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-2008-D-0205: Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)

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FDA's recommendations in this draft guidance are generally welcomed and will provide clarity on CMC information for IND applications for human gene therapy. The following specific comments are provided for FDA consideration:

Section/ Lines	Comment/Issue	Proposed Change
IV. SUMMARY OF QUALITY INFORMATION (MODULE 2 OF THE CTD)		
	D. Product Handling at the Clinical Site	
256 – 265	Draft guidance recommendation: "Your summary in Module 2 should also include information for product handling at the clinical site prior to administration (such as thawing, washing, or the addition of diluent or adjuvant, loading into a delivery device, and transport to the bedside) and summary information on product stability prior to and during administration (e.g., in-device hold times and temperatures)."	Proposed change: "Your summary in Module 2 should also provide product handling details to retain product quality and safety as applicable for the product."

	Comment: The recommendations regarding shipping and handling considerations, specifying washing, appear to be applicable mainly to ex vivo gene therapy and cell therapy products. They may not be applicable to gene therapy products at the IND stage in entirety. We recommend FDA to clarify to what type of gene therapy products these recommendations would apply. We recommend a risk-based approach to these recommendations, as the considerations will depend on the type of products and the stage of development.	
267 – 274	Draft guidance recommendation: "Details regarding product stability after preparation for delivery and delivery device compatibility data should be included in Module 3 (sections 3.2.P.8 and 3.2.P.2.6, respectively) of the CTD (Ref. 2). Instructions for drug handing and preparation for administration at the clinical site (e.g., Pharmacy Manual or Instructions for Use) should be provided in the "Clinical Study Reports" section of your IND (section 5.3 of the FDA "M4E(R2): The CTD – Efficacy; Guidance for Industry," dated July 2017 (Ref. 9)). Detailed information about the delivery device may be included in "Regional Information" (section 3.2.R of the CTD) (Ref. 2)." Comment: We recommend that the information regarding product stability after preparation for delivery and delivery device compatibility data, as well as detailed information about the delivery device be considered on a case by case basis at the IND submission stage depending on the product type and delivery method.	
V. MANUFACTURING PROCESS AND CONTROL INFOMRATION (MODULE 3 OF THE CTD)		
A. Drug Substance (3.2.S)		
1. General Information		
b. Structure		
310 – 313	Guidance text: "Some examples of additional information for structure and structural	Proposed change: Viral vectors manufactured for *ex vivo* modification of cells may, with

	elements of different gene therapy products are outlined below: • For viral vectors” Comment: Defining viral vectors that are used for *ex vivo* gene therapy, and which are not intended to form part of the final product, as drug substance encumbers production facilities with additional regulatory requirements. ASGCT recommends that FDA define viral vectors that are used for *ex vivo* gene therapy as raw materials in line with the EMA Draft Guidance Document (23 March 2015), which states: "Regulation defines the raw materials for ATMPs as follows: Materials used during the manufacture of the active substance (e.g. culture media, growth factors) and that are not intended to form part of the active substance shall be considered as raw materials (Dir. 2009/120)."	proper supply chain control, be defined as raw materials.
	2. Drug Substance Manufacture	
	b. Description of Manufacturing Process and Process Controls	
	ii. Manufacturing Process	
401 – 406	Draft guidance recommendation: “The description of your manufacturing process should include a flow diagram(s) and a detailed narrative. Your description should clearly identify any process controls and in-process testing (e.g., titer, bioburden, viability, impurities) as well as acceptable operating parameters (e.g., process times, temperature ranges, cell passage number, pH, CO2, dissolved O2, glucose level).” Comment: There may be overlap based on how “process controls,” “in-process testing,” and acceptable “operating parameters” are interpreted. It would be helpful if FDA could clarify what is meant by “process controls” by providing examples, and how they differ from “in-process testing” and “operating parameters.”	

	iv. Vector Production	
440 – 441	Draft guidance recommendation: "You should outline any in-process testing to ensure vector quality as appropriate (e.g., titer, impurities)." Comment: We recommend that detailed in-process testing to ensure vector quality not be expected at the IND stage for vectors for all types of gene therapy products, and should depend on the type and complexity of the product and the stage of development, because there may be limited process knowledge at the early stage of IND submission.	
	c. Control of Materials	
493 – 499	Draft guidance recommendation: "You must provide a list of all materials used in manufacturing (21 CFR 312.23(a)(7)(iv)(b)) and a description of the quality and control of these materials. This information may be provided in tabular format and include the identity of the material, the supplier, the quality (e.g., clinical-grade, FDA-approved), the source of material (e.g., animal, human, insect), and the stage at which each material is used in the manufacturing process (e.g., culture media, vector purification)." Comment: We request FDA to clarify what they mean by "FDA-approved" quality for the materials used in manufacturing for gene therapy products.	
499 – 504	Draft guidance recommendation: "This includes information on components, such as cells, cell and viral banking systems, and reagents, as described in more detail below; it also includes raw materials and equipment, such as culture bags, culture flasks, chromatography matrices, and tubing, that come into contact with the product." Comment: We recommend a differentiation between critical raw materials from other raw materials. Some of the raw materials listed, e.g. culture bags, culture flasks, chromatography matrices, and tubing, would typically not be critical raw materials. While	Proposed addition: "While information on critical raw materials (media, resins, etc.) is warranted at the IND stage, the information on non-critical raw materials may be collected during the IND stage and provided to FDA at the time of BLA submission. The critical and non-critical materials will depend on the product and their impact on the product safety and quality."

	information on critical raw materials (media, resins, etc.) may be warranted at the IND stage, the information on non-critical raw materials may not be appropriate with the initial IND submission. The latter may be collected during the IND stage and provided to FDA at the time of BLA submission.	
	i. Reagents	
521 – 525	Draft guidance recommendation: "For purpose of this guidance, reagents (or ancillary materials) are those materials used for manufacturing (e.g., cell growth, differentiation, selection, purification, or other critical manufacturing steps) that are not intended to be part of the final product." Comment: For definition purposes, it would be helpful to clarify whether "reagents" includes raw materials, or if reagents are considered distinct from "raw materials." If distinct, it would be helpful to add a separate sub-section on "raw materials" in the section on control of materials. Also, if distinct, it would be helpful to clarify the difference between ancillary materials and raw materials.	Suggest wording change to help clarify: "For purpose of this guidance, reagents, are those materials (or ancillary materials) used for manufacturing (e.g. cell growth).....that are not intended to be part of the final product, which can include specific raw materials as long as they are not part of the final product…."
	viii. Master Cell Banks Used as Substrates for Production of Viral Vectors	
832 – 833	Draft guidance recommendation: "Insect cell lines with known viral contamination should be avoided." Comment: It is not always possible to completely avoid viral contamination of cell lines. It would be helpful to add flexibility to this recommendation in line with the ICH guidance Q5AR1 on Viral Safety Evaluation of Biotech Products. Section III on cell line characterization in subsection C on acceptability of cell lines discusses the concept that some cell lines will contain endogenous viral sequences, and recommends that sponsors perform a risk analysis that includes the viral clearance evaluation data.	Proposed change: "Insect cell lines with known viral contamination should be avoided when possible." Proposed addition of reference to ICH Q5AR1 guideline here in text and to list of references in guidance.

835 – 841	Draft guidance recommendation: "Identify your cells through tests that distinguish them from other cell lines used in your facility." Comment: It would be helpful to clarify the recommendation to specify whether this recommendation should be followed routinely or at certain time points, e.g. after changeover or when the cells are banked. Also, it would be helpful to specify the timing of applicability of this recommendation, e.g. before original IND submission to provide information with original IND submission, or after original IND submission with the information provided to FDA with the BLA submission.	
843 – 848	Draft guidance recommendation: "Establish stability of the cell bank. Stability can be assessed by measuring viability of cells over time after cryopreservation. We also recommend a one-time test of end of production cells (EOP) or mock production cells of similar passage history, to be tested for their suitability to produce your vector. For stable retroviral vector producer cells, we recommend that you test the genetic stability of the gene insert in the EOP cells." Comment: We align with and appreciate the recommendation for a one-time test of end of production cells (EOP) or mock production cells of similar passage history, to be tested for their suitability to produce the vector for establishing stability of the cell bank. However, we request FDA to consider that such data not be expected with the initial IND submission, but perhaps the data can be collected during the IND stage, and submitted to FDA at the time of BLA submission. It would be helpful if FDA clarifies their expectation for the timing for applicability of the recommendation. In addition, clarifying the expectation for confirming genetic stability would be helpful.	
852 – 859	Draft guidance recommendation: "Assess the ability of new cell lines to form tumors. We recommend that you perform tumorigenicity	

	tests for cell lines that have not been previously characterized for their potential to form tumors." Comment: We request clarification of the recommendation to assess the ability of new cell lines to form tumors and to perform tumorigenicity tests for cell lines that have not been previously characterized for their potential to form tumors. More detail on the criteria and expectations would be helpful. We recommend that the final guidance specify FDA's expectations for methodology, frequency, and time points for such tests. We suggest that this data and information not be expected with the original IND submission, and a one-time test for tumorigenicity for new cell lines be acceptable.	
x. Bacterial or Microbial Master Cell Banks		
911	Guidance Text: "Transgene expression or activity" Comment: Testing of bacterial master cell banks for expression or activity of the transgene carried on the plasmid harbored by the bacteria is not straightforward, as in most cases expression is under the control of a eukaryotic promoter. Verification of the identity of the expression construct contained within the bacterial stock should be sufficient for release of the bacterial MCB.	Proposed change: replace "expression or activity" with "identity" Proposed text: "transgene identity"
xi. Master Viral Banks		
1016 – 1020	Draft guidance recommendation: "You should perform sequence analysis of the gene insert, flanking regions, and any regions of the vector that are modified or could be susceptible to recombination. The entire vector sequence will be necessary to confirm identity for licensure." Comment: We recommend that the limitations of the sequencing technique be recognized, e.g., it is not possible to sequence all the regions when using Sanger sequencing. It would be helpful to note that it may not be possible to sequence all the regions beyond the GOI. Also, it would be helpful to clarify the	Proposed change: Add "when possible" to qualify the recommendation. Proposed text: "When possible, you should perform sequence analysis of the gene insert, flanking regions, and any regions of the master viral bank that are modified or could be susceptible to recombination. The entire master viral bank ~~vector~~ sequence ~~will be necessary~~ is important to confirm identity for licensure."

	terminology and specify that the recommendation applies to viral vector banks only, in line with the section title.	
d. Control of Critical Steps and Intermediates		
1052 – 1066	Guidance Text: Intermediates in gene therapy manufacturing may also include DNA plasmids that are used in the manufacture of other gene therapy products, such as AAV or lentiviral vectors. Comment: ASGCT recommends the guidance document stipulate that if plasmids do not directly become part of the drug substance or drug product, then they may be defined as starting materials or reagents, and their quality ensured by appropriate controls for critical starting materials, similar to cell and viral banks. Thus, the recommendations on providing information on the plasmid manufacturing process and plasmid specifications should be moved from Section D, "Control of Critical Steps and Intermediates," to Section C, "Control of materials."	Proposed change: Delete the sentence "Intermediates in gene therapy manufacturing may also include DNA plasmids that are used in the manufacture of other gene therapy products, such as AAV or lentiviral vectors." Move the recommendations on plasmid production to Section C Control of Materials.
3. Drug Substance Characterization		
b. Impurities		
i. Process-Related Impurities		
1177 – 1186	Guidance text: We recommend that you limit the amount of residual DNA for continuous non-tumorigenic cells to less than 10 ng/dose and the DNA size to below approximately 200 base pairs. If you are using cells that are tumor-derived (e.g., Hela) or with tumorigenic phenotypes (e.g., 293, also known as HEK293T) or other characteristics that give rise to special concerns, more stringent limitation of residual DNA quantities may be needed to assure product safety." Comment: The World Health Organization's current standard of 10 ng host cell DNA/dose is not supported by experimental data quantitating the oncogenic risk associated with contaminating host cell DNA.[i-2] The risk of	Proposed change: "We recommend that sponsors document levels of contaminating host cell DNA and strongly transforming oncogene DNA in products."

	residual contaminating host cell DNA from potentially oncogenic cell lines is similarly difficult to predict and may also be immeasurably low. ASGCT therefore recommends documenting levels of contaminating host cell DNA and strongly transforming oncogene DNA in products, as opposed to complying with an arbitrary set limit of 10 ng HC DNA/dose.	
4. Control of Drug Substance		
c. Validation of Analytical Procedures		
1444 – 1448	Draft guidance recommendation: "In your original IND submission, you should provide a detailed description of the qualification protocol (e.g., samples; standards; positive/negative controls; reference lots; and controls evaluated, such as operators, reagents, equipment, dates) and data supporting the accuracy, reproducibility, sensitivity, and specificity of the method." Comment: The recommended detailed description of the qualification protocol and data supporting the accuracy, reproducibility, sensitivity, and specificity of the method may not be possible to provide with the original IND submission in some instances. It would be helpful to provide additional flexibility with the timing of the data submission. Also clarify whether reference lot is acceptable for comparability if the same method is not available at time of clinical lot testing.	Proposed change: "In your original IND submission, you should provide a ~~detailed~~ description of the qualification protocol (e.g., samples; standards; positive/negative controls; reference lots; and controls evaluated~~, such as operators, reagents, equipment, dates~~) and data supporting the accuracy, reproducibility, sensitivity, and specificity of the method, when such data is available at the time of submission of the original IND."
1456 – 1458	Draft guidance recommendation: "In addition, you should validate tests used to determine dose prior to initiating clinical studies to demonstrate efficacy or support licensure." Comment: It would be helpful to specify the phase of development associated with this recommendation. Validated tests to determine dosing may not be available during phase 1 trial stage, but may be expected during phase 3 in most circumstances. Additional flexibility would be helpful.	Proposed change: "In addition, when possible, you should validate tests used to determine dose prior to initiating clinical studies to demonstrate efficacy, or to support licensure at the time of BLA submission."

	d. Batch Analysis	
1479 – 1489	Draft guidance recommendation: "You should include a table with test results for all of the batches (or lots) of DS that you have manufactured. For early stage INDs, this may include only toxicology lots or developmental batches and a single manufacturing run for clinical grade material. Please note that batches manufactured in different ways should be clearly identified in the submission. We recommend that you annually update this section of your IND as new batches are produced. You should indicate any batches that fail to meet release specifications and any action taken to investigate the failure (as outlined in "Process Validation and/or Evaluation (3.2.S.2.5)" (section V.A.2.e. of this guidance). We recommend that you retain samples of all production lots for use in future assay development, validation, or comparability studies." Comment: During early stage IND, there may be no process validation. Process validation, as recommended here, is typically conducted in phase 3, and results of any batches that fail to meet release specifications and any action taken to investigate the failure as outlined in "Process Validation and/or Evaluation," will likely be submitted with the BLA. It would be helpful to provide additional clarity in this regard. The parenthetical referencing "Process Validation and/or Evaluation" may not be applicable here.	
	B. Drug Product	
	4. Control of Excipients	
	b. Analytical Procedures	
1806	Guidance text: "You should describe your analytical procedures for testing excipients." Comment: We request clarification of whether manufacturer CoA is acceptable for excipients.	
	5. Control of Drug Product	
	b. Analytical Procedures	
	i. Sterility	

1952 – 1959	Guidance Text: "However, if the product undergoes manipulation after thawing (e.g., washing, culturing), particularly if procedures are performed in an open system, you may need to repeat sterility testing. We recommend that you incorporate the results of in-process sterility testing into your acceptance criteria for final product specifications." Comment: In-process sterility testing is very important to ensure safety for GT products. We request FDA to provide recommendation on how to define responsibilities between the sponsor and the medical institution, and explain the key aspects that should be incorporated in the quality agreement under the circumstances that the product undergoes manipulation after thawing (e.g., CAR T cells need washing and resuspending before administration).	

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

[1]Sheng-Fowler L., Tu W., Fu H., Murata H., Lanning L., Foseh G., Macauley J., Blair D., Hughes S.H., Coffin J.M., et al. A mouse strain defective in both T cells and NK cells has enhanced sensitivity to tumor induction by plasmid DNA expressing both activated H-Ras and c-Myc. *PLOS One* 2014; 9(10):e108926.
[2]Sheng-Fowler L., Cai F., Fu H., Zhu Y., Orrison B., Foseh G., Blair D.G., Hughes S.H., Coffin J.M., Lewis A.M. Jr., et al. Tumors induced in mice by direct inoculation of plasmid DNA expressing both activated H-ras and c-myc. *Int J Biol Sci.* 2010;6(2):151-62.