA's ability to advance the future of drug development through the addition of staff with expertise in statistical modeling

and innovative clinical trial designs. We convened two impactful meetings through the Accelerate Cure/Treatments for Alzheimer's Disease Coalition on combination therapy development for Alzheimer's disease. These meetings highlighted that modeling and simulation will be important in the early development of drug-drug combinations and that adaptive clinical trials employing advanced statistical methods will be essential in testing any multi-drug regimen for Alzheimer's disease. We are optimistic that combination therapy will be a successful part of Alzheimer's disease treatment in the future. The proposed fees in Section J for model-informed drug development and complex design review will provide the Agency with additional staff and funding for public meetings to guide FDA's and industry's incorporation of innovative drug development methods.

The Alliance for Aging Research has first-hand experience with the FDA's Drug Development Tool (DDT) Qualification Process. Our Accelerate Cure/Treatments for Alzheimer's Disease Coalition was represented in the Critical Path Institute's efforts to qualify multiple tools for use in clinical trials for Alzheimer's disease. The Alliance-led AIM Coalition is currently pursuing qualification of two functional assessments to be used as performance outcome (PerfO) measures for a subset of sarcopenic patients. We feel strongly that the DDT Qualification Process should continue because it provides a unique space for collaboration among multiple stakeholders to advance measure development in the public domain often using pooled resources. We support the dedication of funds under Section J, number 6 a-f of PDUFA VI to expand base capacity within the qualification review team and to host a series of public meetings resulting in guidance that strengthen the DDT Qualification Process. As with Section J, we believe FDA should continue maintaining a repository of qualification submissions.

Hiring and Staff Retention

Section III of the Commitment Letter improves FDA hiring and staff retention practices. In our view this is one of the most critical components of the Commitment Letter because the agency will only be successful in carrying out all of the activities we care about in PDUFA VI if it has the best and the brightest people and continued stability in its' workforce. To do this, FDA needs to compete on a level playing field with the private sector and other federal agencies for highly-skilled individuals.

We recognize that the FDA lacks a number of tools that would allow it to maintain a robust hiring and retention function, which is why the Alliance for Aging Research pushed for a focus on hiring during PDUFA VI, and during the development of the House of Representative's 21st Century Cures Act and the Senate's Innovation Initiative. We are pleased to see that industry is putting resources toward hiring and retention processes at FDA, and there are several proposed enhancements under Section III that we would like to highlight.

The first is Section III A, modernization of FDA's hiring system. Two highlights of this section are 1) FDA's commitment to reviewing and cataloguing existing position announcements in order to implement a comprehensive online position classification system, and 2) the FDA's planned efforts to transition away from time-limited individual position vacancy announcements. Shifting to common vacancy announcements for use by multiple offices with continuous posting will create the greatest opportunity for applicants with key scientific and technical expertise to

apply for positions regularly needed across FDA's drug review programs. We think that both of these are positive steps forward.

The second noteworthy section is Section III B, augmentation of hiring staff capacity. Because of chronic challenges in retaining and recruiting enough human resources professionals, FDA needs to supplement in-house staff with external expertise. PDUFA VI would allow the Agency to retain a qualified hiring contractor. Employing this contractor will assist FDA in successfully meeting goals for recruitment of human drug review program staff. The contractor will conduct a comprehensive review of current hiring processes in an effort to identify capabilities leading to success, as well as potential problems or delays in hiring within the drug review program. FDA and industry will regularly assess progress in hiring and retention throughout PDUFA VI, but a welcome opportunity for stakeholders is that they will be able weigh in on FDA's progress through a minimum of three public meetings between 2017 and 2022.

The third section of note is Section III C, establishing a dedicated unit within the Office of Medical Products and Tobacco with a continuous focus on hiring and staffing issues so that the FDA can keep pace with scientific and technologic advances. The unit would proactively reach out to qualified candidates and competitively recruit to fill vacancies. It would also analyze compensation and other factors that affect retention of key staff on an annual basis.

Last but not least we strongly support Section III D, FDA's hiring goals for PDUFA VI. This section demonstrates the Agency's commitment to accountability and a desire to measure progress in targeting hires within the human drug review staff. We applaud you for taking this step.

Thank you again for the opportunity to comment on the PDUFA VI Commitment Letter. We look forward to working with Congress on enacting legislation to reauthorize this important program and hope to serve as a resource to the FDA as you implement the transformative initiatives supported by PDUFA VI. If you have any questions, please do not hesitate to contact us. Inquiries can be directed to the Alliance's Public Policy Associate, Ryne Carney, at (202) 293-2856 or by email at rcarney@agingresearch.org.

Sincerely,

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