December 9, 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Comments for Docket No. FDA–2018-D-2238: FDA Draft Guidance, Human Gene Therapy for Hemophilia

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FDA's recommendations in this draft guidance are generally welcomed and will provide clarity for development of gene therapy products for hemophilia.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

Section/ Line	Comment/Issue	Proposed Change
III.	**CONSIDERATIONS FOR PRODUCT DEVELOPMENT**	
59	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 – 72	Guidance Text: "For early-phase clinical trials, a sponsor should be able to evaluate the identity, purity, quality, dose and safety of a GT product. A potency assay to assess the biological of the final product, 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. To support licensure of a GT product, manufacturing processes and all testing methods for product release must be validated (21 CFR 211.165(e)." Comment: Because these sentences do not provide new, more specific information related to CMC specifically related to gene therapy for hemophilia, ASGCT recommends only stating that CMC considerations are the same as those described for other GT products and referencing the July 2018 draft guidance on Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug (IND) Applications, as is done in lines 61 – 63, without repeating additional information contained in that guidance, to enhance clarity.	Proposed change: Delete these sentences.
IV.	**CONSIDERATIONS FOR FACTOR VIII/FACTOR IX ACTIVITY MEASUREMENT ASSESSED BY DIFFERENT CLINICAL LABORATORY ASSAYS**	
94 – 96	Guidance Text: "The discrepancies preclude reliable interpretation of factor activity measurements and present a challenge when factor activity levels are proposed as surrogate endpoints for hemostatic efficacy." Comment: The language used currently seems to suggest that factor activity assays should not be used due to the discrepancies, while sponsors are able to mitigate the challenge, as described subsequently in the guidance.	Proposed change: "The discrepancies ~~preclude~~ hinder reliable interpretation of factor activity measurements and present a challenge when factor activity levels are proposed as surrogate endpoints for hemostatic efficacy."
132 – 135	Guidance Text: "During clinical trials, we recommend that sponsors consider: • Performing a comparative field study with patient plasma samples using assays routinely performed in clinical laboratories to evaluate the range of discrepancies."	Proposed change: "During clinical trials, we recommend that sponsors consider: Performing a ~~comparative field~~ study with patient

	Comment: Because sponsors may not have sufficient patient plasma to conduct a traditional large-scale field study, ASGCT recommends that sponsors propose to FDA performing a study that indicates that assays are providing comparable data.	plasma samples using assays routinely performed in clinical laboratories to evaluate the range of discrepancies."
V.	**CONSIDERATIONS FOR PRECLINICAL STUDIES**	
153 – 164	Guidance Text: The following elements are recommended for consideration when developing a preclinical program for an investigational GT product for treatment of hemophilia… • Biodistribution studies are conducted to assess the pharmacokinetic (PK) profile of a GT product. Comment: In circumstances where 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.
166 – 167	Guidance text: "(e.g., blood, lymph node fluid)." Comment: It is difficult to collect adequate volumes of lymph node fluid in certain animal models such as in rodents. We recommend deleting the example of lymph node fluid.	Proposed change: "(e.g., blood~~, lymph node fluid~~)."
177 – 181	Guidance text: "To support translation of effective and safe dose levels determined in preclinical studies to clinical trials, the assay for vector titer determination of the preclinical lots should be identical to the assay used for clinical lots. The assays for measuring factor activity in animals administered the GT product should be consistent to the assays used in humans. The factor activity assays are discussed in detail under section IV. of this document." Comment: Recommendation for an "identical" vector titer determination assay is challenging considering that vector characterization during early preclinical development often involves unqualified methodology.	Proposed change: "To support translation of effective and safe dose levels determined in preclinical studies to clinical trials, the assay for vector titer determination of the preclinical lots should be consistent with ~~identical to~~ the assay used for clinical lots. The assays for measuring factor

	Requiring that identical methods be used to determine vector titers for preclinical and clinical development could detract sponsors from improving assay methodology. We recommend that instead a focus should be on providing data to ensure that the methods used to quantify titers in preclinical and clinical lots return consistent results.	activity in animals administered the GT product should be consistent to the assays used in humans. The factor activity assays are discussed in detail under section IV. of this document."
185 – 186	Guidance text: "the potential for reproductive/developmental toxicity" Comment: It would be helpful to clarify what additional nonclinical studies may need to be considered to address the potential for reproductive/developmental toxicity distinguishing between the type of gene therapy and vector, e.g. considerations may vary depending on whether AAV or lentivirus is used.	
VI.	**CONSIDERATIONS FOR CLINICAL TRIALS**	
	A. Efficacy Endpoints	
215 – 217	Guidance text: "2. Accelerated approval: • Factor activity may be considered as a surrogate endpoint for primary efficacy assessment under the accelerated approval pathway." Comment: In this section, ASGCT recommends that FDA identifies the required endpoint/s for the post-approval confirmatory trial for hemophilia.	
219 – 221	Guidance text: "However, to support the use of this surrogate endpoint, we recommend that you: • Resolve discrepancies in factor assay results from various assay methods prior to considering a target factor activity as a surrogate endpoint for primary efficacy assessment." Comment: The current wording may be suggestive that discrepancies in factor assay results from various assay methods need to be eliminated, which may not be possible. However, sponsors may mitigate these discrepancies by providing explanation for them.	Proposed change: "However, to support the use of this surrogate endpoint, we recommend that you: ~~Resolve~~ Explain discrepancies in factor assay results from various assay methods prior to considering a target factor activity as a surrogate endpoint for primary efficacy assessment.
224 – 225	Guidance text: "Determine a target factor activity	

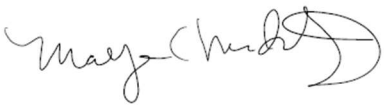
	level within the range of factor activity of normal population." Comment: It would be helpful to define or describe further what FDA considers to be the "range of factor activity of normal population." The activity level should provide confidence that the demonstrated efficacy is reasonably likely to predict clinical benefit. It is also important to note that factor activity arising from gene therapy products differ depending on whether they are measured using one-stage versus chromogenic assays. Therefore acceptable levels will need to be established per product for both types of assays to reduce uncertainty due to assay differences.	
	B. Study Design	
234 – 236	Guidance text: "1. Pre-administration Considerations We recommend: • Enrolling patients who have not required dose adjustments to their prophylactic replacement therapy for at least 12 months as this may best facilitate efficacy determination following administration." Comment: We recommend that the agency provide greater flexibility in the period without prophylactic dose adjustment prior to enrollment. Simple duration of the period without a dose change may not necessarily be the best measure of stable function. We suggest that the language be changed to address stable disease and not fixed dose.	Recommended change: "Enrolling patients who are well controlled in their disease by prophylactic replacement therapy for at least 12 months as this may best facilitate efficacy determination following administration.
	C. Study Population	
286 – 297	Guidance text: "Hemophilia affects both children and adults. Since many similar rare diseases are pediatric diseases or have onset of manifestation in childhood, pediatric studies are a critical part of drug development." Comment: This statement and the subsequent paragraph provides principles for pediatric studies. While the guidance provides broad, standard ethical principles for conducting pediatric studies, it does not provide recommendations with regard to evaluating gene therapy products in pediatric patients. It would be helpful for the Agency to include additional recommendations for development in this special population, including the appropriate time to start	

	pediatric studies.	
	E. Study Monitoring	
325	Guidance text: "1. Short-term Monitoring (first 2 years following GT product administration)" Comment: The guidance is not clear how short-term monitoring correlates with the extent of follow-up needed for BLA submission purposes. Additional discussion would be helpful to distinguish the protocol requirements from the requirements for filing.	
336 – 339	Guidance text: "Periodic monitoring for levels of vector-related antibodies and assessing interferon-gamma secretion from peripheral blood mononuclear cells by ELISPOT assay (more frequent monitoring may be appropriate if immune-mediated hepatic dysfunction is suspected)." Comment: ELISPOT requires large sample, and ASGCT recommends it should not be routine testing. We recommend that ELISPOT only be required if there are elevations in liver enzymes or an unexplained decline in factor activity. Also, it would be helpful to describe the target for ELISPOT.	
346 – 364	Guidance Text: "2. Long-Term Monitoring (≥2 years following GT product administration)" Comment: ASGCT recommends that the agency states that the use of existing public registries is allowed for long-term follow up monitoring.	
346 – 364	Guidance Text: "2. Long-Term Monitoring (≥2 years following GT product administration)" Comment: ASGCT recommends that clarification be provided of which long-term monitoring recommendations in this section are for efficacy (vs. safety).	
350 – 352	Guidance text: "Monitoring for adverse events for at least 5 years after exposure to non-integrating GT products and 15 years for integrating GT products (Ref. 16)." Comment: For non-integrating GT products, the draft guidance on Long Term Follow-Up After Administration of Human Gene Therapy Products, July 2018, indicates that the typical long-term follow-up, when needed for non-integrating vectors, is	Recommended change: "Monitoring for adverse events for ~~at least 5 years~~ 2 – 5 years after exposure to non-integrating GT products and 15 years for integrating GT products (Ref. 16)."

	product-specific (2 – 5 years) for replication-negative vectors (lines 523 and 533), which ASGCT recommends be utilized for gene therapy products for hemophilia. We also recommend referencing that guidance document in this section.	
354 – 356, 360 – 362	Guidance text: "Monitoring for adverse events to include: eliciting history of and non-invasive screening for hepatic malignancies; physical examination; and laboratory testing for hepatic function. "Monitoring for the emergence of new clinical conditions, including new malignancies and new incidence or exacerbation of pre-existing neurologic, rheumatologic, or autoimmune disorders." Comment: ASGCT recommends clarifying that monitoring for malignancies refers to passive monitoring.	Guidance text: "Monitoring for adverse events to include: eliciting history of and non-invasive screening for hepatic malignancies through passive monitoring; physical examination; and laboratory testing for hepatic function." "Monitoring for the emergence of new clinical conditions, including passive monitoring for new malignancies and new incidence or exacerbation of pre-existing neurologic, rheumatologic, or autoimmune disorders."
IX.	**REFERENCES**	
452	As mentioned above regarding lines 350 – 352, ASGCT recommends referencing, after reference 16, the draft guidance—Long Term Follow-Up After Administration of Human Gene Therapy Products, July 2018.	

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

Sincerely,



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Chair, ASGCT Clinical Trials and Regulatory Affairs Committee