Alliance for Regenerative Medicine

July 28, 2020

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

Re: Comments for FDA Docket Number: FDA-2019-D-5392; Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations; Draft Guidance for Industry; Availability

The Alliance for Regenerative Medicine (ARM) is the preeminent international multi-stakeholder advocacy organization focused specifically on the issues facing regenerative medicine and advanced therapies. Working with our members and policymakers, we foster investment, research & development, and successful commercialization of safe, effective, and transformational therapies for patients around the world. We promote legislative, regulatory and reimbursement initiatives necessary to facilitate access to life-saving advances in regenerative medicine worldwide. ARM is comprised of more than 350 leading small and large companies, non-profit research institutions, patient organizations, and other sector stakeholders dedicated to realizing the promise of regenerative medicine for patients around the world.

Our life science company members are directly involved in the research, development, and clinical investigation of cell and gene therapy products, as well as the submission of investigational new drug (IND) applications, and Biologics License Applications (BLA) for such products to the Food and Drug Administration (FDA). Many of our member companies have products under development covering a broad range of conditions, which among other considerations, take the regulatory incentives including orphan drug designation (ODD) and orphan drug exclusivity (ODE) into consideration as product development programs are planned and undertaken.

ARM commends the FDA for the issuance of the draft guidance on interpreting sameness of gene therapy products under the orphan drug regulations, which would help incentivize new gene therapy product development as well as facilitate patient access to new therapies by providing clarity on FDA's thinking on this important topic. In this letter, ARM provides comments and suggestions for the Agency's consideration as they finalize the draft guidance and for future iterations of guidance.

General Comments

As an initial matter, ARM recognizes that, although scientific advances in gene therapy have shaped the field for many years (decades) now, regulatory science based on actual review and approval of gene therapy products for broad use remains a new area for FDA and other health authorities, with only a handful of product approvals thus far. Opportunities to consider, inform, and apply regulatory policies stemming from the Orphan Drug Act have been even less frequent. As such, ARM appreciates FDA's approach in this initial draft guidance, which we believe allows for broad flexibility as the science advances and FDA gains more experience with product reviews, and ODD and ODE determinations for gene therapy products.

Consistent with this understanding of the current regulatory environment for gene therapy products, in this comment letter, ARM has several recommendations and highlights areas where it would be helpful for FDA to provide additional updates and clarifications to stakeholders, once a determination of "sameness" has been made for an adequate number of products such that to allow for FDA to extrapolate generalizable policy themes and regulatory decision-making trends across those decisions.

Principal molecular structural features in sameness determination

ARM appreciates the recommendations provided in the draft guidance clarifying that the FDA generally intends to consider certain key features such as transgenes and vectors used in gene therapy products to be "principal molecular structural features" under 21 CFR 316.3(b)(14)(ii) when two gene therapy products are intended for the same use or indication. To the extent (and when) generalizable across reviews, ARM requests more clarity on the FDA's thinking on how the Agency intends to make a determination of sameness for two vectors, including two vectors with different serotypes from the same viral class (e.g., adeno-associated virus 2 (AAV2) vs. adeno-associated virus 5 (AAV5)). FDA should consider whether differences in principal molecular structural features of the products, including different capsids of an AAV vector-based product, would support a determination that two products are the same or different for the purpose of orphan exclusivity. We encourage FDA to ensure that scientific principles remain a key factor to support regulatory decision-making regarding sameness for the purpose of orphan exclusivity.

Minor differences in the principal molecular structural features in same drugs

ARM aligns with the clarification in the draft guidance that FDA generally does not intend to consider the principal molecular structural features (transgenes and vectors) to be different for purposes of 21 CFR 316.3(b)(14)(ii) if there are only minor differences in the transgenes and/or the vectors. ARM requests the Agency to consider a public meeting with prior release of a discussion guide for notice and comment in advance of the public meeting to inform the Agency's policy development, e.g. with regard to minor differences in the principal molecular structural features including the transgenes and/or the vectors. Facilitating dialogue via public meeting would provide appropriate means for the Agency to share learnings as they gather more experience as well as a notice and comment period for stakeholders prior to further guidance.

Additional features "can contribute to the therapeutic effect" and "may be considered to be principal molecular structural features"

ARM appreciates clarification in the draft guidance that when applicable, FDA generally intends to consider additional features (e.g., regulatory elements, cell type that is transduced) of the final gene therapy product to inform the sameness determination for purposes of 21 CFR 316.3(b)(14)(ii), depending on "additional features of the final product that can contribute to the therapeutic effect." When two gene therapy products express the same transgene and have or use the same vector, it would be helpful to understand what factors the Agency may consider to determine that the additional features of a product "can contribute to the therapeutic effect" and "may be considered to be "principal molecular structural features" within the meaning of 21 CFR 316.3(b)(14)(ii)." Additionally, to the extent considered by the Agency, it would be helpful to understand whether the FDA might consider the cell type transduced to be an additional factor that "can contribute to the therapeutic effect," and therefore may be considered to be "principal molecular structural feature" mainly or only for cell-based ex vivo gene therapy products or for all types of gene therapy products, including in vivo gene therapy products.

Lessons learned from sameness determinations for gene therapy products

ARM recognizes that the field is new; all stakeholders including industry and the Agency, need more experience with the sameness determination for different gene therapy products to understand the nuances. Once FDA feels it has enough experience, ARM asks that the Agency share its collective experience as general principles as to why ODD/ODE is granted or not granted, while ensuring no proprietary confidential information is publicly shared. Based on FDA's experience in adjudicating the sameness determinations, it would be helpful if the Agency could provide additional information on relevant considerations discussed earlier in this comment letter. These include, for example, unique considerations for the different types of gene therapy products to provide more clarity on a product type basis.

In conclusion, ARM appreciates the opportunity to provide comments on this draft guidance to the Agency. Please reach out to us if you have any questions about our comments or if we can assist the Agency in any way as they finalize this important guidance.

Sincerely,

Robert J. Falb
Director, U.S. Policy and Advocacy