December 10, 2018

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

Re: Comments for Docket No. FDA–2018-D-2258: FDA Draft Guidance, Human Gene Therapy for Rare Diseases

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 3,000 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.

FDA's recommendations in this draft guidance are generally welcomed and will provide clarity for development of gene therapy products for rare diseases. The following specific comments are provided for FDA consideration:

Section/ Lines	Comment/Issue	Proposed Change
II.	**BACKGROUND**	
40 – 42	Guidance text: "Additionally, many rare diseases exhibit a number of variations or sub-types. Consequently, patients may have highly diverse clinical manifestations and rates of disease progression with unpredictable clinical courses." Comment: We recommend highlighting the lack of natural history data in rare diseases.	Proposed addition: "Additionally, many rare diseases exhibit a number of variations or sub-types. Consequently, patients may have highly diverse clinical manifestations and rates of disease progression with unpredictable clinical courses. There is also limited natural history data available for many rare diseases, further complicating drug development. These challenges are also present for the development of GT products."

III.	CONSIDERATIONS FOR PRODUCT DEVELOPMENT	
47	Guidance Text: "Considerations for Product Development" | Comment: The primary purpose of this section is to note that CMC considerations for product manufacturing, testing, and release of GT products are the same as those described for other GT products, so ASGCT recommends changing the title of the section to reflect that focus.	Proposed change: "Considerations for ~~Product Development~~ Chemistry, Manufacturing and Control (CMC)"
63 – 66	Guidance text: "These factors make it even more critical that a sponsor of a GT product for a rare disease establish a well-controlled manufacturing process along with suitable analytical assays to assess product CQA as early in development as possible, optimally before administration of the GT product to the first subject." Comment: We recommend FDA clarify the standard for "a **well-controlled** manufacturing process" considering the stage of product development. Also, we recommend adding flexibility by recognizing that the manufacturing process may continue to be refined with appropriate controls and bridging where appropriate.	
66 – 69	Guidance Text: "Importantly, as the phase 1 study may provide evidence of safety and effectiveness, characterization of product CQA and manufacturing CPP should be implemented during early clinical development, and innovative strategies such as the production of multiple small lots versus a single large product lot may be considered." Comment: While it may be possible and appropriate to characterize the product CQAs during early clinical development, it may be challenging to characterize manufacturing CPPs during early clinical development. We recommend FDA add more flexibility with the recommendation to characterize the manufacturing CPPs during early clinical development.	Proposed change: "Importantly, as the phase 1 study may provide evidence of safety and effectiveness, characterization of product CQA and, when feasible, manufacturing CPP, should be implemented during early clinical development, and innovative strategies such as the production of multiple small lots versus a single large product lot may be considered."

98 – 99	Guidance Text: "Importantly, if product comparability cannot be demonstrated, additional clinical studies may be needed." Comment: FDA's expectation should be clarified for product comparability for GT products, including circumstances when analytical comparability will be sufficient and when additional data, such as preclinical studies, will be needed. Also, any existing FDA or ICH guidance on comparability for biological products that the sponsors can rely on for recommendations for comparability for GT products should be referenced.	
IV.	**CONSIDERATIONS FOR PRECLINICAL STUDIES**	
131 – 132	Guidance Text: Biodistribution studies should be conducted to assess the pharmacokinetic (PK) profile of a GT product Comment: In circumstances in which a vector that has the same extrinsic properties (e. g., capsid serotype) and is manufactured, formulated and delivered by the same means as another vector encoding a different transgene for which biodistribution has already been well characterized, a sponsor should be able to cross-reference the existing data rather than conduct a biodistribution study. Specific guidance should be provided as to when existing vector biodistribution data can be used to support clinical trials of vectors that differ only by transgene product.	Recommended change: "Biodistribution studies should be conducted to assess the pharmacokinetic (PK) profile of a GT product, except when the biodistribution of the vector being used has been well defined and well characterized. If the product differs only in the transgene encoded, biodistribution studies do not need to be repeated."
132 – 134	Guidance Text: "These data encompass the distribution profile of the vector from the site of administration to target and non-target tissues, including biofluids (e.g., blood, lymph node fluid, cerebrospinal fluid (CSF)) as applicable." Comment: Collecting adequate volumes of lymph node fluid or CSF from animal models, especially from smaller animal models such as rodents or mice can present significant challenges. Sample pooling may be required to get adequate volumes to conduct	Proposed change: "These data encompass the distribution profile of the vector from the site of administration to target and non-target tissues, including biofluids (e.g., blood~~, lymph node fluid, cerebrospinal fluid (CSF))~~ as applicable.)"

	assays/studies, which may also be a problematic approach.	
150	Guidance Text: "the potential for developmental and reproductive toxicity;" Comment: Developmental and reproductive toxicity studies are not routinely conducted.	Proposed change: "1) the potential for developmental and reproductive toxicity, when appropriate;"
V.	**CONSIDERATIONS FOR CLINICAL TRIALS**	
	A. Study Population	
210 – 221	This section provides principles for pediatric studies. While the guidance acknowledges that most rare diseases are pediatric diseases or have onset of manifestations in childhood, and that pediatric studies are a critical part of drug development, it fails to provide any recommendations with regard to evaluating gene therapy products in pediatric patients. Instead broad, standard ethical principles are provided. While these principles are of the utmost importance when conducting pediatric studies, to further the development of these novel therapies for pediatric patients, it would be helpful for the Agency to include additional recommendations for development in this special population.	
	B. Study Design	
255 - 256	Guidance Text: For some GT indications (e.g., a genetic skin disease), the use of an intra-subject control design may be useful. Comment: ASGCT requests that FDA indicate important factors in determining whether intra-subject controls for locally administered gene therapies is appropriate (e.g., for eye and/or ear, for certain phases of the trial, etc.).	
	C. Dose Selection	
298 – 300	Guidance Text: "For early-phase studies, clinical development of GT products should include evaluation of two or more dose levels to help identify the potentially therapeutic dose(s). Ideally, placebo controls should be added to each dose cohort." Comment: While placebo-controlled dose finding may be ideal, it is often unrealistic,	"For early-phase studies, clinical development of GT products should include evaluation of two or more dose levels to help identify the potentially therapeutic dose(s). ~~Ideally~~ If feasible, placebo controls should be added to each dose cohort."

	presenting significant challenges in the rare disease setting. We recommend qualifying the recommendation for placebo-controlled dose-finding studies for settings in which it is feasible.	
306 – 308	Guidance Text: "Efforts should be made early in the GT product development program to identify and validate biomarkers and to leverage all available information from published investigations for the disease of interest (or related diseases)." Comment: "Validating" biomarkers within the context of a rare disease can present significant challenges in drug development. Validated biomarkers can be used when available. However, to encourage identification of biomarkers in rare diseases, it may be acceptable to provide data and literature to support the validity of biomarkers. If the recommendation to validate biomarkers is retained, it would be helpful to clarify the expectations to "validate" biomarkers in this context.	Proposed text: "Efforts should be made early in the GT product development program to identify ~~and validate~~ biomarkers and to leverage all available information from published investigations for the disease of interest (or related diseases) to support validity."

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

Sincerely,

Maritza C. McIntrye, PhD
Chair, ASGCT Clinical Trials and Regulatory Affairs Committee