Alliance for Regenerative Medicine

August 23, 2020

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

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

The Alliance for Regenerative Medicine (ARM) appreciates the opportunity to provide its comments regarding the reauthorization of the Prescription Drug User Fee Act (PDUFA). ARM believes that the PDUFA, since its enactment in 1992 and subsequent reauthorizations, has provided the means to improve the drug review and approval process and provided FDA with additional resources, thereby providing for more timely patient access to important, new therapies.

ARM is the leading international advocacy organization dedicated to realizing the promise of regenerative medicines and advanced therapies. ARM promotes legislative, regulatory and reimbursement initiatives to advance this innovative and transformative sector, which includes cell therapies, gene therapies and tissue-based therapies. Early marketed products have demonstrated profound, durable, and potentially curative benefits that are already helping thousands of patients worldwide, many of whom have no other viable treatment options. Hundreds of additional product candidates contribute to a robust pipeline of potentially life-changing regenerative medicines and advanced therapies. In its 11-year history, ARM has become the voice of the sector, representing the interests of 350+ members worldwide, including small and large companies, academic research institutions, major medical centers, and patient groups.

ARM appreciates the support that the FDA has provided in advancing the development of cell and gene therapies by, among other things, publishing important guidances, participating in key sector meetings and convening public sessions to provide information and seek stakeholder input on timely topics. ARM looks forward to the agency's ongoing commitment to work with the sector.

Increased Funding for Additional CBER Reviewers

Over the next several years, regenerative medicines – including cell and gene therapies – will be brought to the market at a rapid pace. When PDUFA was last reauthorized in 2017, ARM calculated that there were 580 developers conducting more than 480 clinical trials globally. Just three years later, ARM now estimates that there are approximately 950 developers

conducting over 1000 clinical trials worldwide, including 594 in Phase II and 95 in Phase III[1]. Last year, FDA's leadership stated that, "We anticipate that by 2020 we will be receiving more than 200 INDs per year, building upon our total of more than 800 active cell-based or directly administered gene therapy INDs currently on file with the FDA. And by 2025, we predict that the FDA will be approving 10 to 20 cell and gene therapy products a year based on an assessment of the current pipeline and the clinical success rates of these products."[2]

In order to meet this challenge, the FDA needs more properly trained staff with the expertise to evaluate these applications. Attracting and retaining staff who can assess biologic license applications, particularly in a cutting-edge field of regenerative medicine in which the number of applications is increasing significantly, is vital, especially because the majority of these therapies are targeting rare or orphan diseases that often lack other clinically effective treatment options . Therefore, **ARM recommends that the user fee program funding be appropriately designed to ensure FDA has the necessary resources to recruit, train and retain CBER reviewers.**

Improvements to the INTERACT Meeting Process

ARM appreciates the Agency's formalization of the pre-pre-IND meeting in the form of Initial Targeted Engagement for Regulatory Advice on CBER Products (INTERACT). These meetings are particularly important to developers of cell and gene therapies as they provide an opportunity for the product developer to discuss important issues with FDA early in development. PDUFA reauthorization provides an opportunity to improve INTERACT meetings and **ARM recommends the following:**

- Extend INTERACT: Provide an informal venue for information exchange with the agency around a development program in early stages;

- Timelines for INTERACT: Establish PDUFA timelines for INTERACT meetings in guidance, including revising the existing timeline, such that meetings are held within 75 calendar days of request receipt;

- Clear Guidance on INTERACT Criteria: Set forth in guidance more specific criteria for acceptance or refusal of an INTERACT meeting, including, e.g.,: examples of the types of topics for which an INTERACT meeting will be granted; a discussion of level of detail and data expected;

- Written Feedback: Set forth in guidance more details on the extent and format of feedback expected from INTERACT meeting, including a commitment to written feedback, with an option for sponsors to provide a response, should a teleconference

[1] Alliance for Regenerative Medicine, Q3 2019 Quarterly Report

[2] https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-and-peter-marks-md-phd-director-center-biologics

not be deemed necessary by the Agency, should a teleconference not be deemed necessary by the Agency. In those instances when INTERACT meetings are not granted, the reasons for such denial should be clearly conveyed to the sponsor; clear feedback on FDA's rationale as to a why an INTERACT meeting was denied will help inform a sponsor's consideration of other regulatory and clinical options;

- Second Optional Formal Meeting: Create an opportunity for a second, optional formal meeting (e.g., Type C meeting) prior to pre-IND meeting. It is anticipated that an additional early meeting type would not result in additional resource constraints, because it will result in less meetings/ FDA interactions needed later in development.

Prosecuting Unregulated Stem Cell Clinics

Mirroring the growth in the regenerative medicine sector, there has been, regretfully, a significant increase in the number of unregulated stem cell clinics marketing non-FDA approved products advertised directly to patients. It has been estimated that in 2009 there were two stem cell clinics in the United States and by 2017 the number had grown to over 700[3]. A study published in early 2018 found that the number of new U.S. stem cell clinics with websites doubled on average every year between 2009 and 2014 and that up to 100 new websites appeared each year between 2014 and 2016[4].

This explosion in the number of stem cell clinics has proven to be a significant oversight challenge for the FDA. In 2017, the agency announced that it would adopt a "risk-based" enforcement policy targeting the worst of the bad actors.

ARM applauded the agency for this action at the time and still believes it was a strong step in the right direction. Nonetheless, the continued increase in the number of clinics providing unapproved and potentially unsafe treatments leads ARM to conclude that a "risk-based" enforcement approach is not robust enough to adequately regulate these burgeoning businesses. Therefore, **ARM recommends that the agency dedicate increased resources to establish and implement strong, swift, and consistent legal actions against these questionable clinics and prosecute those that are in violation of the law.**

Provide Additional Regulatory CMC Flexibility for Gene and Cell Therapies

ARM applauds FDA for embracing novel approaches to clinical development, including through innovative trial designs and analysis and endpoints, to speed the availability of new treatments for serious or life-threatening diseases to address unmet medical needs. FDA's expedited

[3] L. Turner, "The U.S. Direct-to-Consumer Marketplace for Autologous Stem Cell Interventions," *Perspectives in Biology and Medicine* 61, no. 1 (2018): 7-24, https://muse.jhu.edu/article/694817

[4] P.S. Knoepfler and L.G. Turner, "The FDA and the U.S. Direct-to-Consumer Marketplace for Stem Cell Interventions: A Temporal Analysis," *Regenerative Medicine* 13, no. 1 (2018): 19-27, https://dx.doi.org/10.2217/rme-2017-0115.

programs[5] have successfully compressed clinical development and regulatory review timelines. Of great significance, the recently finalized Human Gene Therapy for Rare Diseases Guidance emphasizes the opportunity for compressed cell and gene therapy timelines, indicating that sponsors should consider designing their first-in-human study to be an adequate and well-controlled trial with the potential to support marketing approval.

Equally important is enabling flexibility in Chemistry, Manufacturing and Controls (CMC) components of development and review to overcome the current CMC challenges as a bottleneck on the critical path in the review, approval, and ability to bring cell and gene therapies to patients faster. Unlike a traditional small molecule, where processes are applied similarly across the lifecycle, cell and gene therapy products are manufactured with highly dynamic and complicated processes requiring complex manipulations. These challenges are particularly acute for products to treat rare diseases, many of which are severe or life-threatening with few or no treatment options. In such cases, CMC evaluation should similarly consider the severity and unmet need of the treated population. A risk-based, iterative approach to CMC would speed availability of cell and gene therapies to patients and has the potential to confer consistency and clarity to developers, thus preserving valuable FDA time and resources. Furthermore, risk-based, evidence approaches will be critical to assuring the benefits and safety of these promising new therapies for patients. For these reasons we request that FDA find a regulatory pathway forward that is appropriate for cell and gene therapies while ensuring that the products are safe and effective with reproducible quality from early clinical trials through commercialization.

Indeed, FDA has acknowledged that CMC review of gene therapy product applications account for approximately 80 percent of review resources while clinical review accounts for approximately 20 percent[6]. FDA and manufacturers should review the work being conducted for the CMC aspects of development and eliminate testing and assays that do not impact the final outcome of these transformative therapies. We need to stop force fitting cell and gene therapies into a paradigm designed for traditional small molecules and large biologic therapeutics. Now is the time to take a fresh look at the standards we are holding cell and gene CMC so as to and determine if they are relevant. Importantly, this position is consistent with the agency's recent effort to develop a new integrated review process. These issues should be addressed during PDUFA VII negotiations as they delay patient access to medicines with life-changing potential. Therefore, **ARM recommends that FDA consider opportunities to better utilize and define regulatory flexibility during CMC reviews of cell and gene therapy products, while maintaining FDA's rigorous approval standards, including:**

---

[5] Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics – May 2014. Expedited Programs for Regenerative Medicine Therapies for Serious Conditions – February 2019.

[6] https://www.fda.gov/news-events/speeches-fda-officials/remarks-alliance-regenerative-medicines-annual-board-meeting-05222018

- Determining, based on a risk-based assessment, the appropriate flexibility in CMC data requirements pre- and post-approval and the acceptable tolerance for CMC uncertainty at the time of BLA approval for products addressing unmet medical needs for a serious or life-threatening condition; allowing submission of CMC data during review and post-approval to avoid significant delays in expedited development, including when seeking accelerated approval. To that end, FDA should consider amending the Expedited Programs guidance (see footnote 5) to add language on CMC and incorporating such language in the forthcoming guidance on benefit-risk assessment for new drugs and biologics.

- Providing progressive, continual CMC advice and expectations throughout a product's entire life cycle, starting with pre-IND dialogue, accounting for iterative CMC development, in conjunction with iterative clinical development and dialogue;

- Offering customized CMC guidance by product type (for example, CAR-Ts, genetically modified hematopoietic stem cells, adeno-associated viral vectors, lentiviral vectors, etc.), promoting consistency within product type and streamlining requirements harmonized with EMA where feasible.

- As FDA gathers additional experience with CMC reviews of cell and gene therapy products, FDA should consider hosting a public workshop with stakeholders. In order to facilitate constructive dialogue, the Agency should release a discussion paper and request for feedback in advance of the public meeting.

Greater Use of Patient Insights in the Drug Development and Review Process

As has been noted, cell and gene therapies hold immense promise for patients with serious conditions, but these therapies also leverage rapidly emerging science, present new development challenges and add complexity to treatment decisions for patients and their families. Patient engagement is an important aspect of ensuring that advanced therapies deliver on their promise.

To ensure incorporation of the patient voice in development and regulatory decision making for advanced therapies, there is need for a dedicated forum to present and discuss patient experience data together with patients, patient advocacy groups (PAGs), FDA, and sponsors in the context of a drug development program. Each drug presents a unique benefit-risk profile and calls for dedicated discussion of the patient's perspective for a drug development program, which cannot be substituted by a general disease-area based collection of patient perspective, such as patient-focused drug development (PFDD) meetings or other such broader efforts. This is especially important for advanced therapies as they may present unique benefit-risk profiles and the perspectives of patients should inform the benefit-risk assessment.

ARM recommends that FDA formalize Patient Engagement (PE) Meetings for focused discussion of patient experience with the goal to effectively incorporate the patient voice in development and regulatory decision making as early as possible for advanced therapies. Like

other types of PDUFA meetings, these meetings should be tied to the development of a specific product. The meetings should allow sponsors to include patients, caregivers, and PAGs to share their experience with the disease and/or the drug with FDA that is valuable in the context of the drug development program, e.g. survey results, share their experience with the disease and/or the drug with FDA that is valuable in the context of the drug development program to inform regulatory decisions such as to inform the benefit-risk assessment, inclusion in the label, and FDA's approach to the post-approval Risk Evaluation and Mitigation Strategies (REMS). This is especially important for advanced therapies for rare diseases, where low patient population numbers may limit determination of statistical significance. There is value in qualitative patient experience data and patients sharing their experience with the disease and/or the therapy directly with FDA.

Utilization of Real World Data and Real World Evidence

FDA's willingness to utilize Real World Data (RWD) and Real World Evidence (RWE) is an important issue for ARM, developers, and patients. The acceptability of natural history studies, patient registries and similar RWD are pivotal in allowing timely development of cell and gene therapies, in particular those meant to treat rare patient populations and/or those dealing with degenerative diseases. RWD has the potential to be a more sensitive endpoint than traditional endpoints and provide early evidence of efficacy. FDA continuing to partner with sponsors to explore RWE to bring desperately needed therapies to patients is essential.

The acceptability of RWE rather than enrolling placebo patients for regenerative medicine is particularly critical when the prevalence of disease is very low, and patients risk irreversible progression while awaiting treatment. When FDA accepts natural history studies instead of placebo this ameliorates patient recruiting obstacles and alleviates the hardship of participating in a clinical trial without the possibility of treating their disease during that time.

FDA's flexibility in allowing RWE to support safety has been pivotal in approval of regenerative medicines. FDA's continued commitment to RWE such as patient registries is critical to continued innovation. **ARM recommends that FDA hold a public meeting to focus on the unique issues associated with utilization of RWD and RWE for cell and gene therapies.**

Lessons learned from COVID-19

The COVID-19 pandemic has impacted virtually every element of society. Within FDA, it has forced the reevaluation of what previously had been standard practices and procedures and required process changes, including adjustments to clinical trial rules. During the pandemic, FDA and sponsors have collaborated to seek ways to ensure that the "gold standard" of product review set by the agency is not compromised while making any necessary changes in light of the demands of the pandemic and need to expeditiously review potential COVID-19 cures and treatments. **ARM recommends that FDA develop and publish a report containing an analysis of pandemic-related disruptions to standard processes, policies, and procedures;**

modifications adopted to address the disruptions; and an evaluation of best practices. The report should be published and made available for public comment.

Conclusion

The regenerative medicine sector is the next frontier in the fight against some of society's most devastating diseases and disorders. These therapies have just begun to demonstrate their power to improve patient lives, but there is still much work to be done. ARM is looking forward to continuing to work with FDA, and other key stakeholders, to address the policies needed to advance the sector so that these cutting-edge treatments can meet their potential and be accessible to patients in need.

Thank you for the consideration of our recommendations.

Sincerely,

Director, U.S. Policy and Advocacy