

# ALLIANCE<sub>for</sub> *Regenerative Medicine*

March 29, 2018

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Director  
Center for Biologics Evaluation and Research (CBER)  
Food and Drug Administration (HFM-2)  
10903 New Hampshire Avenue  
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Dear Dr. Marks

We are writing on behalf of the Alliance for Regenerative Medicine (ARM) to acknowledge the Center for Biologics Evaluation and Research's (CBER) efforts to develop guidance to foster the development of gene therapy products. In particular, CBER's 2018 guidance agenda highlights FDA's plan to develop and issue disease-specific gene therapy guidances, including the guidance on Gene Therapy for the Treatment of Hemophilia planned for 2018.

As you know, 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. Today, ARM has more than 290 members and is the leading global advocacy organization in this field. Our 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 FDA.

Our member companies have gene therapy products under development covering a broad range of conditions including hemophilia. As such, we welcome the agency's efforts to draft disease-specific gene therapy guidance, with current progressive applications and capabilities in mind, that harnesses modern and efficient parameters for evaluation and approval, and we appreciate the greater clarity and predictability such guidance can offer.

Given our experience in this area, we would be pleased to offer our assistance as FDA considers the issues that will be addressed in the guidance. The following are general comments regarding FDA's proposal to develop disease-specific gene therapy guidance:

- **Selected Diseases:** ARM appreciates that FDA has disclosed its intent to develop gene therapy guidance specific to hemophilia. We note the agency plans to develop other disease-specific guidance documents. We would like to understand FDA's approach to selecting the conditions

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for which it feels guidance may be necessary. We also recommend that FDA engage external stakeholders such as ARM in identifying other diseases that may benefit from specific guidance.

- **Expert Input:** We would like to understand FDA’s approach to obtaining expert input as it develops content for the guidance. We acknowledge that this field is evolving at a rapid pace, and recognize the importance of ensuring that expert stakeholders are involved in informing FDA’s thinking. Given our experience in this area, and the significant implications of future guidances for our membership, we urge FDA to work with ARM as it develops these guidances. This collaboration may be facilitated through a public meeting where FDA engages in dialogue with external stakeholders to try to understand where guidance would be most beneficial.

The following are specific considerations related to FDA’s planned Hemophilia Guidance. We recommend that FDA take the following factors into consideration:

- **Potential endpoints:** FDA has suggested that non-traditional endpoints should be considered in clinical trials evaluating gene therapy for hemophilia. We encourage FDA to offer examples of endpoints the Agency would find acceptable to support approval of gene therapy products for hemophilia. We urge the Agency to include language in the guidance recognizing factor activity levels as a primary endpoint to support approval of a gene therapy product for hemophilia. This will ensure universal understanding and acceptance within FDA and with external stakeholders of factor activity levels as an acceptable endpoint for clinical studies evaluating gene therapy for hemophilia. While historically, annualized bleeding rate (ABR) has been used as the primary endpoint in pre-licensure studies of new factor VIII and IX products, recent results achieved with AAV gene therapies render a need to reevaluate this approach as ABR alone does not have the capacity or sensitivity to distinguish the improved outcomes and greater efficacy possible with gene therapies. We refer you to the editorial article [\*Establishing the appropriate primary endpoint in haemophilia gene therapy pivotal studies\*](#),<sup>1,2</sup> which in turn references other articles attesting to the following facts:
  - ABR has a major subjective component, in that the patient or the physician needs to distinguish a bleeding episode from arthritic pain. False positive and false negative rates between the patient’s perceptions of joint bleeding and arthritis compared with concurrent ultrasound evaluation are high.<sup>3</sup>

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<sup>1</sup> Pierce G. F., Ragni M. V., *et al.* Establishing the appropriate primary endpoint in haemophilia gene therapy pivotal studies. **Haemophilia**. 23(5): 643-644 (2017).

<sup>2</sup> Also see Machin N. and Ragni M.V. Measuring success in hemophilia gene therapy using a factor level & outcomes yardstick. **Expert Review of Hematology**. 11(2): 83-86 (2018)

<sup>3</sup> Ceponis A., Wong-Sefidan I., *et al.* Rapid musculoskeletal ultrasound for painful episodes in adult haemophilia patients. **Haemophilia**. 19: 790-8 (2013).

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- Factor VIII and factor IX activity levels have long been established as direct measures of severity of hemophilia. Factor activity levels are a direct manifestation of the gene defect, as they are directly linked to the pathophysiology of the disease. Patients with mild (>5%), moderate (1%-5%) and severe (<1%) disease have distinct and separable phenotypes based upon activity levels. These are measured by bleeding rates, severity of bleeding, severity of sequelae including joint damage, and risk of mortality.
- **Patient reported outcome (PRO) tools and patient experience data:** PROs have been developed and validated in hemophilia and specific guidance on their use versus other PRO tools would be welcome. Additionally, we encourage FDA to consider the importance of the patient experience data and its incorporation in the comprehensive evaluation of the risk benefit profile for hemophilia gene therapy products.<sup>4</sup> The potentially curative benefit of gene therapy products for hemophilia will require increased reliance on the benefits provided to patients with hemophilia and likely a unique approach than has been applied historically.

FDA's guidance presents an opportunity to clarify that for trials evaluating gene therapy products for the treatment of hemophilia, clotting factor activity level is a more accurate and objective primary endpoint to assess efficacy than ABR.

- **Types of clinical studies that can generate the quantity and quality of data needed for approval given that hemophilia is a rare disease:** In developing considerations for the guidance, we encourage FDA to recognize and address challenges associated with designing clinical trials for hemophilia considering the limited patient population. The high degree of clinical benefit in studies so far supports getting such promising new therapies to patients sooner, while using a balance of flexibility and innovative approaches to ensure and maintain a robust safety profile. This is consistent with comments made by FDA Commissioner Gottlieb at the World Economic Forum on January 26, 2018 where he indicated that in cases showing certain and strong benefit/efficacy, long-term risk analysis can be conducted in the post-market setting.

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<sup>4</sup> See Recht M., Konkle B.A. Recognizing the need for personalization of haemophilia patient-reported outcomes in the prophylaxis era. *Haemophilia*. 22: 825–832 (2016).

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Again, we welcome and strongly support the agency's effort to help innovators move forward with gene therapy product development by modernizing what FDA needs to evaluate and approve innovative products and we stand ready to assist in any way.

Sincerely,



Janet Lynch Lambert  
CEO

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 (CBER), U.S. Food and Drug Administration (FDA)

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