

**Testimony of Cynthia A. Bens, Vice President of Public Policy
Alliance for Aging Research**

**United States Senate
Committee on Health, Education, Labor and Pensions
Hearing on “FDA User Fee Agreements: Improving Medical Product Regulation and
Innovation for Patients, Part II”**

April 4, 2017

Chairman Alexander, Ranking Member Murray, and Distinguished Members of the Committee:

It is an honor and a privilege to speak with you today on behalf of the Alliance for Aging Research, about the reauthorization of the Food and Drug Administration’s Prescription Drug User Fee Act (PDUFA) and Medical Device User Fee Act (MDUFA) programs.

I am Cynthia Bens, the Vice President of Public Policy at the Alliance. 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. We believe that advances in research help people live longer, happier, more productive lives and reduce health care costs over the long term.

Most of us are keenly aware that our population is aging at an unprecedented rate. Ten thousand Baby Boomers are turning 65 each day. This is up from 6,000 per day just 6 years ago. People age 85 and older are the fastest growing segments of our population. Right now, approximately 10 percent of the U.S. population is age 80 or older. This 80+ age group will reach 30 percent of the U.S. population by 2050.

Many older adults today are fortunate to experience better health as they age than previous generations. But the truth is that most older adults still face significant periods of illness and disability later in life, often from multiple chronic conditions that require complex care management. They develop one or more forms of cardiovascular disease, cancer, diabetes, bone and joint degeneration, muscle wasting, vision and hearing loss, neurological diseases, and incontinence.

In our view, the need for innovative treatments and medical devices that help respond to the physical declines people face with age has never been greater. We believe that we will only realize the benefits of these innovations if the FDA has access to the resources and expertise necessary to evaluate them, industry is certain that their products will be assessed in a timely manner, and patients are at the center of new product development.

For more than a decade, the Alliance for Aging Research has worked directly with the FDA, other patient advocates, researchers, and industry on ways to streamline the regulatory process for the benefit of older adults. We understand that user fees play an essential role in maintaining FDA review processes that efficiently deliver safe and effective medical products to patients who need them, and that is why we engage in the prescription drug and medical device user fee reauthorization processes.

Historical Perspective on the PDUFA and MDUFA Programs

Prior to the last reauthorization of PDUFA and MDUFA, patient organizations were not allowed to engage in the negotiations between the FDA and industry. Thanks to your committee's leadership and the support of your colleagues in Congress, the Alliance for Aging Research and other groups were represented throughout the patient/consumer stakeholder consultation phase leading up to PDUFA V and MDUFA III. We had an opportunity to provide feedback to the FDA as negotiations were taking place and propose enhancements to be included in the final commitment letter that emerged from the negotiations.

Engagement from the all stakeholders during the PDUFA V and MDUFA III negotiations resulted in final agreements that provided resources to strengthen review capacity at the Center for Drug Evaluation and Research (CDER) and the Center for Devices and Radiological Health (CDRH); advance regulatory science activities across medical product divisions within the FDA; and begin a movement toward more patient-centered medical product development, both inside and outside of the agency.

The Alliance for Aging Research was honored to offer patient perspectives to CDER and CRDH through monthly stakeholder consultations and public meetings held over the last year as the agency negotiated the PDUFA VI and MDUFA IV agreements. PDUFA VI and MDUFA IV contain critical commitments and funding for the FDA that we strongly support.

We are thankful the reauthorization of the user fee agreements is a priority for this Committee, and that patient benefit maintains a central role. We call your attention to the following sections of the agreements that provide additional resources for CDER and CDRH's workforce, expand patient-focused medical products development activities, improve FDA's capacity to advance the use of innovative clinical trial designs, and harness the potential of real-world evidence in regulatory decision making. These provisions will enhance FDA's ability to evaluate safe and effective treatments in a manner that will be meaningful to patients.

PDUFA VI Agreement Benefits to Patients

I.) Strengthening CDER's Workforce

The FDA lacks several 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 21st Century Cures Act. The 21st Century Cures Act took some positive steps to loosen restrictions on hiring for high-level vacancies but we are pleased to see that industry is putting resources toward more general hiring and retention

processes at FDA in the PDUFA VI agreement. There are several proposed enhancements under Section III of the PDUFA VI agreement to ensure CDER's workforce stability and establish first-ever goals for hiring.

Section III of the PDUFA VI agreement improves CDER's hiring and staff retention practices. This is one of the most critical components of the agreement because the agency will only be successful if it has the best and the brightest people in its' workforce. To do this, CDER needs to compete on a level playing field with the private sector and other federal agencies for highly-skilled individuals.

Section III A. of the PDUFA VI agreement modernizes CDER's hiring system. Two highlights of this section are 1) a commitment to implement a comprehensive online position classification system and 2) a transition away from time-limited individual position vacancy announcements. Shifting to common vacancy announcements—to be used by multiple offices for continuous posting—will provide the greatest opportunity for applicants with key scientific and technical expertise to apply for positions regularly needed across FDA's drug review programs.

Section III C. of the agreement establishes a dedicated unit with a continuous focus on hiring and staffing. This unit will help CDER keep pace with scientific and technologic advances by proactively reaching out to qualified candidates and competitively recruiting to fill vacancies. It will analyze compensation and other factors that affect retention of key staff on an annual basis. The PDUFA VI agreement also allows the agency to retain a qualified hiring contractor to augment CDER's existing hiring staff capacity. Employing this contractor will assist FDA in successfully meeting goals for recruitment of human drug review program staff.

CDER was required to implement the Breakthrough Therapy Pathway during PDUFA V. This pathway was intended for new drugs that showed exceptional promise for effectively treating a disease or patient population with an unmet need. This Breakthrough Pathway has been more successful than was intended and resulted in patients having quicker access to truly innovative

products for serious and life-threatening conditions. Unfortunately, this pathway has placed a strain on the agency because it is resource-intensive and did not come with additional funding under PDUFA V. PDUFA VI provides the addition of more than 30 staff to assist with this expedited pathway, which will help streamline approvals and ensure pathway integrity.

PDUFA VI also makes critical changes to the FDA's communications with sponsors that will help expedite drug development. CDER will maintain dedicated staff to provide communications training to their medical product review divisions, to better facilitate responses to general questions from sponsors and ensure timely resolution of issues with specific new drug applications. PDUFA VI fees will support an independent assessment of current communications practices and a public workshop to examine the results of this assessment.

II.) Expanding Patient-Focused Drug Development

The Alliance for Aging Research has been a strong advocate for the Patient-Focused Drug Development (PFDD) Initiative since the PDUFA V negotiations. At the urging of our Aging in Motion (AIM) coalition, a disease of aging called sarcopenia was selected for an FDA-led PFDD meeting. The meeting will be held later this week. The 27 PFDD meetings held by FDA on select diseases are providing FDA medical reviewers with a fuller understanding of patient and caregiver experiences with a disease and their hopes for successful treatment. The Alliance supported the continuation of FDA-led PFDD meetings as part of PDUFA VI and we are pleased that FDA will have the flexibility under Section J of the agreement to utilize user fee funds for disease-specific meetings, if they determine them to be useful.

PDUFA VI will add staff with expertise in patient-focused methods to be embedded into the review divisions. It is anticipated that these individuals will provide clinical, statistical, psychometric and health outcomes skills to enhance FDA's capacity and guide the incorporation of patient-reported outcomes and other patient-focused measures into drug development programs.

To compliment the internal changes at FDA in PFDD, the PDUFA VI agreement 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 FDA's review divisions. The proposed public process in PDUFA VI maintains and clarifies FDA's role, while providing much-needed user fee funding for external capacity building. To help ensure that there is efficient use of patient group and industry resources when pursuing the development of novel patient-focused drug development tools, CDER will create and maintain a repository of existing clinical outcome assessments, patient-focused meeting resources, and other patient-focused efforts.

Since PDUFA V, we have supported the dedication of user fees to develop a transparent and structured benefit-risk framework for drug evaluation. Understanding the components of FDA's benefit-risk assessment and how these components are applied in the context of regulatory decision-making continues to be of keen interest to industry and the patient advocacy community. PDUFA VI updates CDER's benefit-risk implementation plan, calls for a public meeting and the addition of a draft guidance to enable more productive activities that capture patient experiences, and allows for the communication of those findings to CDER throughout the drug development process.

III.) Advancing Innovative Clinical Trials

In 2012 and 2013 the Alliance convened two impactful meetings 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. PDUFA VI greatly enhances CDER's ability to advance the future of drug development through the addition of staff with expertise in statistical modeling and innovative clinical trial designs. Section J of the PDUFA VI agreement addresses model-informed drug development and complex design review by providing CDER with additional staff and funding for public meetings to guide FDA's and industry's incorporation of innovative clinical trial methods.

The Alliance for Aging Research has first-hand experience with the FDA's Drug Development Tool (DDT) Qualification Process. We participated in efforts to qualify multiple tools for use in clinical trials for Alzheimer's disease and we are currently pursuing qualification of two functional assessments to be used as endpoints in clinical trials for sarcopenic patients. We feel strongly that the DDT Qualification Process should continue because it provides a unique space for collaboration and resource pooling among multiple stakeholders, including patients, to advance patient-centered endpoints that are made available in the public domain. PDUFA VI expands base capacity within the qualification review team and provides them with funding to host a series of meetings resulting in guidance that will strengthen the DDT Qualification Process.

The PDUFA VI agreement also details a process for early consultation with drug sponsors on the use of new surrogate endpoints in clinical trials. The meetings described in the agreement 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. Meetings like these will identify any knowledge gaps that require attention. While we do not yet have qualified biomarkers for use as surrogates to test drugs for many diseases of aging, we know that clinical trials utilizing surrogate endpoints will be increasingly important as drug development moves toward early intervention and prevention of age-related diseases. Establishing this dedicated process for meetings on surrogates between FDA and industry that can occur as early as end of Phase 1, is a priority for us.

IV.) Harnessing the Potential of Real-World Evidence

The PDUFA VI agreement enhanced 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, even though they are often most of the users for a given intervention. 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. PDUFA VI fees will support multi-stakeholder public workshops, methodology-development pilot programs and regulatory guidance. We believe that this represents a sound, comprehensive approach to harnessing the potential of real-world evidence for patients, product sponsors, and the agency.

MDUFA IV Agreement Benefits to Patients

I.) Supporting CDRH's Workforce

Having expert CDRH staff to carry out user-fee-funded activities is paramount. Without the necessary number and types of staff, CDRH will not be able to meet the ambitious performance goals for which the MDUFA IV resources are intended. MDUFA IV provides CDRH with needed funding to hire across medical device review activities and cultivate existing staff. Specifically, Section III, B. of the MDUFA IV agreement permits CDRH to apply user fees for the improvement of its scientific and regulatory review capacity. With these fees, CDRH intends to increase the retention rate of high-performing supervisors, reduce the ratio of review staff to

supervisors, hire new device application reviewers, and utilize recruitment support to augment existing human resource services.

The Alliance for Aging Research is supportive of Section IV. E of the MDUFA IV agreement that seeks to bolster the third-party review program within CDRH. We advocated for the use of MDUFA III fees for the third-party review program so that CDRH's staff would have more time to devote to higher-risk device applications. It is our understanding that third-party review continues to be valuable for lower-risk devices, but the program requires improvements to make it more efficient. We are glad that CDRH continues to have the resources and flexibility to employ outside experts as needed under MDUFA IV and that there will be improvements made to the third-party review program to ensure its integrity.

MDUFA IV will lead to significant reductions in the time it takes the FDA to review the most common types of medical device applications. This will not only benefit industry, but also accelerate patient access. Under MDUFA IV, the FDA has committed to reduce the days for review of 510(k) applications and for premarket approval (PMA) applications. FDA also set goals for reviewing *de novo* applications. The number of *de novo* requests has increased steadily since the pathway was created. The limited resources currently available to the agency for *de novo* requests have resulted in missed target dates for review in all but 40 percent of cases. Section II. E of the MDUFA IV agreement specifies that the agency set a goal of reviewing 70 percent of *de novo* requests on time by FY 2020.

II.) Expanding Patient-Centered Medical Device Development

The Alliance for Aging Research applauds the FDA for fostering the use of patient preference information in the review and approval of medical devices. CDRH was a leader among regulators in aggressively pursuing a transparent and structured benefit-risk framework. Finalizing a benefit-risk guidance for devices was one of CDRH's first actions in MDUFA III implementation. The benefit-risk guidance, first issued by FDA in 2015, broadly defines the

benefits they are interested in understanding. The type of benefit CDRH specifically calls out are not just a device's impact on clinical management of a disease and patient health, but also patient satisfaction, improvement in quality of life, improvement in function, reduction in lost function, reduction in probable mortality, and symptom relief. For diagnostics, benefit could be assessed on public health impact, the ability to identify a specific disease and potentially prevent its spread, predicting future disease onset, providing earlier diagnosis of diseases, or identifying patients more likely to respond to a given therapy.

The benefit-risk guidance also laid out the ways in which CDRH assesses the magnitude of benefit, the probability of a patient experiencing benefit, and the duration of benefit. The guidance provides details, some examples, and a copy of the worksheet that reviewers use in their benefit-risk determinations.

Benefit-risk calculation is discussed frequently but there is the potential for this type of exercise to be more tokenism than substance. CDRH got the substance of the patient experience right, and that is because they actively engaged with the patient advocacy community to best characterize disease severity and unmet need from the start.

Of late, industry has begun including patient-centered endpoints in development programs, signaling a growing interest by industry to employ patient-reported outcomes in device trials with more regularity. FDA has responded by drawing patient representatives earlier into the device review process, developing a systematic benefit-risk framework for the evaluation of new devices, and creating a Patient Engagement Advisory Committee.

Section IV. F of the MDUFA IV agreement details activities that CDRH will take to further advance patient input and involvement in the regulatory process. CDRH will develop scientific expertise and expand staff capacity to respond to device submissions containing publicly available, and validated, patient preference information or patient reported outcomes. This section also calls for public meetings to discuss approaches for incorporating patient preference

information and patient reported outcomes as evidence in device submissions, as well as other methods of advancing patient engagement. CDRH will also explore ways to use patient input to inform clinical study design and reduce barriers to patient participation by facilitating recruitment and retention. The MDUFA IV agreement calls on the FDA to identify priority areas in which patient preference information could inform regulatory decision making and requires publication of these priorities in the *Federal Register*.

III.) Utilizing Real-World Evidence

The Alliance sought the application of MDUFA IV resources to elevate CDRH's ability to further real-world evidence generation for the purposes of informing regulatory activities. We believe that the collection of data generated through routine clinical care can help broaden our understanding of how products are working in the real world, support the incremental process of medical device development, and lead to optimal care.

Under Section IV. H of the MDUFA IV agreement, CDRH can utilize user fees to hire staff with expertise in the use of real-world evidence and establish a Coordinating Center for the National Evaluation System for health Technology (NEST). NEST will link health claims, electronic records, and registry data. In the future, these activities have the potential to decrease the number of stand-alone clinical trials, increase enrollment efficiencies, and make patient follow up less burdensome.

With MDUFA IV funds, the NEST Coordinating Committee will undertake a pilot program to explore the usability of real-world evidence for determining expanded indications for device use, new device approval, and device malfunction reporting. The NEST pilot program is particularly meaningful for our organization since older adults are not adequately represented in many clinical studies for devices.

The Alliance for Aging Research requests one change to the MDUFA IV agreement. Section IV. H. states that “Industry representation on the NEST governing board will make up at least 25 percent of the governing board membership.” MDUFA IV generally references anticipated representation of the patient community on the NEST governing board. We believe that the enacting legislation should detail the composition of the remaining 75 percent of the governing board and include representatives of patient populations most likely to be affected by increased utilization of real-world evidence (e.g. the elderly, those with multiple chronic conditions, women, etc.). If patient preference is truly a priority for the FDA and industry, representation by patient representatives on the NEST governing board should be more clearly outlined.

Conclusion

As mentioned previously, the Alliance for Aging Research strongly supports the continuation of the prescription drug and medical device user fee programs through the negotiated PDUFA VI and MDUFA IV agreements. The Alliance advocates for increased overall funding of the FDA, with strong emphasis on finding the right balance between user fees and appropriated funding. We think that the size and scope of the proposed fees within the PDUFA VI and MDUFA IV agreements is appropriate and necessary to increase the efficiency of regulatory processes, reduce the time it takes to bring safe and effective medical products to market, and put patients at the heart of new product development.

Despite the opportunities afforded by PDUFA VI and MDUFA IV, we are all in jeopardy if the FDA’s budget authority remains flat or is significantly reduced in the coming fiscal year. As you are aware, not all FDA activities can be supported through user fees, nor should they be. Crucial safety and surveillance activities as well as oversight of over-the-counter medications and other products, currently fall outside of the user fee programs. While FDA appropriations are not under the jurisdiction of this Committee, it is our hope that you will join us in calling for sufficient budget authority to maintain the overall health of this essential agency.

Thank you for the opportunity to present our views today. The Alliance for Aging Research is grateful that the Committee is making the reauthorization of the user fee programs a priority and we look forward to working with you on enacting legislation for these important programs.

I am happy to answer any questions you may have.