Biotechnology Innovation Organization
1201 New York Ave., NW
Suite 1300
Washington, DC, 20005
202-962-9200

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

Re: Docket No. FDA-2023-N-0398: Methods and Approaches for Capturing Post-Approval Safety and Efficacy Data on Cell and Gene Therapy Products.

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the listening meeting and the opportunity to provide feedback on the important topic of **Methods and Approaches for Capturing Post-Approval Safety and Efficacy Data on Cell and Gene Therapy Products**. BIO's feedback on the four topic areas is listed below.
BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

BIO provides the following feedback in response to FDA's 4 topic areas of consideration so that FDA may consider this feedback as it develops draft guidance on this topic, per PDUFA VII:

Topic 1: Development and establishment of product-based and/or disease-based registries

BIO believes that both product and disease-based registries are crucial for longer term follow up on effectiveness and safety in general but are of particular importance for cell and gene therapies given the relatively new treatment modalities. The strength of registries is the increased quality and availability of study specific data; however, they are limited because sample size is often too small to robustly inform an analysis. For these reasons, BIO recommends that new methods be developed to increase enrollment and generalizability of registry populations.

Disease-based registries are often started by an individual applicant in response to FDA-issued post-marketing requirement (PMR) and will be established to be fit-for-purpose to address a specific scientific question. BIO recommends that methods be developed to account for the overuse of single registries by multiple applicants to respond to the same PMR for a class of products. We further recommend that FDA consider the potential for collaboration across industry to more effectively use a disease-based registry to assess products in the same class.

Regarding registries for heritable diseases, BIO believes it is important to document genotyping methods and to capture information on laboratories used for each patient, as test results may vary across methods and labs. In addition, BIO recommends that study teams should be prepared to update enrolment criteria once new relevant genes are discovered for the disease of interest.
Population-based registries may be available in certain countries (e.g., Sweden and Denmark), but these registries may have a limited number of patients for ultra-rare diseases due to the smaller population. Additionally, multiple registries may be required to fulfil post approval requirements from different regulatory authorities. BIO strongly encourages the agency to continue to engage with international health authorities to promote a more robust safety profile of a drug via harmonization of registry standards.

Finally, BIO recommends that FDA develop recommendations on best practices for third-party registries which could be helpful to those establishing such registries, as well as to applicants in being able to assess the quality and reliability of an existing registry for post-approval data collection. Examples of topics for best practice recommendations include the processes of data collection, and the processes of tracking of data completeness, accessed data, changes made, and loss to follow-up.

Topic 2: Real-World data collected in clinical settings, through digital health technologies, electronic health records (EHR), insurance claims databases, and other administrative databases, and population-based data sources.

Post-Market safety study design is driven by regulatory expectations which in turn reflects the regulators level of comfort, previous experience, and internal working knowledge regarding study design elements. BIO recommends that FDA's guidance provide information on best practices for successfully submitting protocols using new data sources and/or new methodological approaches in non-interventional studies. Examples may include a list of document types or information in submissions that would help regulatory decision making.

While we understand that some endpoints cannot be adequately replaced solely with Clinical Outcome Assessment (COA) and Digital Health Technology (DHT) data, BIO recommends identifying circumstances in which these data could serve as a sole source of safety and/or efficacy data.

In addition, BIO suggests that FDA's guidance should include recommendations on best practices for early contact with FDA to discuss registry proposals. Although industry is advised to reach out to regulators early and to discuss study design plans prior to submission of a compete protocol, FDA generally does not signal support for proposals until they are seen in full. This provides risk to applicants for meeting deliverable deadlines and deters applicants from proposing innovative RWD-based study designs.

Regarding the use of real-world data (RWD), long-term follow-up is a significant challenge in the setting of registry-based studies, as patients are often lost to follow-up due to a variety of reasons. To address this, when there is a validated algorithm to identify outcomes and sufficient capture of exposure and key covariates, RWD

may be used as a preferred approach to assess long-term outcome. Finally, RWD has emerged as an alternative and have been used successfully to study pregnancy outcomes, as recognized in FDA draft guidance.[1]

In addition, to the above recommendations, BIO provides the following general feedback regarding certain types of data sources:

1. Insurance claims and administrative databases typically do not include genotype of patients which can complicate comprehensive data collection. For rare diseases, specific International Classification of Disease (ICD) codes may not be available, which makes it difficult to identify patients in EHR, insurance claims or administrative databases.

2. Sponsors often leverage existing databases of RWD including insurance claim databases, electronic health records (EHRs) and population-based data sources as a complementary tool for the collection of safety and efficacy data for cell and gene therapy products. However, there may be differences between an endpoint measurement in the RWD setting versus a recognized standard assessment (such as International Myeloma Working Group (IMWG) criteria). Such differences may limit the utility of the RWD in the interpretability of data collected. In these scenarios, a collaborative approach with the Agency is required to develop novel methodology for comparing real-world endpoint with that which was measured in the clinical trial. BIO encourages the Agency to work closely with sponsors to address such endpoint challenges.

Topic 3: Alternative study designs, including decentralized studies.

BIO strongly encourages FDA's forthcoming guidance to provide information on alternative study designs for cell and gene therapy studies, including decentralized trials. BIO recommends that the guidance:

1. Describe best practices for encouraging patients and providers to participate in decentralized studies,
2. Describe how FDA will consider the use of new technologies designed to curate reliable and accurate data,
3. Provide examples of alternative study designs that have been accepted by FDA and were used to address safety concerns, and
4. Describe considerations regarding remote informed consent.

Topic 4: Determination of specific safety or efficacy outcomes for which collection of post-approval safety or efficacy data may be necessary for cell or gene therapies.

BIO generally recommends that post-approval monitoring of oncogenicity and durability of response is of particular importance. BIO encourages the use of pragmatic or RWD-based approaches to ascertain outcomes for which there are significant operational challenges to collect desired data. BIO recommends that the forthcoming guidance identifies mechanisms to access and integrate data sources (e.g., FDA Sentinel, Electronic

[1] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postapproval-pregnancy-safety-studies-guidance-industry

Health records, Insurance Claims, Real-World Evidence) to conduct pharmacoepidemiologic safety evaluations. An important application of this might be to determine the general background risk of oncogenicity in target populations to contextualize malignancies that could emerge in patients treated with cell or gene therapies. An example is to contextualize the theoretical risk of cancer in persons treated with liver-directed adeno-associated viruses (AAV)based gene therapies.

In addition to what might be necessary to collect post-approval, BIO requests that FDA considers whether revisions can be made to current post-approval requirements and recommendations. For example, BIO suggests that FDA consider whether there is an opportunity to decrease the length of long-term follow up required for gene therapy products, including genetically modified cells, based on the totality of data (e.g., 5-10 yrs. vs. 15 yrs.). BIO also recommends that FDA consider alternatives to capturing post-approval information on all patients and instead considers setting a defined number of patients. Both a shortened length of follow-up and a reduction in number of patients followed may address concerns related to patient retention. Finally, BIO recommends that FDA considers whether it is necessary to collect and analyze biopsy samples in all subsequent malignancies, especially, non-T-cell malignancies.

BIO also recommends that FDA consider adoption of risk proportionate post-approval safety surveillance strategies when determining what safety outcomes require further data collection. One strategy is to focus on important identified or potential risks and missing information that could impact benefit-risk evaluations and for which there are safety hypotheses based on findings from non-clinical and clinical studies or community safety concerns. Another strategy is to adapt safety surveillance strategies to level of risk. For example, there may be a greater risk of delayed adverse reactions with use of integrating viruses, or viruses capable of latency reactivation, and genome-editing products and lower risk with adenovirus and adeno-associated viruses (AAV). In conclusion, BIO thanks the Agency both for the listening meeting on this topic, and the opportunity to provide feedback to inform your upcoming draft guidance on this same topic.

Sincerely,

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Sam Gunter
Director, Science & Regulatory Affairs
Biotechnology Innovation Organization