May 26, 2023

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

Re: Docket No. FDA-2023-N-0398 for *Methods and approaches for capturing post-approval safety and efficacy data on cell and gene therapy products, Public Listening Meeting; Request for Comments*

Dear Sir/Madam:

The Alliance for Regenerative Medicine (ARM) appreciates the opportunity to present at the US Food and Drug Administration (FDA) listening session on April 27, 2023 on *Methods and approaches for capturing post-approval safety and efficacy data on cell and gene therapy products* and to now summarize in writing and expand upon those comments.

The Alliance for Regenerative Medicine (ARM) is the leading international advocacy organization championing the benefits of engineered cell therapies and genetic medicines for patients, healthcare systems, and society. As a community, ARM builds the future of medicine by convening the sector, facilitating influential exchanges on policies and practices, and advancing the narrative with data and analysis.

We actively engage key stakeholders to enable the development of advanced therapies and to modernize healthcare systems so that patients benefit from durable, potentially curative treatments. As the global voice of the sector, we represent more than 475 members across 25 countries, including emerging and established biotechnology companies, academic and medical research institutions, and patient organizations.

General Comments

First and foremost, ARM encourages FDA to provide clarity on the agency's consideration of input from patients, caregivers, and patient communities when providing guidance on post-approval data collection methods for cell and gene therapies. We also encourage FDA to share and apply its learnings on flexibility in data collection obtained from the decreased ability to do in-person data collection during the COVID-19 pandemic.

ARM supports minimizing the burden of post-approval data collection for patients and caregivers and facilitating efficient data collection processes for health care providers and

sponsors, while ensuring the safety and efficacy of these therapies. When creating guidance on this topic, we recommend that FDA define the scope of post-approval data to include:

- Required confirmatory trials on clinical efficacy for products receiving accelerated approval, and
- Required long-term follow-up (LTFU) safety studies.

We recommend reiterating within such guidance that reporting data on efficacy post-traditional approval is at the sponsor's discretion, per the January 2020 final guidance document, *Long Term Follow-Up After Administration of Human Gene Therapy Products.* Doing so may facilitate consistent application of this guidance.

Efficacy data from voluntary LTFU studies may be helpful for expanding labeled indications of a therapy. Guidance would be helpful on the requirements of post-approval efficacy data to support label expansion.

Current guidance is clear that regenerative medicine advanced therapy (RMAT) designated products receiving accelerated approval may be able to fulfill post-approval requirements from clinical evidence obtained from sources other than traditional confirmatory clinical trials, including patient registries, or other sources of real-world evidence (RWE), such as electronic health records. ARM recommends clarifying that RWE data are acceptable sources of post-approval data for confirmatory studies more broadly for all cell and gene therapies receiving accelerated approval.

Development and establishment of product-based and/or disease-based registries

Well-designed registries are a key tool for collecting outcomes in the post-approval setting. However, a gap often exists between the amount and type of data collected in existing disease registries and data required from the agency for post-approval studies. ARM would appreciate FDA provision of guidance on assessing existing registries for use in post-approval data collection, including evaluating the data elements that are collected. Beyond the creation of a guidance document, interactions between regulators and registry holders could assist in bridging this gap.

Another challenge with the use of registries for post-approval data collection is that limited numbers of existing registries include data from the majority of US cell and gene therapy centers. However, designing and running new registries may be prohibitively resource intensive for sponsors and could increase clinician burden as clinical sites may need to enter data into multiple registries. Such complexity of data collection for healthcare providers could contribute to an increase in missing data, as well as hesitation to adopt these novel therapies at their medical institutions. Additionally, multiple registries may be required to fulfill post-approval requirements from different regulatory authorities.

To address these challenges, public/private collaboration could be used to create more centralized registries for post-approval data collection, with a consistent core of required

variables, plus add-on modules for product-specific variables of interest. FDA could also contribute, along with other regulators internationally, to creating a model for safety data collection across regulatory bodies.

Within upcoming guidance, FDA recommendations on a standard approach to safety data outcome collection for sponsors and third-party registries could be helpful to those establishing such registries, as well as to sponsors in being able to assess the quality and reliability of an existing registry for post-approval data collection.

When finalizing the draft guidance on assessing registries as real-world data (RWD), we suggest FDA provide key examples of how RWD from registries have been used successfully and unsuccessfully in the post-market setting for cell and gene therapies. Accessible and efficient data systems could improve data quality in registries. For example, electronic data transfer from the electronic health record to a registry data system may allow for tokenization of individual patients and enable LTFU of patients in their community setting.

Alternative study designs, including decentralized studies, and RWD collection

Decentralized studies can enable RWD collection that facilitates assessment of meaningful aspects of health in real-life settings. These studies are best facilitated using deployment of electronic data capture, involving careful implementation of electronic clinical outcome assessments (eCOAs) and digital health technologies (DHTs). eCOA and DHT data are often interpreted in concert with analysis of electronic health records to understand clinical benefit and changes in clinical status over time.

ARM supports the use of fit-for-purpose digital collection of RWD to reduce post-approval data collection burdens for patients, healthcare providers, and sponsors. These approaches may contribute to improved patient access, diversity, and retention in trials, and reduce participant burden over the course of a study (especially in longer observation periods).

DHTs that are used in a home setting, such as wearable sensors, are particularly convenient for patients and have the additional benefits of being able to capture data over a longer period than single point-in-time measurement collection in a research or clinical setting. DHTs help assess concepts reliably observable in real-world settings and increase data efficiency and integrity over long observation periods. While ARM recognizes that some endpoints cannot be adequately replaced solely with COA and DHT data, we recommend identifying circumstances in which these data could serve as a sole source of safety and/or efficacy data.

To enable greater use of RWD post-approval, we encourage a collaborative approach with the agency to develop novel methodologies for comparing endpoints using RWD post-approval to endpoints used pre-approval, when they differ.

Determination of specific safety outcomes that may be necessary for cell or gene therapies

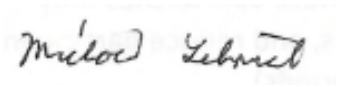
For gene therapies using AAV vectors, sponsors should continue to monitor for signs of tumorigenicity in the post-approval setting if there are relevant translatable signals in preclinical data that warrant such monitoring. Oncogenicity is a theoretical risk of treatment with AAV gene therapy in humans that can be monitored over time through post-approval patient registries. Sponsors should employ standard pharmacovigilance measures in the post-approval setting in line with AAV-specific recommendations in FDA's 2020 final guidance on *Long-Term Follow-Up After Administration of Human Gene Therapy Products.*

ARM does not recommend surgical biopsies as a routine standard procedure for post-approval monitoring after AAV gene therapy given the risk, discomfort and burden for patients associated with the procedure. Routine monitoring approaches as appropriate for the disease area and product should be considered. ARM encourages and supports development of noninvasive methods for monitoring, including liquid biopsies and other markers.

ARM supports an informed approach to the frequency of safety monitoring that prioritizes patient safety while considering the ability of patients and their caregivers to meet frequency requirements. Sponsors and the agency should seek input from the patient community to assist in guiding the development of reasonable expectations on the frequency of follow-up requirements. To enhance patient retention, periodic evaluation of study protocol deviations, noncompliance, patient attrition, and refusals to enroll should be allowed to help inform potential protocol amendments in consult with regulatory agencies to best serve patient needs.

Thank you for your consideration of these comments and for your shared commitment to this important topic in the cell and gene therapy field.

Sincerely,



Michael Lehmicke
Vice President, Science and Industry Affairs