July 28, 2020

Division of Dockets Management (HFA-305)
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2019-D-5392 for "Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations."

Dear Sir or Madam:

On behalf of the 25 to 30 million Americans with one of the over 7,000 known rare diseases, the National Organization for Rare Disorders (NORD) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to provide comments on the Agency's draft guidance for industry titled *"Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations."*

NORD is a unique coalition of voluntary health organizations dedicated to helping people with rare "orphan" diseases and assisting over 300 organizations that serve them. NORD is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and patient services.

It is estimated that there are over 7,000 rare diseases, which are defined in the United States as diseases affecting 200,000 or fewer people. Prior to the Orphan Drug Act of 1983, there were only 34 treatments available for patients living with rare diseases. NORD played a pivotal role in the enactment of the ODA. The goal of the ODA is to encourage investment in and the development of drugs for rare diseases by offering incentives for drug development for rare diseases despite often affecting very small populations. These incentives include research grants, tax credits for qualifying clinical trial expenses, waiving FDA user fees to submit a drug product application, and upon approval, seven years of exclusivity for the drug's indicated use for that specific rare disease. The incentives in the ODA have been a huge success, going from less than 35 in 1983 to over 800 FDA-approved indications for rare disease treatments today.

Yet, over 90 percent of rare diseases still do not have an FDA-approved treatment indicated to treat the disease. The barriers and significant obstacles that hinder the pursuit of rare disease therapies to meet the substantial unmet medical needs of patients with rare disorders requires the continued partnership of FDA, patients, investigators, and sponsors. By putting forth this draft guidance, FDA is once again showing its commitment to facilitating innovation and treatments for rare diseases. NORD thanks the Agency for this commitment.

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Estimates suggest that anywhere between half to two-thirds of the 7,000 rare diseases begin in childhood.[1,2] Many continue to be fatal in these young children.[3] Yet, scientific advancements leading to early diagnosis and improved treatments have resulted in more children with rare diseases surviving into adulthood.

Gene therapies can be targeted for patients with a specific genetic abnormality. This is a particularly exciting development for rare disease patients because many rare diseases are a result of a genetic disorder[4] and currently, most patients do not have any other treatment options. CBER stated at a recent meeting that there are now more than 900 gene therapies being actively investigated.

Upon FDA's approval of one of the first gene therapies, then-Acting FDA Commissioner Ned Sharpless said, "With each new approval, we see this exciting area of science continue to move beyond the concept phase into reality. The potential for gene therapy products to change the lives of those patients who may have faced a terminal condition, or worse, death, provides hope for the future. The FDA will continue to support the progress in this field by helping to expedite the development of products for unmet medical needs..."[5] Without question, this success is profound and offers a lot of hope to others living with rare diseases that they too might benefit from a gene therapy in the near future.

The FDA's draft guidance on *Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations* provides guidance to industry on how FDA would evaluate a gene therapy to determine whether it would qualify for orphan-drug designation. Specifically, the draft guidance proposes that if two gene therapy products are intended for the same indication, then FDA will evaluate the "principal molecular structural features" of those products as determined by the transgenes and vectors used. The guidance indicates that if there are only minor differences in the transgenes and/or the vectors, FDA generally will not consider the principal molecular structure to be different. But the Agency leaves open the possibility that additional features of the final product may be considered in determining sameness. NORD hopes that, as the science develops and the Agency gains experience, FDA will share its thinking around additional features that do or do not contribute to sameness. But, as a general principle, NORD believes this approach strikes the balance sought to be achieved under the Orphan Drug Act between spurring innovation on the one hand and permitting competition when appropriate.

Although the science on gene therapies is still very new and evolving, providing a clear overview of FDA's thinking as this guidance does will help drug developers better understand the parameters and the Agency's decision-making process. As proposed in the draft guidance, we

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[1] Sanford Research. Pediatrics & Rare Diseases. https://research.sanfordhealth.org/fields-of-research/pediatrics-and-rare-diseases. Accessed on November 19, 2019.
[2] Bavisetty S., Grody, W., Yazdani, S. Emergence of pediatric rare diseases. Rare Dis. 2013; 1: e23579. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3932940/. Accessed on November 19, 2019.
[3] Institute of Medicine. Rare Diseases and Orphan Products. Pp. 89-91. https://www.ncbi.nlm.nih.gov/books/NBK56189/pdf/Bookshelf_NBK56189.pdf. Accessed on November 19, 2019.
[4] https://omim.org/statistics/geneMap
[5] https://www.fda.gov/news-events/press-announcements/fda-approves-innovative-gene-therapy-treat-pediatric-patients-spinal-muscular-atrophy-rare-disease

believe FDA's interpretation of "sameness" for gene therapy products is consistent with 21 CFR 316.3(b)(14)(ii),[6] the definition of what a same drug means if the drug is composed of large molecules. In other words, FDA's evaluation will consider the principal molecular structure of the products and determine if two gene therapies have or use different transgenes and/or vectors. If two gene therapy products use different transgenes and vectors, FDA generally intends to consider them to be different drugs. If two gene therapies express different transgenes but have or use the same vector, FDA generally intends to consider them different drugs; this also would hold true if the two gene therapies, have or use vectors from a different viral class, but express the same transgene. It is important that FDA's determination of "sameness" does not depend upon whether every detail is the same. NORD believes this draft guidance mostly strikes an appropriate balance and ensures regulatory flexibility in the future.

However, given that the science and technology is still very new and quickly evolving, it is important for FDA to maintain open communications with drug developers and be flexible as new data and understanding of gene therapies emerge. For example, additional guidance will be necessary on the meaning of "minor differences" in transgenes and vectors. This lack of clarity could affect how sponsors approach their gene therapy development program and impact investments and innovation. Therefore, as the Agency gains more knowledge and experience, it will be critical for FDA to clearly communicate what constitutes minor differences, how it arrived at this determination, and the process for drug developers to glean this information in order to maximize the incentives afforded to them under the ODA. NORD suggests using approaches like an iterative guidance that is updated in a step wise approach, like those utilized during the COVID-19 pandemic, a discussion guide, or a forum in which the Agency could respond to stakeholder questions on sameness over time.

Another component of the draft guidance that will be worth elaborating on, when appropriate, is the additional features of the final gene therapy that FDA generally intends to consider. More information will need to be provided to sponsors as soon as possible, as this too has the potential to impact their development programs. If FDA intends to undertake these considerations of the final gene therapy product, at what point in the development process will this be discussed with the sponsor and will orphan designation be determined?

In FDA's final guidance for industry on *Human Gene Therapy for Rare Diseases*, FDA recommends early communications with CBER's Office of Tissues and Advanced Therapies (OTAT).[7] FDA suggests that these meetings could occur even before submission of an IND, as an Initial Targeted Engagement for Regulatory Advice on CBER products (INTERACT) meetings. It is likely that many drug sponsors will take FDA's advice and request these early-stage meetings as they plan their gene therapy development program. During these meetings it will be helpful if FDA is prepared to indicate whether the gene therapy under consideration is a good candidate or not for orphan drug designation. NORD supports, for the final guidance, the inclusion of guidelines around when concerns about sameness should be brought to the Agency, early determinations of this kind can help inform a program's progression. Following these meetings, it will be important for the Agency to quickly and clearly communicate with the

[6] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=316.3
[7] https://www.fda.gov/media/113807/download

sponsor should any of the non-binding regulatory advice change that could affect the direction of the development program.

Given the small populations affected by rare diseases, it would be helpful if new gene therapies can benefit as many people living with a rare disease across the globe. Therefore, NORD urges FDA to engage and collaborate with foreign regulatory authorities as much as possible. Harmonizing international policies and processes from the outset will allow innovative gene therapies to reach maximum potential benefit for the global rare disease community.

NORD appreciates the opportunity to comment on this important draft guidance and looks forward to working with FDA to ensure rare disease patients are able to fully benefit from these exciting and potentially life changing gene therapies. For questions regarding NORD or the above comments, please contact me at rsher@rarediseases.org, or 202-588-5700.

Sincerely,

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