July 27, 2020

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 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FDA Docket Number: FDA-2019-D-5392; Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations; Draft Guidance for Industry

Dear Sir/Madam:

BioMarin appreciates the opportunity to provide comments on the FDA Draft Guidance for Industry titled "Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations."

BioMarin is a global biotechnology company that develops and commercializes innovative biopharmaceuticals for rare diseases driven by genetic causes. Our focus is on developing therapeutics, including gene therapy products, that provide meaningful advances to address the unmet medical needs of patients who live with serious and life-threatening rare diseases. BioMarin remains steadfast in its mission to bring innovative treatments to market that will make a big impact on small patient populations.

We are submitting the following general comments for consideration as the Agency works to finalize the draft guidance. BioMarin's comments are intended to provide suggestions which, when addressed in the final guidance, could provide greater clarity to sponsors, and in turn, support more efficient and successful development of innovative gene therapy products to treat patients suffering from rare diseases.

General Comments

We commend the Agency for its efforts to develop guidance for industry on this important topic and provide clarity on FDA's approach to determining sameness for gene therapy products for the purpose of orphan-drug designation and exclusivity under the orphan drug regulations. Overall, we agree with the framework outlined in the draft guidance, which focuses on defining the principal molecular structural features of gene therapy products, as well as FDA's case by case approach to addressing "minor" differences, and the impact of additional features that may also be considered to be the principle molecular structural features for gene therapy products. As FDA's policy is finalized and implemented, we encourage the Agency to provide opportunities to sponsors to consult with FDA early in development to understand how their products in development will be evaluated for sameness determination for the purpose of orphan drug exclusivity as well as the data or evidence that would be needed to achieve the determination desired by the sponsor.

Maintaining Incentives for Innovation While Also Providing Patients Access to More Options for Therapy

We believe that the broad flexible case-by-case approach outlined in the draft guidance will allow the Agency to make science-based decisions in consideration of individual gene therapy products. FDA has precedent with small molecules as well as biological products, including monoclonal antibody products,

where the Agency has been successful in striking a balance between maintaining incentives for innovation, while also facilitating patient access to more options of approved products when sufficiently different.[1]

Considering the cost and complexity of research, development, and manufacture of gene therapy products, coupled with the difficulties in recovering those costs for products developed for rare diseases given the small patient numbers, there is need to maintain incentives for gene therapy product development for rare diseases. Orphan drug marketing exclusivity is paramount among such incentives to support innovation for development of treatments for the over 7000 rare diseases affecting patients. Maintaining incentives is also important to support and retain the biopharmaceutical innovation industry in the United States. The current landscape of uncertainty surrounding eligibility for incentives, including orphan drug marketing exclusivity, could discourage innovation in the budding gene therapy product industry. Therefore, we caution against disincentivizing innovation by ensuring that FDA's approach to determining sameness is scientifically sound and justifiable. We understand and emphasize the public health need to facilitate access to more options for approved therapies to patients, especially considering the high cost associated with development. We encourage the Agency to continue to tread carefully and strive to strike the right balance between incentivizing innovation and providing patient access to more options for gene therapy products for their condition.

Recommendations on Defining the "Same Use" or Indication in the Context of Gene Therapy Products

As discussed in the background section of the draft guidance, the orphan drug regulations define "same drug" for a drug composed of large molecules (macromolecules) as a drug that contains the same principal molecular structural features (but not necessarily all of the same structural features) and is intended for the "same use or indication" as a previously approved drug, except that, if the subsequent drug can be shown to be clinically superior, it will not be considered to be the same drug. The draft guidance provides helpful recommendations regarding the principal molecular structural features for a gene therapy product that will be used to support FDA's determination of "sameness." However, the draft guidance does not provide recommendations on how the "same use" or indication will be defined, given that unique considerations abound when defining the indication or patient population for use of certain gene therapy products. For example, it would be helpful if the Agency shared their current thinking on the impact of pre-existing immunity to gene therapy products, e.g., when using companion diagnostic antibody screening assay for defining the patient population for a particular gene therapy product, on determining whether two products are intended for the "same use" or indication.

Specific Comments on the Draft Guidance Recommendations

Transgenes and Vectors as Principal Molecular Structural Features

We agree with FDA's policy to consider certain key features such as transgenes and vectors used in gene therapy products to be "principal molecular structural features" under per 21 CFR 316.3(b)(14)(ii). We find helpful FDA's discussion in the draft guidance that if two gene therapy products have or use vectors from a different viral class (e.g., gammaretrovirus vs. adeno-associated virus (AAV)), FDA generally intends to consider them to be different drugs because they will not contain the same principal molecular structural features, even if they express the same transgene. Such policy appears consistent with FDA's

[1] *See* Orphan Drug Regulations, 57 Fed. Reg. 62076, 62078 (Dec. 29, 1992) (establishing the clinical superiority threshold to strike an appropriate balance by not only encouraging "the development of safer and more effective orphan drugs," but also "protect[ing] the primary incentive that Congress created in the [ODA]."

current approach for biologicals. We appreciate FDA's clarification that FDA intends to make the determination of whether two vectors from the same viral class (e.g., AAV2 vs. AAV5) are the same or different on a case-by-case basis. Considering that there is tremendous development of gene therapy products using AAV-based vectors, it would be helpful to further clarify FDA's thinking regarding factors that FDA may consider in making the determination that vectors within the same viral class are the same or different.

Minor Differences Between Principal Molecular Structural Features

We align with the Agency's proposed policy that two gene therapy products will not be considered different drugs based solely on minor differences between their transgenes and/or vectors. Such policy also seems consistent with FDA's current approach for biologicals based on past precedent. It would be helpful if FDA could provide examples of the types of differences the Agency would consider to be minor differences in the transgenes and/or the vectors such that FDA would not consider two gene therapy products to be different drugs based solely on those minor differences.

Additional Features that "can contribute to therapeutic effect"

We appreciate FDA's policy to generally consider additional features (e.g., regulatory elements, cell type that is transduced) of the final gene therapy product when they "can contribute to the therapeutic effect" and that these features may be considered to be "principal molecular structural features" within the meaning of 21 CFR 316.3(b)(14)(ii). This is sound policy given the complexity of gene therapy products and need to make science-based decisions that support the balance between maintaining incentives for innovation while facilitating patient access to more options for products. However, minor tweaks or changes to the product design that do not contribute to the therapeutic effect in a substantive way should not be allowed to break the exclusivity of a previously approved "same" drug for the "same use" or indication.

Further, we recommend that FDA accept different types of data and data sources to inform their decision-making. It would be helpful if the Agency could provide examples of the type of data (e.g. discovery data or nonclinical data) that would inform FDA's determination regarding whether the additional features (e.g., regulatory elements such as a different promoter) can contribute to the therapeutic effect such that the additional features may be considered to be principal molecular structural features under 21 CFR 316.3(b)(14)(ii).

BioMarin commends FDA for development and timely issuance of guidance for industry on this important topic. The guidance is an important step in facilitating innovation as well as patient access so that new gene therapy products are developed to ultimately provide patients with innovative treatments for rare diseases. We look forward to the final guidance.

Sincerely,

Adora Ndu, PharmD, JD
Vice President, Regulatory Affairs
Policy, Research, Engagement (PRE), & Reg International
BioMarin Pharmaceutical Inc.