December 10, 2018

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

Comments for Docket No. FDA-2018-D-2236: FDA Draft Guidance, Human Gene Therapy Retinal Disorders.

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.

Overall the guidance recommendations are well-received. Additional details specific to retinal disorders would be helpful, such as extrapolating dose from preclinical data and toxicology. In addition, we offer the following specific comments for FDA consideration:

Section/ Lines	Comment/Issue	Proposed Change
II.	**CONSIDERATIONS FOR PRODUCT DEVELOPMENT**	
32	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)"
42 – 43	Guidance text: "A potency assay to assess the biological activity of the final product, with relevant lot release specifications, should be established prior to the initiation of clinical trials intended to provide	Suggested change: A potency assay to assess the biological activity and/or expression of the

	substantial evidence of effectiveness for a marketing application." Comment: The requirement of a potency assay to assess activity can be very difficult with a very complex mechanism of action (i.e., finding a cell line that is sufficiently transduced with vector, and expresses transgene if tissue-specific promoter used). For rare diseases, only a couple of batches of drug may be manufactured; we recommend considering a matrix of assays that measure expression as an alternative.	transgene, with relevant lot release specifications, should be established prior to the initiation of clinical trials intended to provide substantial evidence of effectiveness for a marketing application.
III.	**CONSIDERATIONS FOR PRECLINICAL STUDIES**	
95 – 98	Guidance text: "Biodistribution studies should be conducted to assess the pharmacokinetic profile of a GT product (Ref. 3)." 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."
115 – 119	Guidance text: "However, due to differences in ocular size and anatomy in rodents as compared to the human eye, animals with more 'human-like eyes,' such as rabbits, pigs, dogs, or nonhuman primates, may also provide applicable safety information. Inclusion of the larger animals also facilitates relevant experience with the surgical procedures and delivery systems intended for clinical use." Comment: The use of a surrogate vector may be required to perform safety and efficacy studies in larger animals. These vectors should be comparable to the clinical candidate in mechanism and manufacturing process to appropriately translate results to inform clinical candidate.	Proposed change: Add to end of line 119, "Larger animal studies should be designed to answer specific safety questions using vectors that are comparable to the clinical candidate in mechanism and manufacturing process, while limiting the number of animals used."
129 – 133	Guidance text: "As the clinical development program for an investigational GT product advances to late-phase clinical trials and possible marketing approval,	Proposed change: "As the clinical development program for an

	additional preclinical studies may be indicated. Further testing may be necessary to address factors such as any significant changes in the manufacturing process or formulation, which may affect comparability of the late-phase product to product administered in early-phase clinical trials." Comment: More detailed guidance on the circumstances in which additional preclinical studies might be warranted is requested. In particular, detailed discussion on the types of manufacturing changes that warrant new GLP toxicology studies would assist developers in assessing the impact of manufacturing changes on development timelines and budgets. We recommend referencing in this section the draft guidance from 2016, Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information.	investigational GT product advances to late-phase clinical trials and possible marketing approval, additional preclinical studies may be indicated if CMC comparability is not robust between manufacturing process or formulation of the late-phase product to product administered in early-phase clinical trials. The sponsor should ensure the new material is efficacious and tolerable prior to dosing patients. Further discussion with agency should be held if additional toxicology studies are warranted."
IV.	**CONSIDERATIONS FOR CLINICAL TRIALS**	
	A. Natural History Studies	
153 – 157	Guidance text: "Early in product development, sponsors should evaluate the depth and quality of existing natural history data. When such information is insufficient to guide clinical development, FDA recommends that a sponsor perform a careful natural history study to facilitate the product development program, although FDA does not require these studies." Comment: ASGCT recommends wording that more clearly indicates natural history studies are not required. In addition, an example would be helpful of the facilitation of product development through a natural history study.	Proposed change: "Early in product development, sponsors should evaluate the depth and quality of existing natural history data. When such information is insufficient to guide clinical development, a natural history study could benefit product development, although FDA does not require these studies."

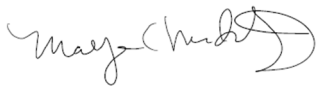
	B. Study Design	
162 – 174	Guidance text: "To facilitate interpretation of clinical data, inclusion of a randomized, concurrent parallel control group is recommended for clinical trials, whenever possible. Administration of the vehicle alone may serve as a control. In general, while intravitreal injection of the vehicle alone is often feasible as a placebo control, it may not be considered ethically acceptable unless the physical properties of an injection in a closed space have a potential therapeutic benefit. When ethically acceptable, such a control is especially helpful early in clinical development, to evaluate bioactivity of the investigational GT product and possibly to provide initial evidence of its clinical efficacy. However, FDA acknowledges the risks associated with intravitreal and subretinal injection procedures and vehicles; without any prospect of direct benefit, these risks may not be acceptable under certain circumstances, such as for pediatric patients (21 CFR Part 50, Subpart D). Other possibilities to vehicle controls include alternative dosing regimens, alternative dose levels, and existing products approved for the indication being sought." Comment: For ultra-rare and rare retinal diseases, we recommend allowing use of a well-controlled prospective natural history study. ASGCT does not find it is ethical to treat with vehicle control in retinal disorders, specifically when the administration procedure may pose an unacceptable risk.	Proposed change: "Other possibilities to vehicle controls include a well-controlled prospective natural history study, alternative dosing regimens, alternative dose levels, and existing products approved for the indication being sought."
182 – 189	Guidance text: "To further reduce potential bias, sponsors should include adequately-designed masking procedures. Differences between the procedure used for product delivery and a sham procedure may enable patients to distinguish the eye which received the product from that which received the sham treatment. FDA recommends at least two treatment arms, utilizing different doses but the same product administration procedures, to minimize patients' ability to identify their treatment arm, in addition to a sham control group. In addition to facilitating masking, the second treatment arm has value as a dose-ranging control." Comment: We recommend providing examples of masking procedures that are appropriate, especially	

	taking into account that sham surgical procedures may not be ethical.	
191 – 204	Guidance text: "Although use of the contralateral eye to which the GT product is not administered as a control may potentially be considered, it is generally not recommended due to the following: • For most indications in which GT products are likely to be used, the treated eye and contralateral eye are often at different stages of disease at the time of trial entry. In addition, disease progression in the two eyes is not necessarily similar over the relatively short duration of the trial. • When a patient is exposed to different procedures in the two eyes, (e.g., one eye receives a GT product and the other eye receives sham procedure), it frequently leads to unmasking, which can confound the interpretation of the study results, particularly for endpoints where patient effort can make a difference, such as visual function measures." Comment: ASGCT does not believe the contralateral eye other should be sham treated. If the disease stage differs in the eyes, a relative difference scale could be designed from treatment to end of study to use contralateral eye as a control.	
	D. Study Use	
249 – 251	Guidance text: "Such data should indicate that the initial dose is not only reasonably safe, but also has therapeutic potential, particularly when the administration procedure carries substantial risks." Comment: Gene therapy dose response curves are often steep and the efficacious dose range is small. The titering variance is also large. If the efficacious dose range is within ~ one log, it does not make a lot of sense to artificially make multiple dose cohorts when they may not be differentiated in terms of safety or efficacy. Finding MTD is not as important as finding best long-term efficacious dose in gene therapy.	Proposed change: "Such data should indicate that the initial dose is not only reasonably safe, but also has therapeutic potential, particularly when the administration procedure carries substantial risks. Dose cohort number should consider the above parameters and not strive to find MTD."
	F. Study Endpoints	
296 – 308	Guidance text: "However, for trials of GT products, early assessment of potential clinical benefit is also important, particularly for rare diseases with a limited number of patients available to participate in clinical	

	development. To guide further clinical development, FDA encourages sponsors to explore a wide spectrum of potential clinical endpoints and other clinical effects in early-phase trials. For example, sponsors may include endpoints based on retinal imaging (optical coherence tomography, retinal photography, fluorescein angiography), visual acuity (low and high luminance), visual fields, color vision, contrast sensitivity, other measures of visual function (i.e., how well the eye and visual system function), and functional vision (i.e., how well the patient performs vision-related activities of daily living). For later-phase trials intended to provide substantial evidence of clinical effectiveness to support a marketing application, primary efficacy endpoints should reflect clinical benefit, such as improvement in function or symptoms." Comment: The section emphasizes clinical or functional endpoints but does not address the potential for surrogate endpoints. In line with recommendations included in other gene therapy guidance documents, we recommend that the guidance encourage the use of novel surrogate endpoints when feasible. For example, anatomical changes can be used as surrogate endpoints if they are quantifiable and related to the disease progression/recession. As the science evolves, there may be more surrogate endpoints to consider.	
V.	**REFERENCES**	
394	As mentioned above regarding lines 129 – 133, ASGCT recommends referencing, after reference 3, the draft guidance from 2016—Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information.	

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

Sincerely,



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