



June 14, 2022

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

**Re: Comments for Docket No. FDA-2021-D-0398: Human Gene Therapy Products Incorporating Human Genome Editing; Draft Guidance for Industry**

Dear Sir/Madam:

The American Society of Gene & Cell Therapy (ASGCT) appreciates the opportunity to comment on the draft guidance document, *Human Gene Therapy Products Incorporating Human Genome Editing*. ASGCT is a nonprofit professional membership organization comprised of more than 5,500 scientists, physicians, clinicians, 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. Many of our members have spent their careers in this field performing the underlying research that has led to today's robust pipeline of transformative therapies. By bringing together members from diverse backgrounds, ASGCT strives to be a catalyst for transformative medicine using genetic and cellular therapies to control and cure human disease. We appreciate FDA's ongoing willingness to hear from stakeholders about ways to improve and adapt policies to consider the unique attributes of these therapies.

**I. General Comments**

ASGCT appreciates that FDA is working to provide additional guidance to gene therapy sponsors to further promote development of new therapies for patients. We believe that this guidance broadly strikes an appropriate balance between setting baseline expectations for sponsors and providing needed flexibility to evaluate data for individual development programs based upon the benefit-risk of the unmet medical need and the condition being treated. That said, ASGCT does have a number of specific suggestions for adjustments or edits that we believe would represent improvements in the final guidance.

**II. Specific Comments**

***1. Selection of GE Components (lines 66-159)***

Section III.A of this guidance, "General Considerations," implies that best available or optimal gene editing components be selected when developing a GE technology. For example, the guidance includes the following on lines 119-120 about the delivery method: "*When determining the optimal delivery method of the GE components, it is important to consider the advantages*

*and limitations of each potential method...*” This implied expectation also includes the method by which the DNA sequence will be achieved, and the type of genomic modification needed for the desired therapeutic effect.

While we agree that developers should consider the advantages and limitations of components, we respectfully request that the final guidance address two important clarifications:

- These advantages and limitations should not be compared or evaluated in relation to other products under development. We believe each development program and the resulting BLA should be in the context of potential of unmet need, available therapies, severity of the condition, the intended patient population, and the safety, efficacy and quality data provided in the BLA.
- These advantages and limitations should take into account that over the full course of a product development program, technologies may evolve. This should not be a regulatory barrier to development of a particular product or have a negative impact on how FDA reviews a BLA if the safety, efficacy and quality data of such BLA meet licensure standards.

## **2. General Chemistry, Manufacturing, and Controls (CMC) Considerations (lines 161-351)**

### a. General Thoughts

ASGCT appreciates the inclusion of GE-specific CMC considerations in this draft guidance, and we offer in the table below a few specific suggestions for potential line-item changes. More generally, as ASGCT shared at our 2021 FDA Liaison Meeting,<sup>1</sup> advances in manufacturing and analytical techniques have improved control and characterization of products in the gene therapy field writ large, including in GE applications, but the link between product characteristics and clinical performance is still evolving. Small clinical trial populations that are characteristic of gene therapy product development make statistical analysis of CMC data from gene therapy batches challenging. Rapid innovation in the GE field warrants a CMC framework that remains flexible, risk-based, and correlated with the extent of clinical experience. ASGCT would like to reiterate several recommendations from our 2021 FDA Liaison Meeting that are applicable to GE product development:

- We encourage FDA to take a pragmatic approach to the application of statistical analyses of specifications early in development. With limited data, these may not be as meaningful as robust qualitative analysis. Additionally, we recommend that FDA and sponsors use available data and science-based risk assessment to guide the evolution of specifications at the appropriate point of development (including post-marketing if so justified).
- When considering potency assays, ASGCT recommends FDA allow a risk-based approach in the context of the unmet medical need of the patient population in its

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<sup>1</sup> *Recommendations on CMC Expectations for Gene and Cell Therapy Products.*

<https://asgct.org/global/documents/advocacy/2021-fda-liaison-meeting/final-cmc-issues-for-liaison-meeting.aspx>

requirements for potency assays of CGT products. The development of one strong potency assay addressing the main mechanism of action(s) of the final drug product should be sufficient for product release, obviating the need for other potency assays as product release tests. Additional measures of potency should be continued throughout development, but as general characterization assays with no acceptance criteria. Expectations for potency assay qualification and specification setting need to take into account the complexity of the assay, known correlation with clinical outcomes, and data availability. Finally, ASGCT urges FDA to allow continuous validation of potency assays during review and post-licensure to refine acceptance criteria for products where high replicate batch data is challenging (e.g., autologous products or those that have especially complex modes of action).

b. Level of Material Control Required

As we noted above, ASGCT appreciates the inclusion of GE-specific CMC considerations in this draft guidance, in addition to the previous guidance *Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs); Guidance for Industry* (January 2020).<sup>2</sup> However, ASGCT is concerned that the current recommendations could be overly burdensome and unnecessary for certain GE products. ASGCT requests that FDA further consider the level of material control needed relative to nature of the materials, frequency of use, and proximity to patients. Specifically, the Society would like to request that FDA consider adding additional language in the final guidance that reflects the nature of the materials (synthetic vs bioactive; nuclease vs. nucleic acid) and how frequently it is anticipated to be used during the product life cycle.

For example, consider a sponsor using a plasmid in combination with a nuclease to edit a stem cell that would be further manufactured into a Master Cell Bank (MCB), then a Working Cell Bank (WCB), then differentiated into a therapeutic product. Once the GE cell is created, there is no need to use the plasmid again because the GE stem cell is replenishable and can serve as the seed stock to support all future clinical phases. This is a one-time use of the plasmid, and the proximity of the initial cell to the patient is considerably downstream.

- If the sponsor has already manufactured the **one-time** use plasmid under non-GMP conditions with approved Phase I/II trials in progress and/or successfully completed, the guidance seems to suggest that the sponsor would need to re-make all components under GMP and re-establish the GE cell clone in order to support late phase/commercial development (lines 218-224): “For most Phase 1 clinical investigations, sponsors should follow the recommendations in FDA’s *Guidance for Industry: CGMP for Phase 1 Investigational Drugs for the manufacture of these components* (see 21 CFR 210.2(c); Ref.5). However, for later Phase studies and for licensure, GE components must be manufactured according to CGMP standards (21 CFR Parts 210 and 211), with particular consideration for control of reagent quality, manufacturing process, and analytical methods.” This seems unnecessary.

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<sup>2</sup> *Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs): Guidance for Industry*. <https://www.fda.gov/media/113760/download>

- In addition, in this instance, how should the sponsor approach stability testing for both the bacterial and plasmid cell bank? Lines 235-240 offer guidance that does not seem applicable to a one-time use situation, but which casts a broad net in terms of when such stability tests would be required: *“We also recommend GE components be assessed for stability. Outlines of stability protocols and any available stability data should be provided in the IND. Stability studies should be conducted on all GE components (e.g., lyophilized and reconstituted materials), if applicable. Stability studies should include stability-indicating tests assessing critical product attributes, such as purity and functionality, that may be affected during storage.”*

In some cases, commercial entities intend to make hundreds of one-time use plasmids. As a result of this guidance, effectively all one-time use plasmids should be made under GMP for all clinical phases through commercialization, from the very beginning, or the manufacturer risks having to recreate the initial cell, MCB and WCB at each phase of clinical study as GMP requirements increase (and then establishing comparability back to the original product). The challenge with such a recommendation would be multi-faceted. First, all nonclinical and early phase data to support safety and efficacy is based on cells derived using non-GMP material. Second, the cost to manufacture under GMP would represent an unexpected cost and time burden to the sponsor, further delaying the production of a therapeutic product. And finally, proximity to the patient is significantly downstream of the critical raw material which entails manufacture of multiple banks (MCB and WCB) that undergo significant testing and are further differentiated into drug product that is, again, thoroughly tested.

Therefore, ASGCT respectfully requests that FDA clarify in the final guidance whether FDA’s intention is that a sponsor in this situation must always ensure both bacterial MCB and plasmids are manufactured under GMP at the start. ASGCT recommends flexibility for certain components, consistent with phased GMP requirements.

### **3. Distinguishing In Vivo and Ex Vivo GE Applications (lines 272-351)**

ASGCT appreciates the sections of the guidance in which FDA specifies recommendations for in vivo and ex vivo human GE drug product types (lines 272-351). As the science for these different human GE drug products continues to evolve, FDA may want to consider clarifying whether recommendations for in vivo and ex vivo approaches are meant to be the same or different in other areas of the guidance, such as III.B subsection 2 on “Genome Editing Component Manufacture and Testing” (lines 226-233). ASGCT’s goal is to ensure that, where it occurs in the guidance, conflation of in vivo and ex vivo approaches is intentional.

### **4. Study Endpoints (lines 592-599)**

As an organization representing a diverse group of stakeholders in the gene therapy and gene editing fields, who have varying levels of regulatory experience on their development teams, ASGCT believes FDA should be clear and direct in this guidance regarding regulatory expectations for study endpoints. The guidance states:

*“For efficacy studies, the primary endpoint should also reflect a clinically meaningful effect of the GE product”* (lines 594-596).

This is inconsistent with previous FDA guidances. FDA's recent *Human Gene Therapy for Neurodegenerative Diseases: Draft Guidance for Industry*,<sup>3</sup> which applies to GE products as well as other gene therapies, states:

*"[i]n 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** [emphasis added] surrogate endpoints that are reasonably likely to predict a clinical benefit...[u]se 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"* (pg. 11, para. 5).

Furthermore FDA's *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*,<sup>4</sup> which applies broadly to all products, notes:

*"The two types of endpoints that can be used as a basis for accelerated approval are: (1) a surrogate endpoint that is considered reasonably likely to predict clinical benefit and (2) a clinical endpoint that can be measured earlier than IMM that is reasonably likely to predict an effect on IMM or other clinical benefit (also see section VII.D.2.)... A clinical benefit is a positive therapeutic effect that is clinically meaningful in the context of a given disease..."* (pg. 17, para. 3).

The current language in this draft suggests that for GE products, the agency has a different policy view on the use of surrogate endpoints and accelerated approval for these products. If this is the case, ASGCT strongly objects to this assertion and asks for greater clarity from the agency regarding the legal and scientific basis for this determination. If this is not the case, we believe that the same policies FDA has established in previous guidance should be clarified in this guidance for GE products to prevent inconsistent interpretation about expectations for efficacy endpoints between related guidances. Lacking clarification of FDA's intent, ASGCT recommends that this section should be removed from the GE guidance to prevent confusion.

As with all products, we believe that FDA's expectations for safety and durability at the time of approval should be established in the context of the disease and patient population, including severity of the condition, unmet need, and the perspectives of patients.

### **III. Line-by-line Recommendations**

Below, the Society has provided specific line-item recommendations for FDA's consideration.

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<sup>3</sup> *Human Gene Therapy for Neurodegenerative Diseases: Draft Guidance for Industry*.  
<https://www.fda.gov/media/144886/download>

<sup>4</sup> *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*.  
<https://www.fda.gov/media/86377/download>

Page	Comment/Issue	Request/Proposed Change
II. Background		
Lines 56-59	<p><i>“Human GE is a rapidly evolving field, and this guidance encompasses FDA’s current thinking regarding the development of human GE products for clinical studies and licensure. As the field evolves, product design advances, and we gain information on the safety of human GE products, we may revise our recommendations to take into account such changes.”</i></p> <p>ASGCT appreciates this recognition that the field is ever-changing, and rapidly so. The Society is pleased that FDA has expressed openness to revising this guidance to reflect future developments.</p>	ASGCT encourages FDA to keep the possibility of rapid change front of mind so as not to inadvertently fall behind progress in the field. To aid in that effort, the Society would gladly make our member experts available in any way FDA would find helpful.
III. Considerations for Product Development		
A. General Considerations		
Lines 76-89	<p><i>“GE can be achieved by either nuclease dependent or nuclease independent methods... When choosing a specific GE technology, consideration should be given to the mechanism of action (MOA), the ability to specifically target the desired DNA sequence, and the ability to optimize the GE components to improve efficiency, specificity, or stability.”</i></p> <p>ASGCT respectfully notes that the list of GE reagents included within this paragraph of the guidance is not comprehensive; and as FDA notes earlier in the guidance, the field is rapidly evolving and expanding.</p>	<p>We recommend that FDA be explicit that the list included in this paragraph is not intended to be static or all-inclusive, and that novel GE strategies and reagents that are not listed will be expected to follow the guidelines laid out here.</p> <p><i>“GE can be achieved by either nuclease dependent or nuclease independent methods... When choosing a specific GE technology, consideration should be given to the mechanism of action (MOA), the ability to specifically target the desired DNA sequence, and the ability to optimize the GE components to improve efficiency, specificity, or stability. <b>The list of editing technologies presented in this section is not comprehensive. This guidance would apply to technologies not listed here but which would be considered genome editing by the definition provided in Section II.</b>”</i></p>

B. Chemistry, Manufacturing and Controls (CMC) Recommendations		
<p>Lines 218-224</p>	<p><i>“For most Phase 1 clinical investigations, sponsors should follow the recommendations in FDA’s Guidance for Industry: CGMP for Phase 1 Investigational Drugs for the manufacture of these components (see 21 CFR 210.2(c); Ref.5). However, for later Phase studies and for licensure, GE components must be manufactured according to CGMP standards (21 CFR Parts 210 and 211), with particular consideration for control of reagent quality, manufacturing process, and analytical methods.”</i></p> <p>This section does not seem harmonized with the draft guidance <i>Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products</i>, which lacks the same verbiage pertaining to later phase studies and refers only to licensure. From that guidance, lines 236-239: <i>“The vector should be well-characterized prior to initiation of clinical studies. <b>For licensure, the vector must be manufactured according to CGMP standards</b> [emphasis added] (21 CFR Parts 210 and 211) and analytical assays must be validated (21 CFR 211.165(e), Ref. 18).”</i></p> <p>Therefore, while both of the new guidances on GT advocate cGMP standards of manufacture at licensure, the draft guidance for GT Products implies a higher bar for later phase manufacture while the CART guidance does not. This is especially concerning to ASGCT because the high cost of CGMP compliance can significantly impede a sponsor’s ability to successfully advance a product toward commercialization.</p>	<p>ASCGT requests clarity regarding whether the standards in this guidance and the “Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products” are in fact distinct, and if so, the rationale for the distinction as well as defining “later Phase,” especially in the context of products for Orphan diseases.</p> <p>If the standards in the two guidances are not meant to be distinct from one another, we request the language be harmonized.</p>
<p>Lines 286-288</p>	<p><i>“Please also note that certain nanoparticles used for in vivo delivery of GE components may be considered a delivery device.”</i></p>	<p>We request FDA clarify whether delivery “device” is a reference to the definition of a medical device, and therefore would necessitate a combination product</p>

		<p>application. If so, examples of nanoparticle delivery that would and would not be considered medical devices are necessary.</p> <p>If FDA does not intend to regulate these as combination products, ASGCT requests that this sentence be revised to remove that uncertainty.</p>
<b>IV. Considerations for Preclinical Studies</b>		
Lines 376-381	<p><i>“The animal species and/or models selected for in vivo studies should demonstrate a biological response to the investigational GE product or species-specific surrogate endpoint (See section IV.A of this guidance for further discussion). Given the differences in the genomic sequences between humans and animals, analysis of the biological activity may be done in a species-specific context and applied to the clinical product, as appropriate.”</i></p>	<p>ASGCT appreciates FDA’s inclusion of this point. To assist sponsors in meeting FDA’s expectations, we recommend inclusion of a reminder that sponsors will need to justify why they chose the different reagent and the comparability between the animal and human reagent. It would not be appropriate, for one example, to gauge off-target safety in an animal model that uses a different reagent than what is being used in the clinical trial.</p>
<b>A. Product Evaluated in Preclinical Studies</b>		
Lines 423-425	<p><i>“For ex vivo-modified GE products, the clinical cell source should be used for the definitive preclinical studies. If an alternative cell source is used in any studies, scientific justification should be provided for the cell source selected.”</i></p> <p>For some diseases, obtaining the clinical cell source is not possible. For instance, it is unethical to draw blood for research purposes from sickle patients, as it could send them into crisis. In these cases, sponsors have used the same target cell from healthy patients for preclinical studies.</p>	<p>The guidance should reflect FDA practice and include “target human cell” either as an option in addition to or instead of the phrase “clinical cell source.”</p> <p><i>“For ex vivo-modified GE products, the clinical cell source <b>or target human cell</b> should be used for the definitive preclinical studies. If an alternative cell source is used in any studies, scientific justification should be provided for the cell source selected.”</i></p>
<b>B. Assessment of Activity</b>		
Lines 434, 446	<p><i>“We recommend preclinical in vitro and in vivo POC studies assess the following...</i></p> <ul style="list-style-type: none"> <li><i>• Effects of genetic variation on editing activity across the target population.”</i></li> </ul>	<p>We recommend that this section should end with line 444, and the fifth bullet point on genetic variation should be struck.</p>

	<p>All drug candidates and approved products, not only GE products, may have differential efficacy and safety due to genetic polymorphisms (e.g., for a kinase inhibitor, polymorphisms in the on-target protein could affect efficacy, and polymorphisms in off-target kinases could affect safety). We therefore do not believe it is warranted for FDA to ask GE sponsors specifically to pursue those kinds of cross-population studies.</p>	
<b>C. Assessment of Safety</b>		
Lines 456-458	<p><i>“The use of multiple orthogonal methods (e.g., in silico, biochemical, cellular-based assays) that include an unbiased genome-wide analysis is recommended for identification of potential off-target sites.”</i></p> <p>ASGCT believes sponsors should have the flexibility to justify their selected methods, orthogonal or otherwise, rather than being constrained to one approach as this phrasing suggests. As there are multiple methods to identify potential off-target sites and ongoing development of new assays, it may be most appropriate for sponsors to generate lists of potential off-target sites using independent methods, with the expectation that scientific rationale for that list will be provided to FDA.</p> <p>Finally, ASGCT respectfully asserts that the term “unbiased” is inappropriate here. Every assay includes bias to some degree, and sponsors should be responsible for accounting for that in their analyses.</p>	<p>We recommend striking “orthogonal” from this sentence to remove the implied requirement that such an approach must be used to identify off-target sites.</p> <p>We also recommend striking the term “unbiased.”</p> <p><i>“The use of multiple <del>orthogonal</del> methods (e.g., in silico, biochemical, cellular-based assays) that include <del>an-unbiased</del> genome-wide analysis is recommended for identification of potential off-target sites.”</i></p>
<b>V. Considerations for Clinical Studies</b>		
<b>A. Study Population</b>		
Lines 529-531	<p><i>“Therefore, in some instances, subjects with less advanced or more moderate</i></p>	No requested change.

	<p><i>disease may be appropriate for inclusion in first-in-human clinical studies.”</i></p> <p>ASGCT greatly appreciates the inclusion of this line in the guidance and the acknowledgement that it can be appropriate to enroll patients in a given patient population who are not the sickest or have not reached the most advanced state of disease.</p>	
<b>F. Special Considerations for Research Involving Children</b>		
Lines 608-613	<p><i>“Therefore, it is important to enroll at least an initial cohort of adult subjects, whenever feasible, to obtain preliminary data on safety and feasibility, bioactivity, and preliminary efficacy to support enrollment of pediatric subjects. If enrollment of pediatric subjects is justified, then an effort should be made to enroll adolescents prior to enrollment of younger children and infants, as appropriate for the specific disease of interest.”</i></p> <p>ASGCT agrees that when possible, testing a GE product in adults is the best first step followed by testing in adolescents. However, ASGCT member sponsors report that FDA review staff have in some cases included recommendations to consider enrolling adults, even after a company demonstrates why that is not possible based on the impacted patient population or the efficacy endpoints needed to support approval.</p>	<p><i>“Therefore, it is important to enroll at least an initial cohort of adult subjects, whenever feasible, to obtain preliminary data on safety and feasibility, bioactivity, and preliminary efficacy to support enrollment of pediatric subjects. <b>We recognize that certain diseases exist in which children and/or infants are the only populations in which a product can be tested.</b> If enrollment of pediatric subjects is justified, then an effort should be made to enroll adolescents prior to enrollment of younger children and infants, as appropriate for the specific disease of interest.”</i></p>

Thank you for your consideration of these comments. If you have any questions, please contact Christina Mayer, Senior Manager of Government Affairs, at [cmayer@asgct.org](mailto:cmayer@asgct.org).

Sincerely,



David Barrett, J.D.  
Chief Executive Officer