July 22, 2020

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

Re: Comments for Docket No. FDA-2019-D-5392: FDA Draft Guidance for Industry, Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations

Dear Sir/Madam:

The American Society of Gene & Cell Therapy (ASGCT) appreciates the opportunity to comment on this guidance document. ASGCT is a professional membership organization for gene and cell therapy with over 3,500 members. Membership consists primarily of scientific researchers, physicians, other professionals, and students in training. Members work in a wide range of settings including universities, hospitals, biotechnology and pharmaceutical companies, and government agencies. The mission of ASGCT is to advance knowledge, awareness, and education leading to the discovery and clinical application of genetic and cellular therapies to alleviate human disease.

ASGCT appreciates the Food and Drug Administration (FDA) offering its perspective on how it intends to interpret whether gene therapies are the "same" for purposes of interpreting the orphan drug protections in Section 527 of the Federal Food Drug and Cosmetic Act (21 USC 360cc). These safeguards are critical to protecting investments in rare disease products and incentivizing innovations in gene and cell therapies.

ASGCT is supportive of FDA's interpretation that products with different "principle molecular structural features" (such as different transgenes and/or different vector classes) will not be considered the same. We also appreciate that FDA has retained flexibility in how to interpret "principle molecular structural features" for future technologies and products that are not currently available or even contemplated at this time.

However, we have a general request for FDA to provide additional information regarding when in development sponsors should raise questions on sameness to support clarity in the development path. Ensuring openness in providing feedback will be critical in supporting continued development of gene therapy products. Specifically, we recommend sponsors have the option to engage the Agency early in development through meetings that include members of both the Office of Orphan Products Development and the Office of Tissues and Advanced Therapies to ensure effective scientific and

policy-based discussion around the issues. In addition, the Society offers the following specific comments and suggestions in order to help provide additional clarity to developers of gene therapies:

Comment/Issue	Proposed Change
III. INTERPRETING SAMENESS OF GENE THERAPY PRODUCTS	
"FDA intends to make the determination of whether two vectors from the same viral class (e.g., adeno-associated virus 2 (AAV2) vs. adeno-associated virus 5 (AAV5)) are the same or different on a case-by-case basis." Comment: It is not clear what factors FDA may consider when making a decision on a case-by-case basis.	The "case-by-case" basis described could be given additional clarity by providing examples of the types of factors FDA may consider in making the determination that two vectors from the same viral class are the same or different.
"In the scenarios described in the three bullets above, FDA generally does not intend to consider these principle molecular structural features 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. In other words, FDA does not intend to consider two gene therapy products to be different drugs based solely on minor differences between their transgenes and/or vectors." Comment: ASGCT requests clarification and/or examples of what may constitute minor differences.	

"When applicable, FDA also generally intends to consider additional features (e.g., regulatory elements, cell type that is transduced) of the final gene therapy product as described below: • If two gene therapy products express the same transgene and have or use the same vector, determining whether the gene therapy products are the same drug for purposes of 21 CFR 316.3(b)(14)(ii) may also depend on additional features of the final product that can contribute to the therapeutic effect. These additional features may include regulatory elements, or for genetically modified cells, may include the cell type that is transduced. In these cases, FDA generally intends to consider requests for designation and exclusivity of gene therapy products to evaluate whether such additional features may be considered to be 'principal molecular structural features' within the meaning of 21 CFR 316.3(b)(14)(ii)." Comment: ASGCT requests clarification and/or additional examples of features of the final product that can contribute to the therapeutic effect, and of regulatory elements that may be considered in the determination of sameness. The Society also requests clarification regarding to what degree an additional feature needs to contribute to the therapeutic effect to be considered as contributing to product differences.	We suggest that FDA provide examples of regulatory elements that may be considered as "additional features" that may be used in the sameness determination.

Thank you for consideration of these comments. Please do not hesitate to let ASGCT know if you have questions.

Sincerely,

Adora Ndu, PharmD, JD
Chair, ASGCT Regulatory Affairs Committee