American Society of Gene + Cell Therapy

April 6, 2021

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

Re: Comments for Docket No. FDA-2020-D-2101: Human Gene Therapy for Neurodegenerative Diseases: Draft Guidance for Industry

Dear Sir/Madam:

The American Society of Gene & Cell Therapy (ASGCT) appreciates the opportunity to comment on this guidance document. ASGCT is a nonprofit professional membership organization comprised of more than 4,500 scientists, physicians, and other professionals working in gene and cell therapy in settings such as universities, hospitals, and biotechnology companies. 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.

We appreciate that FDA is working to provide additional guidance to gene therapy sponsors and provide specific recommendations for the agency's consideration in the chart below. Overall, ASGCT agrees with the recommendation for sponsors to contact the Office of Tissues and Advanced Therapies (OTAT) prior to submitting an investigational new drug (IND) application and during product development to discuss their product-specific considerations. We acknowledge the challenges in the volume of meeting requests with OTAT; therefore, we recommend that OTAT describe the optimal process for sponsors to secure timely discussions with OTAT when it is needed outside of the formal PDUFA meeting schedule. In addition, we have recommended funding for additional CBER staff to be included within the PDUFA VII reauthorization to facilitate the need for early and regular communication. Because more than one meeting before IND submission would often be helpful for gene and cell therapy products, ASGCT suggests that FDA use any additional PDUFA funds to hold additional INTERACT meetings.

Page	Comment/Issue	Proposed Change
I. CONSIDERATIONS FOR CHEMISTRY, MANUFACTURING AND CONTROLS (CMC)		
Page 2	"Early-phase clinical studies of neurodegenerative diseases involving small study populations, in addition to focusing on safety assessments, may also provide early evidence on effectiveness. Thus, the product's CQAs and manufacturing critical process parameters (CPPs) should be fully evaluated and appropriate controls implemented during the early clinical development phase." Comment: We agree that evaluating a product's CQAs as early as feasible in development is important, especially because early-phase clinical studies involving small study populations may provide early evidence on effectiveness. However, identifying what the CQAs will be for a final licensed and fully scaled product very early in the process, especially pre-clinically, may not be feasible. We recommend that potential CQAs be evaluated as early as possible but ask the agency to provide regulatory flexibility in reviewing CQA data when such processes are not feasible. We also request that the agency include individuals with expertise in CQAs and CPPs in early meetings, such as INTERACT, to provide early dialogue on these issues with sponsors.	"Early-phase clinical studies of neurodegenerative diseases involving small study populations, in addition to focusing on safety assessments, may provide early evidence on effectiveness. Thus, the product's potential CQAs and manufacturing critical process parameters (CPPs) should be ~~fully~~ evaluated and appropriate controls implemented ~~during the~~ as early during clinical development as feasible ~~phase~~."
Page 3	"We recommend that all GT products for neurodegenerative diseases be designed to reduce inflammatory immune responses, reduce the possibility of becoming latent, and not contain foreign genes (e.g., reporter genes) that do not directly contribute to the biological function of the investigational product." Comment: ASGCT suggests clarifying that the FDA recommendation is for inflammatory immune responses and the possibility of becoming latent to be kept at a minimum throughout development.	"We recommend that clinical trials for ~~all~~ GT products for neurodegenerative diseases consider safety and efficacy factors, including minimizing ~~be designed to reduce~~ inflammatory immune responses and~~, reduce~~ the possibility of becoming latent, ~~and~~ as well as not containing foreign genes (e.g., reporter genes) that do not directly contribute to the biological function of

		the investigational product."
Page 3	"We recommend that the GT vectors used to treat neurodegenerative diseases not be grown in tumorigenic cell lines and the residual host cell-DNA levels be set to less than 10 ng/dose, if possible. The endotoxin levels should be kept to less than 0.2EU/kg/dose/hour when the drug product is administered by the intrathecal route." Comment: ASGCT appreciates that FDA added that the residual host cell-DNA levels be kept to this level **if possible**. We continue to caution against listing this suggested limit of 10 ng HC DNA/dose, as this level may be well below a safe dose of host-cell DNA and is difficult to achieve when a product utilizes rAAV vectors. In addition, clarification is requested on whether the recommendation on keeping the endotoxin levels to less than 0.2EU/kg/dose/hour when the drug product is administered by the intrathecal route refers to the drug product only or the drug product plus endotoxins coming through the delivery device.	
Page 3	"Lastly, plasmids can also be a source of process-related contaminants in adeno-associated virus (AAV)-based GT products. Plasmids used to generate recombinant AAV-based products should be of the highest purity. If the plasmids are manufactured in a multiproduct manufacturing facility, they should be tested for the presence of other contaminating plasmids that may have been co-purified." Comment: ASGCT appreciates the Agency's recommendations concerning plasmids manufactured at a multi-product facility. However, we request the Agency to consider other alternate approaches to ensuring purity of the plasmids. These may include need for a risk assessment for the presence of other contaminating plasmids that may have been co-purified for plasmids that are manufactured in a multi-product manufacturing facility. Also, if appropriate, the drug substance manufacturer should ensure that there is appropriate cross-contamination control at the plasmid production and/or release level.	"Lastly, plasmids can also be a source of process-related contaminants in adeno-associated virus (AAV)-based GT products. Plasmids used to generate recombinant AAV-based products should be of the highest purity. If the plasmids are manufactured in a multiproduct manufacturing facility, they should be tested for the presence of other contaminating plasmids that may have been co-purified. Alternatively, the manufacturer may conduct a risk assessment for the presence of other contaminating plasmids

		that may have been co-purified for plasmids that are manufactured in a multi-product manufacturing facility. Also, as appropriate, the drug substance manufacturer should ensure that there is appropriate cross-contamination control at the plasmid production and/or release level for plasmids manufactured in a multi-product manufacturing facility."
Page 4	"For products designed to treat neurodegenerative diseases, where the product may exhibit more than one mode of action, we encourage the evaluation of multiple product characteristics that could be used to establish a matrix or other similar approach to potency evaluation during initial clinical studies. We recommend that a potency test (Ref. 5) that measures relevant biological activities be qualified for suitability (i.e., accuracy, precision, sensitivity, specificity) prior to conducting clinical trials intended to provide substantial evidence of effectiveness to support a marketing application. The potency test should be fully validated prior to submitting a biologics license application." Comment: In sponsors' experience, the Agency recommends a potency assay before Phase 3 studies. Clarification is requested on whether it is always necessary pre-phase 3, or whether doing so pre-BLA filing may sometimes be acceptable.	
Page 4	"In cases where the effect of product changes may not be immediately discernable, sponsors should be prepared to conduct a two-component risk analysis. One component of the risk analysis should be based on a prospective analysis of the effect of product changes using a side-by-side analysis of pre- and post-change product using multiple assay methods. The second component of the risk analysis should involve a retrospective analysis at a future date by	"In cases where the effect of product changes may not be immediately discernable, sponsors should be prepared to conduct a ~~two-component~~ risk analysis and a comparability study. ~~One component of t~~The risk analysis should be based

	preserving sufficient quantities of post-change product samples." Comment: ASGCT suggests using wording that differentiates between pre-change analysis (a risk assessment) and post-change analysis (a comparability study).	on a prospective analysis of the potential effect of product changes using a side-by-side analysis of pre- and post-change product using multiple assay methods. ~~The second component of the risk analysis should involve a~~ After making a product change, retrospective comparability analysis at a future date will be enabled by preserving sufficient quantities of post-change product samples."
Page 4	"Prior to initiating Phase 1 safety studies (21 CFR 312.23(a)(10)(iv) and 21 CFR 312.23(a)(11)), the delivery device, product concentration (tested over the planned dose-range), drug product formulation, final infusion volume, duration and rate of infusion, and temperature should be the same for the device compatibility studies as they will be in the clinic." Comment: ASGCT recommends noting that these factors be similar, while not necessarily identical. For example, depending on lot size/yield, timing and other factors, the material used for the compatibility study may come from a different manufacturing run than the material to be used in the clinic and thus may differ in concentration. Therefore, "similar" is a more appropriate and realistic term than "the same." In addition, clarification is requested on how similar the delivery device should be, e.g., whether it needs to be the same brand, and whether a letter of authorization (LOA) is needed for a device that has not yet been used.	"Prior to initiating Phase 1 safety studies (21 CFR 312.23(a)(10)(iv) and 21 CFR 312.23(a)(11)), the delivery device, product concentration (tested over the planned dose-range), drug product formulation, final infusion volume, duration and rate of infusion, and temperature should be similar or comparable ~~the same~~ for the device compatibility studies as they will be in the clinic."
III. CONSIDERATIONS FOR PRECLINICAL STUDIES		
Page 6	"In addition, for any abnormal findings or lesions, sponsors should determine the frequency, severity, potential cause, and clinical significance."	"In addition, for ~~any~~ significant abnormal findings or lesions, sponsors should determine the frequency,

	Comment: It may not be practical to conduct an in-depth analysis of every finding if there are many trivial findings.	severity, potential cause, and clinical significance."
Page 6	"Scientific justification should be provided to support selection of animal models. These animal models, and their justification, will be evaluated by the FDA in the context of each investigational GT product and proposed clinical indication." Comment: Guidance on which circumstances would elicit a requirement for large animal models would be helpful. Clarification is requested that the duration of toxicology studies should be based on previously published data for the same serotype.	"Scientific justification should be provided to support selection of animal models. These animal models, and their justification, will be evaluated by the FDA in the context of each investigational GT product and proposed clinical indication. The duration of toxicology studies should be based on previously published data, for the same serotype."
IV. CONSIDERATIONS FOR CLINICAL TRIALS		
Page 7	"When the natural history of such monogenic disorders is also well-characterized and relatively consistent (i.e., not highly variable), and when the expected treatment effect is large, self-evident, and closely associated temporally with the intervention, innovative clinical trial designs, rather than randomized, placebo-controlled trials, may be feasible to expedite clinical development. Randomized, placebo-controlled clinical trials, including crossover designs as appropriate, may be the most efficient means of obtaining persuasive evidence of effectiveness." Comment: Clarification is requested on the definition of crossover designs, as referred to here. True crossover designs are not possible in gene therapies because the therapy cannot be discontinued. The challenges to randomized placebo-controlled trial design for rare diseases are noted in the guidance document, *Human Gene Therapy for Rare Diseases.* We recommend similarly considering the use of single-arm trials with historical controls, when there are feasibility issues with conducting a randomized, controlled trial.	"When the natural history of such monogenic disorders is also well-characterized and relatively consistent (i.e., not highly variable), and when the expected treatment effect is large, self-evident, and closely associated temporally with the intervention, innovative clinical trial designs, rather than randomized, placebo-controlled trials, may be feasible to expedite clinical development. Randomized, placebo-controlled clinical trials, including crossover designs as appropriate, may be the ~~most efficient~~ ideal means of obtaining persuasive evidence of effectiveness, when feasible. However, a single-arm trial using historical controls, sometimes including an initial observation period,

		may be considered if there are feasibility issues with conducting a randomized, controlled trial.
Study population, page 9	"If an *in vitro* companion diagnostic is needed to appropriately select subjects for a study (and later for treatment, once the GT product is approved), the sponsor should coordinate submission of the marketing application for the companion diagnostic with submission of the biologics license application for the GT product, to support contemporaneous marketing authorizations (Ref. 13). FDA encourages sponsors to discuss the need for companion diagnostics early in product development." Comment: The Society requests additional clarification on when a companion diagnostic may be able to be used for a particular vector platform (e.g., AAV5) vs. for each individual product.	
Dose selection, page 10	"Invasive surgical procedures may be necessary to administer a GT product (e.g., intracranial delivery to a targeted region of the brain or spinal cord). In such cases, FDA recommends that the sponsor utilize a staged approach: initiating the early-phase study with unilateral administration, and if no significant safety concerns arise, then proceeding to bilateral administration of the GT product." Comment: ASGCT recommends omitting this specific recommendation, since ethical and scientific issues may qualify the circumstances for which this recommendation would be advisable. For example, undergoing a long, invasive surgical procedure twice to obtain therapeutic benefit raises ethical questions. Additionally, unilateral treatment (although more conservative from a risk standpoint) may result in an unacceptably low prospect of benefit, which raises its own ethical concerns. Utilizing re-administration to attempt to achieve some benefit after a failed unilateral dose could raise more safety and ethical issues than using an appropriate bilateral dose initially. Therefore, ASGCT would recommend the Agency use broader terminology.	"Invasive surgical procedures may be necessary to administer a GT product (e.g., intracranial delivery to a targeted region of the brain or spinal cord). In such cases, sponsors should consider risk-mitigation measures. ~~FDA recommends that the sponsor utilize a staged approach.: initiating the early-phase study with unilateral administration, and if no significant safety concerns arise, then proceeding to bilateral administration of the GT product.~~

Study Endpoints, page 11	"In trials intended to provide evidence of effectiveness to support a marketing application, primary efficacy endpoints should be either clinically meaningful endpoints that directly measure a clinical benefit, or surrogate endpoints that are reasonably likely to predict a clinical benefit. Because many neurodegenerative diseases are rare and complex, with limited understanding of their pathogenesis, identification and characterization of a surrogate or intermediate endpoint is often challenging. … When a suitable surrogate endpoint is identified, it may be used to support a marketing application under the accelerated approval pathway.[4] Use of a surrogate endpoint may be appropriate when a GT product directly targets an underlying, well-understood and well-documented monogenic change that causes a serious neurodegenerative disorder. In these cases, the GT product could alter the underlying genetic defect and thereby treat or cure the disease." Comments: ASGCT agrees that identification of surrogate or intermediate endpoints is challenging for neurodegenerative diseases and appreciates that FDA states that surrogate endpoints may be utilized as primary efficacy endpoints. The Society also appreciates that FDA indicates that use of a surrogate endpoint may be appropriate when a GT product directly targets an underlying, well-understood and well-documented monogenic change that causes a serious neurodegenerative disorder.	" … When a suitable surrogate endpoint is identified, it may be used to support a marketing application under the accelerated approval pathway.[4] Use of a surrogate endpoint may be appropriate when a GT product directly targets an underlying, well-understood and well-documented monogenic change that causes a serious neurodegenerative disorder. In these cases, the GT product ~~could alter~~ can provide a functional copy of the gene to enable protein expression and activity that the mutant gene was unable to generate, thus addressing the underlying genetic ~~defect~~ cause and thereby treat~~e~~ing or cur~~e~~ing the disease."
Study Endpoints, page 11-12	"Sponsors proposing to develop surrogate endpoint(s) to support accelerated approval should communicate with the Agency early in product development, preferably well before initiating clinical trials." Comment: We request that FDA provide recommendations on the best meeting forums before the initiation of clinical trials to obtain specific advice on the use of surrogate endpoints to support the use of accelerated approval. Because opportunities for communication with the Agency before trials begin may be limited, we recommend broadening the wording on the preferred time frame. We also recommend ensuring transparency on the use of surrogate endpoints when the Agency's views have changed and ongoing dialogue with the sponsor	"Sponsors proposing to develop surrogate endpoint(s) to support accelerated approval should communicate with the Agency early in product development, preferably ~~well~~ before initiating clinical trials."

	regarding ideal endpoints that will not unnecessarily delay development.	
Patient Experience, page 12	"Patient experience data[5] may provide important additional information about the clinical benefit of a GT product. FDA encourages sponsors to collect patient experience data during product development, and to submit such data in the marketing application." Comment: Clarification is requested on when to collect patient experience data during product development, or if there are instances when collecting this data earlier would be of value. It would be helpful if the Agency clarifies in the guidance that patient experience data is important to inform benefit risk assessment. Further, we suggest that the guidance should express FDA's openness to considering data that helps bring light to patient perspective on benefit risk through qualitative and quantitative data to highlight patient perspective on the benefit risk assessment and the relative importance of treatment characteristics during drug development.	
V. EXPEDITED PROGRAMS		
Page 12	"There are several programs available to sponsors of GT products intended to address unmet medical needs in the treatment of serious or life-threatening conditions. These programs, including regenerative medicine advanced therapy designation, breakthrough therapy designation, fast track designation, accelerated approval, and priority review, are intended to facilitate and expedite development and review of such therapies. In particular, regenerative medicine advanced therapy designation and breakthrough therapy designation call for increased FDA attention to these potentially promising therapies, offering sponsors more frequent interactions with FDA on efficient trial design and overall drug development." Comment: ASGCT recommends that FDA consider additional discussion of CMC flexibility for programs with expedited designations, such as what the European Medicines Agency (EMA) provides. That flexibility is outlined in the EMA guidance document, *Draft toolbox guidance on scientific elements and regulatory tools to support quality data packages for PRIME marketing authorisation applications.*	
VI. COMMUNICATION WITH FDA		
Page 12	"FDA encourages communication with OTAT early in product development, before submission of an IND.	

	Different meeting types are available, depending on the stage of product development and the issues to be considered. These include pre-IND meetings and, earlier in development, INitial Targeted Engagement for Regulatory Advice on CBER producTs (INTERACT) meetings.[6] Early, nonbinding regulatory advice can be obtained from OTAT through an INTERACT meeting, which can be used to discuss issues such as a product's early preclinical program, and/or through a pre-IND meeting prior to submission of the IND (Ref. 16)." Comment: ASGCT acknowledges the resource constraints of the Agency. Because these limitations result in the inability to grant all INTERACT meeting requests, we would welcome insights into the criteria the Agency uses to prioritize requests.	

Thank you for consideration of these comments. Please do not hesitate to let us know if you have questions by contacting Betsy Foss-Campbell, ASGCT Director of Policy and Advocacy, at bfoss@asgct.org.

Sincerely,

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