Alliance *for* Regenerative Medicine

August 3, 2018

Peter W. Marks, M.D., Ph.D.
Director
Center for Biologics Evaluation and Research
Food and Drug Administration (HFM-2)
10903 New Hampshire Avenue
Silver Spring MD 20993-0002

Dear Dr. Marks,

The Alliance for Regenerative Medicine (ARM) applauds and welcomes the Center for Biologics Evaluation and Research's (CBER) recent publication of disease-specific gene therapy guidance documents. We believe this effort will foster modern and efficient development, evaluation, and approval of gene therapy products by providing a regulatory roadmap through guidance. ARM intends to work across its membership to comment on these guidance documents.

ARM is an international multi-stakeholder advocacy organization that promotes legislative, regulatory and reimbursement initiatives necessary to facilitate access to life-giving advances in regenerative medicine worldwide. ARM is comprised of more than 290 leading life sciences companies, research institutions, investors, and patient groups that represent the regenerative medicine and advanced therapies community. Our life science company members are directly involved in the research, development, and clinical investigation of cell and gene therapy products, including gene editing 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 gene therapy products under development covering a broad range of conditions.

Our membership and interest in the field allows the unique opportunity to collaborate with the Agency to determine diseases that may benefit most from disease specific clinical draft guidance development (as described in footnote 2 of the 2018 CBER Guidance Agenda). We also refer to our March 29, 2018 letter where we provided perspective on gene therapy development in hemophilia for consideration in the Agency's planned hemophilia guidance.

FDA's guidance efforts present the opportunity to articulate and differentiate approaches to drug development based on the demonstrated potential of gene therapy. Guidance should aim to clarify regulatory considerations for clinical investigations that may require unique considerations for gene therapy with the overall goal to expedite product development. For example, while historically, annualized bleeding rate (ABR) has been used as the primary

endpoint in pre-licensure studies for hemophilia, Factor VIII and Factor IX activity levels may now be used as a primary endpoint in clinical investigations for gene therapy. The evolution of the regulatory roadmap will allow for expeditious drug development providing durable treatment to patients. It is also recognized that such disease specific guidance will potentially change the evidentiary paradigm for demonstrating safety and efficacy regardless of the therapeutic technology platform.

Notwithstanding the guidance documents already published on July 12, 2013, ARM has recommendations on guiding principles that may be helpful to determining approaches to other disease-specific guidance as well as finalizing the recently published guidances. In line with our objective to support the Agency's efforts, we offer the following points to consider:

- Unmet need: We recommend the Agency consider developing gene therapy guidance documents for diseases that are serious, life-threatening and have unmet medical need.

- Novel endpoints and clinical trial design: Disease specific guidances present the opportunity to differentiate the applicable standard based on the demonstrated potential of gene therapy. We recommend the guidances address opportunities to advance novel endpoints, including those involving biomarkers and use of imaging, and support innovative clinical trial designs to facilitate optimal and efficient development of gene therapy products. It would also be useful for the Agency to clarify for each indication how real-world evidence (RWE) could support clinical development (if/as applicable for the indication).

- Post-approval requirements: The guidances present an opportunity to clarify the agency's expectations for post-approval confirmatory requirements. The Agency may consider providing clear guidance for each condition with examples regarding how post marketing confirmatory evaluations may be fulfilled for Regenerative Medicine Advanced Therapy (RMAT) gene therapy products approved under accelerated approval using real world evidence as well as post-approval monitoring of treated patients using surrogate endpoints that would mitigate the need for a post--market clinical trial with a clinical endpoint.

- Ultra-rare diseases: Thousands of rare and ultra-rare diseases have no available treatment and the advent of gene therapy stands to provide potentially curative options for many if not most of these diseases. Ultra-rare diseases face the challenge of limited research and development, severely limited patient populations, increased cost and risk of manufacturing, and increased regulatory risks due to lack of approved therapy and no well-established roadmap for regulatory approval. These challenges are even more magnified for gene therapy (given the complex biological mechanisms, manufacturing challenges, potential unique safety issues) and may be rate limiting. Providing clarity on the regulatory roadmap for some ultra-rare diseases through guidance, including clarification on appropriate endpoints and clinical trial design will foster gene therapy drug development for such diseases with high unmet medical need.

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- Several sponsors or technologies targeting the same indication with promising data: We recommend the Agency prioritize issuing guidance for diseases for which there is already significant development underway (e.g. neurodegenerative diseases, etc.). This may be determined based on evaluation of products in clinical trials or for which "pre-pre-IND"/INTERACT interactions have occurred, and where it is likely based on the available information that a significant number of sponsors and gene therapy technologies are being developed to treat the indication with promising early data. So ultimately, the impact of having a guidance will bring a clear benefit for the patients suffering from the targeted disease by making product development more efficient and ultimately comparable among each other for patients – using endpoints that are meaningful to them.

- Options for non-viral gene delivery: The delivery of new genetic constructs can be accomplished by electroporation, lipofection or nucleofection to safe-haven sequences particularly with the advent of CRISPR/Cas9 medicated gene delivery technology and CRISPR guide-RNA sequences. This would remove the potential for viral vector re-activation in the patient without impacting the host genome regulatory control elements and reduce off target effects. Knowledge of the target sequence within the host genome is imperative in the design of a therapeutic genetic construct. Of note, regulatory guidance as to whether this approach would be considered gene therapy would be useful. As indicated in the Expedited Programs for Regenerative Medicine Therapies for Serious Conditions Draft Guidance for Industry, gene therapies should "… lead to a durable modification of cells or tissues…" [to] "…meet the definition of a regenerative medicine therapy." FDA should provide guidance on how to obtain clarification as to how a product is classified. In Europe a procedure for "Advanced Therapy Medicinal Product" classification has been set-up. We recommend considering the INTERACT program as an opportunity to help with this determination.

Additionally, with this letter we share perspective on areas that may particularly benefit from disease-specific gene therapy guidance to promote drug development. We leverage the expertise and experience of our member companies as we provide this insight for your consideration.

- Hemoglobinopathies, and Sickle cell disease (SCD) is a good candidate for this exercise, because it meets all the criteria, and it is a public health issue in the United States. The types of gene therapy products under development for this indication include several gene editing products, and gene addition products, focused on increasing non-sickling hemoglobin production. Another reason SCD would be a good candidate is that historically, drug product development has been sparse and challenging for this disease. Lastly, the gene therapy products being developed for this indication have the opportunity to achieve curative outcomes, but these treatments based on hematopoietic stem cell transplantation pose considerable limitations on trial design. Ensuring that the development of these products is efficient by clarifying key

considerations to reach that goal will benefit patients with SCD and the health care system in the US, and ultimately globally.

- Genetic metabolic diseases, such as Alpha-1 antitrypsin deficiency (A1AD) would also meet the general criteria for consideration. A1AD is a rare genetic disorder resulting in severe lung disease or liver disease such as early-onset emphysema, neonatal hepatitis, chronic hepatitis, cirrhosis, and hepatocellular carcinoma. A1AD is due to a mutation in the SERPINA1 gene that results in reduction in the necessary alpha-1 antitrypsin (A1AT). Gene therapy presents the opportunity for efficient drug development using biomarkers such as A1AT in innovative trial designs. Gene therapy products also have the potential to provide significant long term and potentially curative effect for patients affected by A1AD. FDA guidance can clarify the drug development path for the gene therapy products under development, including the opportunity to use biomarkers and incorporation of innovative clinical trial designs.

- Inborn Errors of Metabolism such as Pompe disease, Gaucher disease and Mucopolysaccharide storage diseases may also be considered. These are rare diseases with a high unmet medical need and indeed a number of gene therapy products are under development. The guidances may clarify unique considerations for gene therapy clinical investigations, including use of biomarkers, neurocognitive scales and clinically meaningful outcomes, including those related to known comorbidities.

- Ophthalmic disorders such as retinitis pigmentosa, dry eye syndrome, and age-related macular degeneration are particularly promising candidates for gene therapy, since the eye is both an immune privileged compartment and one into which genes can be delivered with low risk of systemic exposure. The attractiveness of a one-time procedure involving simple eye surgery is not only the relatively low cost but also the single invasive treatment.

- Neurodegenerative diseases. The difficulty of delivering chemical drugs across the blood-brain barrier (BBB) has been one of the major difficulties hampering the successful development of treatments for Alzheimer's disease, Parkinson's disease, ALS, and other neurologic disorders, which cumulatively afflict over 6 million Americans at an annual cost of >$200 billion/yr. The rapidly aging population makes this unmet medical need an urgent national priority. Gene therapy, using viral delivery vectors optimized for BBB penetrance and efficient transduction into, e.g., motor neurons in the case of ALS, has tremendous promise for providing an entirely new approach to prevention as well as treatment in a medical area that currently has none of either. A number of gene therapy companies are planning to advance therapies for these diseases into clinical trials within the next 12 months, making guidance particularly timely. Although behavioral studies are expensive, time-consuming and highly variable for diseases such as Alzheimer's, advances in biomarker development have made great strides recently. Guidance on matters such as acceptable endpoints, adequate statistical power and acceptable pre-clinical model data and safety studies would be especially helpful. We

note, for example, that animal models for neurodegenerative diseases are poor at best and may be misleading, so guidance as to acceptable ex vivo models for efficacy (patient-derived neurons, cerebral organoids, etc.) could greatly advance this field.

- Neuromuscular diseases such as Duchenne Muscular Dystrophy would benefit from a guidance document specifically addressing issues related to the approach to augment the existing guidance on developing gene therapy for the disease. In particular, since the most advanced gene therapy programs introduce a shortened version of the dystrophin gene, FDA should provide guidance whether expression of the mini/micro-dystrophin protein would be an acceptable surrogate endpoint for approval. Furthermore, FDA guidance on the meaningfulness of total protein (western blot) vs % positive fibers (IHC) given the importance of transducing as many muscle cells as possible to achieve clinical benefit would help guide endpoint method development in the field. FDA perspective on next-generation gene editing approaches which have the potential to correct the gene would also be of benefit.

ARM appreciates the opportunity to provide this feedback. We recommend an ongoing dialogue to continue to evaluate and discuss the needs for disease-specific gene therapy guidance to support development in this evolving field. We look forward to continued engagement with the Agency to further development of these innovative therapies.

Sincerely,

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

CC: Scott Gottlieb, M.D., Commissioner, U.S. Food and Drug Administration
Wilson Bryan, MD, Director, Office of Tissues and Advanced Therapies, Center for Biologics Evaluation and Research, U.S. Food and Drug Administration

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