

August 23, 2020

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

RE: FDA-2010-N-0128 for Reauthorization of the Prescription Drug User Fee Act;
Public Meeting; Request for Comments

Dear Commissioner Hahn:

On behalf of the 54 million American adults and children with doctor-diagnosed arthritis, the Arthritis Foundation is pleased to offer comments on the FDA PDUFA July 23rd stakeholder meeting. As you know, arthritis can be complex and difficult to treat, and many people with the disease rely on prescription drugs to remain stable. They may rely on a range of prescription drugs from small molecule to biologics, and their disease is often compounded by co-morbidities like diabetes and heart disease, which may require them to take multiple prescription drugs. For some forms of arthritis like osteoarthritis (OA), there are no disease-modifying therapies, which presents a major unmet need for the more than 27 million Americans suffering from OA.¹

In our 2015 comments on PDUFA VI, we praised the FDA's emphasis on patient-focused drug development (PFDD), noting that patient perspectives are unique and vital to the drug development process, from the decisions on what research to embark upon all the way through to post-market evaluation. Since the last PDUFA reauthorization, the Arthritis Foundation has undertaken several patient-focused projects we think would be of great value to the FDA and that we would like to see incorporated into PDUFA VII, including: two externally-led PFDD meetings; the launch of a patient-reported outcomes measure survey; and a clinical trials finder.

The Arthritis Foundation is particularly invested in advancement of novel ways of gathering actionable data including registry-based studies and trial designs like those envisioned by FDA thought leaders.²³ The worldwide effort to combat the novel coronavirus has, additionally, forced researchers to innovate the conduct of trial execution. We encourage the FDA to embrace learnings from the unprecedented speed

¹ <https://www.arthritis.org/getmedia/e1256607-fa87-4593-aa8a-8db4f291072a/2019-abtn-final-march-2019.pdf>

² <https://pubmed.ncbi.nlm.nih.gov/31313532/>

³ <https://www.nejm.org/doi/full/10.1056/NEJMra1510062>

and resources deployed against the COVID-19 pandemic and apply the best practices to other conditions.

Below please find specific information on the above-mentioned projects along with recommendations on how they can be utilized by the FDA. We would also like to express support for the following recommendations and statements given during the consumer and patient panels during the July 23rd meeting:

- The need to improve representation of minority groups and people over 65 in clinical trials and other FDA efforts
- Ensuring letters are understandable to patients and providers and are seen by the patients and providers for whom they are relevant
- More patient representation and participation at FDA workshops and meetings
- A more robust feedback loop for patients to know how their participation is being used by the FDA
- More financial support to ensure PFDD reports are used across the FDA early on and throughout the drug approval process
- Focus on decentralized clinical trial design, with emphasis on developing experience and practice guidelines
- The need for digital health tools for clinical trial use to be assessed and validated so patients can accurately use them
- Evaluation of learnings from telehealth during the pandemic for future use

Clinical Trial Design

We support the exploration and integration of Real World Evidence (RWE) and digital clinical trials into overall clinical trial design. However, the Arthritis Foundation believes RWE and digital clinical trials are not a substitute for patient engagement. These are both vital parallel processes that address fundamentally different aspects of patient experiences. For example, an RWE program may develop a wealth of data or evidentiary conclusions built on real world data. However, the qualitative feedback of patients involved in design and analysis of the initiative can help researchers design better clinical trials by answering questions about why patients do what they do. By example, a dataset of wearable device data may offer a rich view of patient lives, but may contain gaps when the devices were removed. Patient engagement will be required to understand the conditions under which devices are removed, and the significance of that missing data.

Likewise, we encourage adoption of value-based care concepts in selection and qualification of study endpoints. This process more fully engages patient stakeholders in defining the benefit-risk frameworks used in FDA reviews. We encourage the FDA to prioritize patient-centered core outcome sets, as we believe measures should be based on outcomes identified by patients. We work closely with and support the National Health Council's leadership in this area.

Like many organizations, the Arthritis Foundation is challenged to incorporate the level of diversity that we would like to see in programs like the Arthritis Foundation Live Yes! INSIGHTS Patient Reported Outcomes program and other Foundation-led research efforts. We applaud continued progress on guidance documents such as “Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry” and encourage the agency to operationalize the considerations made in this guidance.

As an extension of this issue, we urge the FDA to stringently apply the authorities of the Pediatric Research Equity Act (PREA) to ensure that research in pediatric populations is conducted during development of covered drugs and biological products. The Arthritis Foundation applauds the agency’s commitment to developing listening sessions and workshops to discuss new approaches to dosing, statistical analyses, and extrapolation. We have participated in many of these efforts and will continue to assist the agency wherever possible. We do encourage PDUFA reauthorization to mandate review of the Automatic Full Waiver list under PREA with the intent to examine JA related inclusions like spondyloarthropathies against data emerging from clinical records and disease registries. In the future, waivers to PREA should be rare, and require evidence of exhaustive attempts by sponsors to work with the rare disease communities to identify alternative experimental approaches to the traditional randomized controlled trial.

Patient-Focused Drug Development

We applaud the FDA for increasing its focus on patient-focused drug development, particularly the launch of the patient-focused drug development (PFDD) program. The immense interest in these meetings led many groups, including the Arthritis Foundation, to conduct their own externally-led PFDD meetings. FDA staff were present for our externally-led PFDD meeting on osteoarthritis in 2017 and on juvenile idiopathic arthritis in 2018.

In both PFDD meetings regulatory staff and members of the research community examined nuances of how symptoms overlap and interact. This was especially important for prioritizing issues like chronic pain against symptoms more directly related to structural damage to joints. Regulators received critical insights on patient perceptions regarding route of administration of novel therapeutics. But they also heard first-hand the consequences of a limited armamentarium and the urgency patients place on development of new options. Our communities live in fear of running out of options and they seek relief in nuanced ways that are not always the focus of the therapeutic development community. These first-hand observations are preserved in the program’s videos and transcripts and summarized in the Voice of Patient reports.⁴

⁴ <https://www.arthritis.org/getmedia/25118249-ea68-45b5-bfe4-c20904ddc32c/FINAL-JIA-PFDD.pdf>

We appreciate the FDA’s recognition of the value of PFDD meetings and the efforts to create fit-for-purpose tools for organizations to use as they consider holding externally-led PFDD meetings. The foresight of offering an externally-led mechanism for the conduct of PFDD meetings is commendable and certainly to the advantage of rare disease communities. With the experience of more than 25 agency-led PFDD meetings, and more than 20 externally-led meetings, we believe the agency should now begin clarifying the regulatory role these meetings serve. Better understanding of the value from the perspective of regulators will allow future organizers to bring new tools to the conduct of these meetings that ensure better tailoring of future meetings to the intended purpose.

In PDUFA VII, we recommend that any policies involving FDA-led PFDD meetings also apply to externally-led PFDD meetings. Executing a PFDD meeting takes an enormous amount of staff time and financial resources, and organizations need to know the findings and recommendations are being incorporated into FDA processes and discussions. We encourage FDA to create processes by which each relevant division within the FDA incorporate the findings from FDA-led and externally-led PFDD meetings. We also encourage the FDA to develop and publicly share reports on how it utilized these meetings in its work.

Patient Reported Outcomes Measures

In our 2015 comments on PDUFA VI, we discussed the importance of Patient Reported Outcomes, as there can be wide discrepancies between patients and clinicians on their perspectives on prevalence and severity of disease. Since that time, we have launched our own Patient Reported Outcomes assessment based on the PROMIS measure sets and incorporating measures of patient perceptions of their ability to coproduce healthcare plans with their care teams, to-date collecting more than 30,000 assessments on the domains of physical health, mental health, and experience of care.

Some specific data points from our INSIGHTS assessment include:

- 92% of respondents reported that pain interfered with their day-to-day activities
- 67% reported feeling anxiety or fear (this percent increased to 88% March-April 2020 during COVID)
- 93% of respondents reported that it is extremely important to get the help they need at their health care professional’s appointment, yet only 57% responded they actually received the help they needed

We believe this type of data can be useful to the FDA in the following ways:

- The findings from our report emphasize the complex symptoms of patients with chronic conditions. These nuances can be lost when considered in the absence of strong commitment to patient engagement in the regulatory process. PDUFA VII

- should continue to mandate collaborative partnership and policies to address the issues highlighted above
- These findings can also inform interventions/therapies around pain interference, mental health, and improving the experience of care for patients
 - This data can be coupled with other rheumatology registry data like the American College of Rheumatology's RISE registry and the Childhood Arthritis and Rheumatology Research Alliance registry to offer a more comprehensive illustration of patient outcomes

Osteoarthritis

In our 2015 PDUFA reauthorization comments we noted that there are no disease-modifying therapies for osteoarthritis (OA). This is still true today and remains a vital priority for the Arthritis Foundation. Survey data shows that 30% of patients do not want total knee replacements; additional treatment options are desired to help patients delay total joint replacements and provide relief for patients with disease in smaller joints.

As noted above, the osteoarthritis community would benefit significantly from consideration toward functional and structural endpoints in addition to pain endpoints for OA therapeutics. Therapeutic options in this condition are quite limited for a disease affecting more than 27 million US citizens and 1 in 4 military service members. In recent history a number of potential products have disappointed the OA community due to failed pain endpoints. This may well be a consequence of endpoints rather than the therapeutics themselves.

We remain concerned about the proliferation of unregulated products, specifically labeled as regenerative medicine including those products labeled as endosomes, stem cell, or stem cell related therapies. While these concerns extend to many conditions, the benefit to osteoarthritis is a frequent claim of providers offering these services. Many such services are being allowed to commercialize without high-quality, scientifically valid clinical studies. We ask that PDUFA reauthorization include review and modification of regulatory provisions such as 21 CFR 1271. The purpose of the review would be to consider the spirit under which these regulations are authorized against the therapeutic claims under which these products are operating. The Arthritis Foundation continues to support clinical research in this field, and specifically advocates for the need for well powered randomized controlled clinical trials to prove efficacy and safety.

FDA Workforce

Along with many other organizations, we recognize the need for additional FDA staff to complete this work. The required knowledge and “bandwidth” to appropriately regulate the therapeutic development space continues to expand, and adaptations prescribed in PDUFA VII will need to be enhanced. As an example, we again point to the proliferation

of purported stem cell therapies that are currently operating outside of appropriate oversight. While this is a consequence of policy and workforce issues, it is an issue deserving of scrutiny during the PDUFA VII considerations. Also, despite the availability of outstanding staff tasked to the oversight of osteoarthritis and other rheumatological products, there have been delays to the final release of the FDA guidance documents, notably for osteoarthritis. Timely release of such documents would help clarify the targets of clinical trials for new OA therapeutics, and improve efficiency of clinical trials for sponsored interventions. Recruitment of additional expertise would help move forward much-needed efforts to develop updated positions on functional and structural endpoints.

Consistent with these examples, the Arthritis Foundation requests consideration of additional staff to the Center for Biologics Evaluation and Research (CBER), and Division of Rheumatology and Transplant Medicine (DRTM).

Thank you for the opportunity to comment on the PDUFA reauthorization. We look forward to collaborating with the FDA through development and implementation of PDUFA VII to improve patient representation throughout the drug development, approval, and post-market processes. Please contact me at ahyde@arthritis.org should you have any questions or would like further information about our comments.

Sincerely,



Anna Hyde

Vice President of Advocacy and Access
Arthritis Foundation