June 14th, 2022

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

Re: Docket No. FDA-2021-D-0398: Human Gene Therapy Products Incorporating Human Genome Editing; Draft Guidance for Industry

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments regarding the *Human Gene Therapy Products Incorporating Human Genome Editing; Draft Guidance for Industry* (Draft Guidance or Guidance).

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

BIO appreciates the Agency release of this Draft Guidance which provides current thinking on important issues related to the development of human genome edited (GE) products. In general, this is a well-written guidance that will be useful until more experience is gained with these therapies. The guidance puts forward reasonable expectations for off-target analysis and safety in the context of gene editing.

BIO would like to request additional content in this Guidance on efficacy, durability, benefit/risk, and a section on the patient experience. We also recommend that the scope of this guidance be extended beyond human somatic cells and include cells derived from adult and pluripotent stem cells. While there may be additional changes needed throughout the Guidance to address scientific considerations associated with other cell types, we think it would be valuable to broaden the scope.

In the letter that follows, BIO provides high level policy recommendations and comments. We also provide detailed, specific comments in the chart that follows this letter.

I. Considerations for Product Development

FDA's Implied Preference for Best Available Technology

Inherent in our role as scientists and developers of GE products is a desire to develop the best product possible. With that said, this is a rapidly evolving field and drug development takes time and significant investment. The point at which foundational investments must be made, partnerships formed, or licensing agreements finalized, may be many years away from when those technologies will be present in an FDA-approved GE product.

We do not agree with the implication in the "General Considerations" section of the Guidance that FDA should expect to see best available technology in a single application. Further, the field is rapidly evolving, and newly discovered and yet untested and unproven technologies, should not be a distraction from an objective and focused review of existing technologies that have matured to the point of being incorporated into GE products.

Chemistry, Manufacturing, and Controls – Consideration of Nanoparticles

BIO requests that FDA provide clarification on the Agency's thinking regarding certain nanoparticles used for *in vivo* delivery of GE components. BIO believes that nanoparticles used in this context drive the performance of the therapeutic product and should be referred to as "excipients" or "functional excipients" instead of "delivery devices".

II. Considerations for Clinical Studies

We appreciate FDA's discussion of important clinical considerations such as study population, dose, treatment plan, and monitoring. As FDA finalizes this Guidance, we recommend a more substantive discussion of the scientific and regulatory considerations regarding study endpoints. Further, we recommend that the clinical studies section, particularly on study endpoints and pediatric studies, be as aligned with the existing Draft Guidance on gene therapy for neurodegenerative diseases as possible. Given that the neurodegenerative Guidance is on the CBER 2022 guidance agenda to be finalized, we recommend that FDA emphasize internal coordination and alignment of policy in updating both Guidances. Here, we provide some specific recommendations on sections of the Clinical Studies section of this Guidance.

Study Endpoints

BIO found the "Study Endpoints" section to be unclear and prone to range of interpretations. First, as a scientific matter, BIO believes that this Guidance should articulate FDA's current thinking regarding the strength of biomarkers, and the role(s) that surrogate biomarkers may plan, in the timely and efficient development of a gene edited product. We believe FDA's policy

in FDA's Human Gene Therapy for Neurodegenerative Diseases Guidance[1] stating that "use of a surrogate endpoint may be appropriate when a gene therapy product directly targets an underlying, well-understood and well-documented monogenic change that causes a serious neurodegenerative disorder" be applied to GE products that repair the underlying, genetic cause of disease.

In the GE Draft Guidance, we request clarity from FDA regarding the intent of the statement that the primary endpoint in a pivotal GE trial should "reflect a clinically meaningful effect." One potential reading of this statement suggests that FDA is restricting the use of accelerated approval for genome editing products since surrogate endpoints that would appropriately be used in accelerated approval might not be considered endpoints that "*reflect* a clinically meaningful effect" (emphasis added). Surrogate endpoints inherently do not have clinically meaningful effects as they are not a direct measure of feeling, function, or survival.

Considering the statutory focus on Accelerated Approval for cell and gene therapy products reflected in the regenerative medicine advanced therapy (RMAT) designations available for these products,[2] we are confident that FDA is not intending to preclude the use of Accelerated Approval for GE products. To avoid confusion, we would recommend that FDA incorporate specific language regarding Accelerated Approval and appropriate endpoints for genome editing products that is consistent with language used in other FDA guidances for cell and gene therapy products.

BIO believes the Guidance would be enhanced by a more comprehensive discussion of how safety, efficacy, durability, and quality of a GE product are factoring into FDA's regulatory decisions. Specifically, given that the field of GE products is rapidly maturing, we believe the Guidance should more fully discuss the benefit-risk considerations at marketing application review, including discussion of how the perspectives of patients will be incorporated.

Study Population

We are concerned that the language used in the Draft Guidance appears very restrictive with respect to clinical enrollment for GE trials. The Guidance recommends enrolling subjects for

[1] https://www.fda.gov/media/144886/download

[2] Section 3033 of the 21st Century Cures Act [21 U.S. Code § 356 (g)(6)] specifies that a drug designated as a regenerative medicine advanced therapy (RMAT) is "eligible for accelerated approval" through "(i) surrogate or intermediate endpoints reasonably likely to predict long-term clinical benefit; or (ii) reliance upon data obtained from a meaningful number of sites, including through expansion to additional sites, as appropriate." While other categories of drugs can be eligible for approval under section 506(c) of the FD&C Act based on surrogate or intermediate endpoints, RMAT-designated products are the only products that are eligible for accelerated approval on the second basis: reliance on data from a meaningful number of sites.

whom no other treatments options are available or acceptable. This is contrary to the transformative potential of GE for patients and does not reflect a proper benefit/risk assessment that should be taken based on the specific product and the specific patient population.

Depending on the nature of the disease and the potential for a differential anticipated risk level of the GE technology (e.g., base editing vs CRISPR-associated Cas9 nuclease), it would be appropriate to consider GE technologies for diseases for which there are available alternatives (e.g., in ALS) as long as the benefit-risk assessment remains acceptable. There are many examples of biologics as the standard of care (e.g., hemophilia products or ERT in general), but patients can still get additional benefit from the constant endogenous expression of a gene product. Therefore, the Guidance should be revised to include a discussion on benefit/risk to provide more flexibility for such patients.

Pediatric Studies of GE Products

The recommendation to enroll adult patients before pediatric patients, when feasible, is in line with previous guidances, however there is no risk/benefit language included in this section. The Draft Guidance does not address circumstances where young children (possibly infants) are the primary intended population (e.g., infant-onset Pompe, SMA1) with early and severe damage and an early intervention is required. In this case, the benefit/risk ratio for infants may be better than for adults, where prior exposure in an adult cohort could likely mean all risk / no benefit.

BIO suggests that FDA include risk /benefit and age-appropriate non-clinical translational studies for pediatrics. We recommend additional context for circumstances where the prospect of direct benefit to the adult population is not expected, where an exception could be considered allowing direct enrolment of pediatric subjects, on the basis on preclinical data to support prospect of benefit in pediatrics. We also believe that age-appropriate non-clinical translational studies would be a more appropriate risk mitigating strategy in these situations.

Additionally, in FDA's Human Gene Therapy for Neurodegenerative Diseases Guidance[3], FDA provides a clear path to pediatric first-in-human (FIH) clinical trials. Specifically, the policy states "to justify conducting a pediatric first-in-human clinical trial that is associated with more than a minor increase over minimal risk, the preclinical program should include studies designed to demonstrate a prospect of direct benefit (21 CFR 50.52) of the investigational gene therapy product (section IV.B.). Preclinical evidence to support a prospect of direct benefit is most important when clinical evidence of effectiveness is not available from adult subjects with the same disease." We believe the policy for pediatric FIH studies in the final GE Guidance should

[3] https://www.fda.gov/media/144886/download

be aligned with and as flexible as the policy in FDA's Human Gene Therapy for Neurodegenerative Diseases Draft Guidance[4].

III. Long-Term Follow Up

The Guidance states that "[p]rior to enrolling, subjects should be asked to provide voluntary, informed consent to long term follow-up (LTFU)." We believe there is some ambiguity in this statement about when informed consent is required. This statement could be read to reference enrollment in the main study rather than the LTFU study. That reading of the statement in the Guidance would eliminate appropriate flexibility for the design of LTFU studies and conflict with the approach to LTFU studies set out in FDA's Guidance, Long Term Follow-Up After Administration of Human Gene Therapy (see Sec. V).

As such, to avoid confusion and preserve the intended flexibility in the Long Term Follow-Up Guidance, we would recommend clarifying the FDA statement at line 584 to read: "Prior to enrolling in a long term follow-up (LTFU) study, subjects should be asked to provide voluntary, informed consent to LTFU." Alternatively, the language could avoid confusion or perceived conflict between guidances by more expressly relying on the Long Term Follow-Up Guidance: "Subjects should provide voluntary, informed consent to long term follow-up (LTFU) consistent with FDA's Long Term Follow-Up After Administration of Human Gene Therapy; Guidance for Industry (Ref. 10).

IV. FDA-Sponsor Communication and Review Efficiency

PDUFA VI and VII provide for FDA to issue written response only (WRO) to all PDUFA meeting request types (except Type A and Type B meetings where a face-to-face meeting or teleconference are requested). In response to workload challenges at the FDA, WROs now constitute over two-thirds of OTAT's responses to meeting requests, including those meeting types for which WRO is not permitted per the PDUFA VI and VII commitments. With FDA's increased use of WRO to complex and critical meeting requests from sponsors, we are concerned about the risk of miscommunications regarding expectations and requirements during review.

We believe generally, and particularly for cell and gene therapies, that use of written response only is inappropriate for complex programs in an area of rapidly evolving science and nascent regulatory experience and policy. We are particularly concerned about the use of WRO for products with RMAT designation. These products have been designated by FDA as the most promising and FDA is directed by Congress to "facilitate an efficient development program for, and expedite the review of, such drugs if the drug qualifies as a regenerative advanced

[4] https://www.fda.gov/media/144886/download

therapy."[5] The RMAT designation, per statute, comes with the promise of additional interactions with FDA during development. Of note, a key focus of RMAT designation is facilitating dialogue and agreement between FDA and sponsors on the endpoints, including novel endpoints, that may be used to accelerate development and approval.

We strongly believe that OTAT should limit use of WROs for key meetings aim to and eliminate use of WRO (unless requested by the sponsor) in the following circumstances:

- Meetings involving RMAT-designated products;
- Meetings involved discussion of pediatric trials of a GE technology; and
- Type A and B meetings, per PDUFA VI and VII.

V. Considerations for Future Guidance on Potency

This Draft Guidance references the January 2011 Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products (Ref 6). This Guidance document was finalized over a decade ago prior to development of many novel cell and gene therapy products. An update to this key guidance document could help better guide Sponsors through the complex questions related to potency assay development for these novel therapeutic modalities.

Conclusion

BIO appreciates this opportunity to submit comments regarding the Draft Guidance *Human Gene Therapy Products Incorporating Human Genome Editing.* We would be pleased to provide further input or clarification of our comments, as needed and we look forward to future opportunities to collaborate with the Agency on this important topic.

Sincerely,

/s/
Katherine Donigan, Ph.D.
Senior Director, Science and Regulatory Affairs
Biotechnology Innovation Organization

[5] https://www.congress.gov/114/plaws/publ255/PLAW-114publ255.pdf

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
Overall	Section 1. Introduction states that "this guidance provides recommendations regarding information that should be provided in an Investigational New Drug (IND) application in order to assess the safety and quality of the investigational GE product…." As written, it is unclear whether all the recommendations in this Guidance apply to the initial IND.	It would be beneficial to clarify. For example, the potency expectations outlined would not be applicable to initial INDs as potency testing typically evolves over development allowing for an enabling assay at initial IND and fully validated assay indicative of MOA by the time of the registrational study (see potency guidance-Ref 6).
Overall	The specificity of the expected assessments reflected in the Guidance, and the early state of the GE field, would make alternative but equally valid approaches difficult.	We suggest the following addition at the end of Line 59 – "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. Sponsors should discuss suitable alternatives to the recommended assessments with the Agency."
Line 22	The Guidance document does not provide specific recommendations related to gene editing of pluripotent stem cell seed banks as precursors to master cell banks (MCB) that will be differentiated to produce regenerative medicine cell therapy products. This is a complex topic for which Sponsors will likely require guidance in the future that may differ from the general recommendations on gene editing of somatic cells as outlined in this Guidance document. If specific	BIO recommends the following addition at the end of the sentence in Line 22: "Recommendations on gene editing of pluripotent stem cell lines to generate precursor cell lines for a master cell bank (MCB) that will be used in production of somatic cell drug products are not within the scope of this guidance document."

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	recommendations around "pre-MCB" gene editing are not intended for this Guidance document, it would be helpful to state that these topics are out of scope.	
II. BACKGROUND		
Lines 49-54	"FDA evaluates human GE products using a science-based approach weighing the benefits and risks of each product. The benefit-risk profile for each product depends on the proposed indication and patient population, the extent and duration of therapeutic benefit achieved, and the availability of alternative therapeutic options. Some of the specific risks associated with GE approaches include off-target editing, unintended consequences of on- and off-target editing, and the unknown long term effects of on- and off-target editing." We request that the Agency acknowledge that gene editing methods may carry different levels of risk and that the risk-benefit assessment and risk management also consider the technology being employed for a given GE product.	BIO suggests the following edit: "FDA evaluates human GE products using a science-based approach weighing the benefits and risks of each product. The benefit-risk profile for each product depends on the proposed indication and patient population, the extent and duration of therapeutic benefit achieved, and the availability of alternative therapeutic options. A risk-based approach is also warranted because GE technologies may carry varying degrees of risks**.** Some of the specific risks associated with GE approaches include off-target editing, unintended consequences of on- and off-target editing, and the unknown long term effects of on- and off-target editing."
III. CONSIDERATIONS FOR PRODUCT DEVELOPMENT		
Sub-Section A. General Considerations / Line 66 **Sub-Section B. CMC Recommend.**	Line 66: "A GE technology may be composed of a single or multiple GE component(s)." Line 180: "GE components, such as guide RNA, can also be optimized to inhibit degradation." Line 186: "GE components can be administered in vivo using nanoparticles, plasmids, or viral vectors, or they can be used to modify cells ex vivo."	We recommend FDA consider adding a definition of what constitutes a GE component. GE component examples are provided at line 66 and 180 with further information at 186. As there is detailed CMC information recommended for each GE component manufacturing site (at B.2), the definition of a component is important to ensure that sponsors recognize what manufacturing sites are in scope.

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Lines 180 & 186		
A. General Considerations		
1. Genome Editing methods		
Line 85	Suggestion for addition in the text to sentence "...not limited to, base editing and synthetic triplex-forming"	BIO suggests the following edit: "…not limited to, base editing, AAV and synthetic triplex-forming"
Lines 84-86	"Examples of nuclease-independent GE technologies include, but are not limited to, base editing and synthetic triplex-forming peptide nucleic acids." The base editing could involve DNA nickase, which is a type of nuclease.	BIO suggests the following edit: "Examples of nuclease-independent GE technologies include, but are not limited to, some forms of base editing and synthetic triplex-forming peptide nucleic acids."
Lines 86-89	The reference to MOA as presented within this section seems to refer to MOA of the gene editing method chosen rather than the MOA of the drug product itself. It could be helpful to clarify the meaning of MOA as presented in this section. In addition to efficiency, specificity, or stability, the GE technology proposed could also improve more explicitly safety (indels, off-target editing). Currently this concept is implicit under specificity. Also, we recommend "and / or", rather than "or" to allow for multiple goals with the specific GE technology.	BIO recommends the following edit: "When choosing a specific GE technology, consideration should be given to the mechanism of action (MOA) of the genome editing component, the ability to specifically target the desired DNA sequence, and the steps taken during early development ~~the ability~~ to optimize the GE components to improve efficiency, specificity, and/or stability."
2. Type and degree of genomic modification		
Lines 102-104	Repair by NHEJ almost always results in introduction of indels, and in fact is part of the MOA of many gene editing components. Recommend updating language to	BIO recommends the following edit:

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	better represent expected editing outcomes for different strategies. The possibility of chromosomal rearrangements should be introduced in this section, alongside the other potential unintended effects of gene editing.	"It is also important to keep in mind that, although these processes can be accurate~~, they can also result in unintended~~ these processes can result in DNA insertions or deletions (indels) with possible unanticipated consequences." We also suggest adding additional sentence: "Multiple concurrent DNA cleavage events, which could be caused by multiplex on-target editing or a combination of on- and off-target effects, can lead to chromosomal rearrangements including translocations."
Lines 106-115	It is unclear where the requested information (regarding degree of genome modification needed for therapeutic effect) should go in the eCTD.	BIO requests that the Agency specify if this information should be provided in Module 3 or Module 4.
Lines 110-111	"For some conditions, clinical data may be available to support a given therapeutic modification threshold." The nature and extent of clinical data that will be deemed acceptable to support a therapeutic modification threshold are unclear particularly given dependence of the threshold on the indication and the intended patient population.	BIO requests that FDA outline considerations for clinical data needed to adequately support a therapeutic modification threshold and/or example(s) to clarify Agency expectations at the time of the IND will be useful.
Lines 113-115	"If clinical data supporting a therapeutic modification threshold are not available, we recommend sponsors provide a justification for the potential efficacy of the achievable modification threshold." We interpret the above statement to imply use of in vitro models could be considered to support an appropriate threshold for therapeutic modification when clinical data are absent. However, mismatches or even a single	BIO asks FDA to clarify whether an in vitro comparison of a surrogate and the investigational GE product will be adequate.

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	mismatch between the target DNA and the guide RNA in different species/models can inherently alter editing efficiency of the investigational in vivo GE product.	
3. *Genome Editing Component Delivery Method*		
Line 126	In those circumstances where it is not possible to find a method to shorten nuclease expression, will the Agency clarify if pre-clinical studies with prolonged post-dose observation periods be sufficient to demonstrate acceptable risk?	BIO requests clarification on whether pre-clinical studies with prolonged post-dose observation periods would be sufficient to demonstrate acceptable risk.
Lines 148-149	"For in vivo genome modification, GE components may be delivered by viral vectors or nanoparticles." For nanoparticles as the delivery method, reference to recent final guidance will be useful.	BIO requests that FDA add reference to the Final Guidance-Drug Products, Including Biological Products, that Contain Nanomaterials for "nanoparticles".
Lines 156-157	"The potential for vector-mediated toxicity as well as pre-existing immunity to the GE component and vector should also be considered." It is unclear whether a single or multiple "GE component(s)" are being referenced in this statement.	BIO requests that FDA define GE components in this context for clarity.
B. Chemistry, Manufacturing and Controls (CMC) Recommendations		
General	The discussion of potency at lines 290-297 (in vivo) and 326-335 (ex vivo) talk about potency assessments of 1) genetic modifications and 2) downstream biologic modifications.	BIO requests that FDA establish expectations regarding when these differing assessments should be developed and available during clinical development (e.g., assay regarding genetic modification, but not biologic modifications, needed at Phase I).
1. Genome Editing Component Design		

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Lines 173-174, 181-182	It is unclear where the requested information (regarding the design and screening of GE components and optimization of their use) should go in the eCTD.	BIO requests that FDA specify where this information should be provided.
2. Genome Editing Component Manufacture and Testing		
Lines 186-196	This paragraph addresses the definition of in vivo GE components very well. However, it does not address how they are defined when used ex vivo.	BIO requests clarity on the definition of GE components when used ex vivo.
Lines 190-191	"A GE component in its final formulation for in vivo administration is generally considered a DP." A definition of a gene editing DP is provided, but not for DS.	BIO requests that FDA define GE components as DS or intermediates to enable understanding of requirements for release/stability on the components.
Lines 193-196	The language used to describe gene editing components is similar to that used to describe the lentiviral vector drug substance in the Draft Guidance titled "Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products" (Lines 113-115). In particular, in Lines 193-196 of this Guidance it is stated that: "If used to modify cells ex vivo, GE component quality is considered critical for the manufacture of the final product because without these components, the resulting cell product would not have the same pharmacological activity."	BIO requests confirmation from FDA that, in contrast to lentiviral vectors used in CAR T cell product manufacturing, which may be considered a drug substance, GE components are considered critical components with different expectations for information needed to support a BLA. BIO also requests clarification from FDA regarding the regulatory expectations around a critical component from early phase development through licensing application.
Lines 201-214	Original text: "We recommend sponsors provide lists of the reagents used during these processes and certificates of analysis. Descriptions of the following should be provided in the IND for each GE component manufacturing site:	BIO recommends the following revision: "We recommend sponsors provide lists of the reagents used during these processes and representative certificates of analysis for non-compendial materials. The quality control and quality assurance programs and procedures should be in place to prevent, detect, and correct deficiencies in the manufacturing process. Description of procedures for tracking and

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	• The quality control and quality assurance programs in place; • Procedures in place to ensure product tracking and segregation; • Procedures in place to prevent, detect and correct deficiencies in the manufacturing process; and • Procedures for shipping of the GE component from the component manufacturing site to the final product manufacturing site." Description of quality control and quality control programs and procedures should be a matter of inspection. For this reason, BIO believes this should not be provided in the IND for each GE component manufacturing site.	segregation of products and procedures for shipping of the GE component from the component manufacturing site to the final product manufacturing site should be provided in the IND for each manufacturing site. ~~Descriptions of the following should be provided in the IND for each GE component manufacturing site:~~ ~~• The quality control and quality assurance programs in place;~~ ~~• Procedures in place to ensure product tracking and segregation;~~ ~~• Procedures in place to prevent, detect and correct deficiencies in the manufacturing process; and~~ ~~• Procedures for shipping of the GE component from the component manufacturing site to the final product manufacturing site."~~
Line 203	A list of information needs to be provided for each manufacturing site of each GE component. However, Lines 186-196, do not address how GE components are defined when used ex vivo.	BIO requests clarity on the definition of GE components when used ex vivo or use a term that more closely matches with ICH terminology, for example, raw materials, source materials or intermediates.
Lines 206-211	These appear to be elements of a quality management system that usually do not need to be described in detail for an IND. We do acknowledge the Agency's expectation that this information be provided in 3.2.A.1 for gene therapy Drug Substances per the 2020 Guidance. But for ex vivo cellular products, it seems difficult to offer a similar line of sight to the vendors' QMSs for GE components used upstream from the DS.	BIO suggests removing lines 206-211. The request for shipping information from the GE vendor site to the final product manufacturing site is reasonable (line 213-214).

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Lines 213-214	"Procedures for shipping of the GE component from the component manufacturing site to the final product manufacturing site."	BIO asks the Agency to clarify if there is a specific concern beyond the need to specify the shipping condition. We would specifically request the Agency share details about their concern in this matter since there seems to be an inference of high criticality which is not apparent to all.
Lines 204-214	"Descriptions of the following should be provided in the IND for each GE component manufacturing site…..:" The requested information requires more explanation. Components (pending definition) may be custom manufactured, manufactured by or for the sponsor, or off the shelf. Depending on the material and source this information may not be available. Also depending on the material, how it is used in the process, and the criticality, this information may not be necessary. These identified controls may not be in place for non-GMP materials. Controls should be appropriate for the material, how it is used, and potential impact to the process and product. Risk assessments may be a useful tool here.	BIO asks that FDA provide additional explanation regarding the information requested.
Lines 221-224	"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."	After Phase I, it is stated that Genome Editing components must be manufactured under CGMP. We request that FDA consider the material designations and the appropriate manufacturing environment for the components.
Line 226	"We recommend each GE component be tested appropriately."	BIO requests clarification on the ways in which these recommendations apply to in vivo or ex vivo products.
Lines 226-229	"In addition to evaluating the sterility, identity, purity and functionality of each component, as applicable, additional testing, such as that for process residuals,	Regarding the need for a functional test for GE components: we note that all components may not require specific functional assay. Some components, such as RNAs, may be chemically-defined materials which should not require functional assay

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	should be included, depending on the manufacturing process."	testing to ensure quality. We therefore request the Agency to provide examples of such components. For example, a plasmid could be released by sequencing and its functionality could be proven by data on the ex-vivo gene therapy cell product.
Lines 226-227	"We recommend each GE component be tested appropriately. In addition to evaluating the sterility, identity, purity and functionality of each component, as applicable, additional testing such as..." It is unclear whether testing is relative to DS or DP. Additionally, assessment of functionality of a GE component may not be feasible in the absence of the other components necessary to achieve the desired biological effect.	Please re-phrase relative to DS and DP. We suggest adding - If not practical to test the final product for sterility/bioburden, identify, purity and functionality then in certain circumstances it may be acceptable to test the "components" for sterility, identity, and purity.
Lines 231-233	"Sponsors should also outline any in-process testing performed to ensure the quality of the components, as appropriate." Final quality attribute testing with proposed acceptance criteria should be included as well.	BIO recommends the following edit: "Sponsors should also outline any in-process and final product testing performed with intended acceptance criteria to ensure the quality of the components, as appropriate."
Line 235	"We also recommend GE components be assessed for stability." A separate raw material section to discuss testing, stability etc. that is separate from DS/DP expectations will provide clarity.	We suggest adding - The stability of the DS and/or DP should be assessed. Further, the stability of the critical raw materials (components) should be assessed to support storage conditions and duration of storage prior to further manufacture if data is not available.
Line 237	It is recommended to perform stability studies for all GE components; however, as previously noted, the	BIO requests clarity on the definition of GE components when used ex vivo.

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	Guidance does not address how GE components are defined when used ex vivo.	
Line 240	It is not clear how FDA expects "functionality" to be demonstrated e.g.: 1. by expression of GE components ex-vivo or in-vivo using the plasmid or vector as the starting material? 2. intended genome editing ex-vivo or in-vivo? 3. expression of sufficient levels of therapeutic moieties as the intended outcome of the genome editing with or without comparison to unintended (off-target) expressions? 4. therapeutic benefit from moieties expressed? Functionality can be demonstrated in a phase-appropriate manner using an assay matrix approach	Provide clarity that functionality can be demonstrated in a phase-appropriate manner using an assay matrix approach. Additional details provided in lines 290-294 may be referenced here.
3. Drug Product Manufacture and Testing		
Lines 242-249	"Drug Product Manufacture and Testing: ..... Please note that for DP intended to be sterile, but that cannot be terminally sterilized, sponsors should provide details on measures taken to ensure aseptic processing."	BIO recommends FDA reference the Guidance for Industry titled 'For the Submission of Documentation for Sterilization Process (fda.gov)'.
Lines 252-255	"To ensure that the DP meets acceptable limits for identity, potency/strength, quality and purity as defined in 21 CFR 312.23(a)(7)(iv), the DP testing plan should incorporate evaluations that address any safety concerns introduced due to the manufacturing process or identified during preclinical studies."	Regarding the need for Drug Product potency: BIO requests that the Agency provide examples of types of potency assays that may be suitable for in vivo and/or ex vivo Genome Editing products.
Lines 255-258	Off-target cleavage site testing should be included as part of DP release testing only when nonclinical studies suggest a potential risk to product safety. Incorporation of this assay at product release should be done only if a scientific, risk-based assessment suggests that these	BIO suggests the following edit: For human GE products consisting of ex vivo-modified cells, this testing should include determination of GE efficiency (e.g., the degree of ~~cleavage~~ editing at the on-target site) and, as

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	methods will provide meaningful information about product quality. The word "cleavage" in the phrase "the degree of cleavage at the on-target site" should be changed to account for other forms of GE (gene insertion, base editing, etc.).	applicable based on results of preclinical studies, specificity (e.g., the degree of cleavage at off-target sites).
Lines 258-259	"The DP should also be tested for sterility."	We request the Agency include a statement saying that rapid microbiological methods can be used. The volume of material for sterility testing should also be minimized.
Lines 268-271	The Guidance document does not provide specific recommendations related to gene editing of pluripotent stem cell seed banks as precursors to master cell banks (MCB) that will be differentiated to produce regenerative medicine cell therapy products. This is a complex topic for which Sponsors will likely require guidance in the future that may differ from the general recommendations on gene editing of somatic cells as outlined in this Guidance document. If specific recommendations around "pre-MCB" gene editing are not intended for this Guidance document, it would be helpful to state that these topics are out of scope.	BIO suggests the following edit: "As discussed, the DP may consist of GE components intended for in vivo administration or may be composed of ex vivo-modified cells. The application of gene editing involving pluripotent stem cell lines to yield precursors to MCB production for somatic cell drug products is not within the scope of this guidance document. In the following sections, we provide recommendations pertaining specifically to each of these human GE DP types:"
i. In vivo-administered Human Genome Editing Drug Products		
Lines 290-294	"When establishing potency assays for in vivo human GE DPs, we recommend that assays be developed to measure the ability of the GE components to perform the desired molecular genetic and downstream biological modifications in the target cells or tissues. We also recommend inclusion of such a potency assay in the DP stability studies."	BIO requests further guidance/examples for acceptable potency testing for in vivo GE products will be important to understand.

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	Difficulties can arise with demonstrating downstream biological modifications in target cells or tissues when a suitable bioassay may not be feasible (e.g. GE product that restores or corrects structure). Surrogate potency tests are not referenced for in vivo GE products.	
Line 290 & 326	At lines 290-297 (in vivo) and 326-335 (ex vivo) FDA discusses potency assessments of 1) genetic modifications and 2) downstream biologic modifications. These discussions do not, however, give clear guidance or expectations on when these potency assessments should be developed and available in the course of clinical development.	BIO believes that clarification about the timing of development of such potency assessments would be valuable, particularly as it relates to early phases of clinical development for GE products.
ii. Ex vivo-modified Human Genome Editing Drug Products		
Line 315	• Off-target editing frequency The relative risk of off-target GE activity is often context dependent. The potential impact of editing at off-target loci should be investigated, based on the location of the off-target sites (intragenic, exonic, etc.) and the cell type(s) to be edited.	BIO suggests adding the following bullet to the list, below "off-target editing frequency": • A description of the off-target sites and the potential impact of editing at these loci
Line 316	• Chromosomal rearrangements Inclusion of indels would align with language on line 471.	BIO suggests the following edit: • Chromosomal rearrangements and acquired indels
Line 318	Residual GE components should be monitored as part of process development studies or during engineering run production. If residual GE components are not detected in these preclinical studies, testing may not be required at product release.	BIO suggests the following edit: Residual GE components (as applicable); and

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Lines 326-335	A surrogate potency assay that quantifies on-target genome editing should be the base case recommendation rather than the exception. This is because these types of molecular assays can be reliably qualified as surrogate potency assays using relevant nonclinical models. Furthermore, this type of molecular assay will likely be less variable than a biological, cell-based functional assay, and thus can be used as a more reliable measure of product quality.	BIO suggests the following edit: "When establishing potency tests for ex vivo-modified human GE DP, we recommend ~~assays be developed that measure the properties of the cells and the intended functional outcomes of the genomic modifications resulting from GE~~ utilizing surrogate methods for assessing product potency (Ref 6). It is critical that the data provided supports a correlation between the output of the surrogate potency test and the functional outcome of the GE as assessed in relevant nonclinical studies. For example, we recommend that a surrogate potency assay~~s~~ for a genome-edited $CD34^+$ hematopoietic stem/progenitor cell product ~~measure both~~ quantify genome modification in the product using a molecular method (i.e., PCR or sequencing based method). Supporting nonclinical studies can be used to correlate this surrogate potency assay to the stem/progenitor cell activity and the functional outcome of the GE. ."
Lines 337-347	Current Draft Guidance states "Please note that if the ex vivo-modified human GE DP is an allogeneic human cell product, where a product lot is meant to treat multiple patients, additional testing and establishment of acceptance criteria may be appropriate." "For example, in addition to meeting the donor eligibility screening and testing criteria outlined in 21 CFR Part 1271, Subpart C, additional donor screening and testing may be warranted." "More extensive analysis of the GE events occurring at both on- and off-target sites, additional adventitious agent testing, establishment of stringent acceptance	BIO requests the following clarifications: 1. Please clarify the Agency's expectations related to additional donor screening and testing that is required, in addition to the testing already required as part of CFR Part 1271, Subpart C. 2. Please clarify the Agency's expectations related to "More extensive analysis of the GE events occurring at both on- and off-target sites" for ex-vivo human GE DP's.

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	criteria for the number of alloreactive lymphocytes and absence of aberrant growth (i.e., if the DP is an allogeneic T cell product) may also be warranted."	
Line 338	GE DP is an allogeneic human cell product. . ."	BIO suggests the following edit: "GE DP is an allogeneic human cell product from pluripotent or adult stem cells"
Line 347	". . . (i.e., if the DP is an allogeneic T cell product) may also be warranted. . ."	BIO suggests the following edit: "…product) and demonstrating lack of residual or contaminating pluripotent stem /progenitor cells may also be warranted…"
Lines 349-350	"Additional in-process, lot release, and characterization testing may be needed for more complex products..."	BIO suggests that FDA mention that for ex-vivo autologous therapies, the amount of product to be used for lot release testing maybe limited. The more we use for release testing, the less we can infuse back to the patient, which may impact engraftment and efficacy in some cases. Consequently, it will be important to prioritize testing for lot release. We recommend that testing considerations be risk-based as needed.
IV. CONSIDERATIONS FOR PRECLINICAL STUDIES		
Entire section	No distinction is made between ex vivo GE and in vivo GE.	BIO requests clarification on what is needed in both cases (in vivo and ex vivo GE) separately.
Entire section		We request that the Guidance acknowledge the existing limitations of animal models, especially for ex vivo gene therapies.
Lines 376-378	"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 product." For human diseases poorly recapitulated in small animal model proof-of-concept studies (e.g., due	BIO requests that FDA provide its thinking regarding situations where animal species and/or models to demonstrate a biological response to the investigational GE product or specific-specific surrogate product for proof-of-concept studies are not available. It would be helpful for the Draft Guidance to

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	to functional redundancies absent in primates), functionality of the corrected/expressed gene product may be the only feasible readout but it may be insufficient for IND based on IV.B of the Guidance.	include discussion of in vitro model systems such as explants, organoids, or iPSC-derived cell systems.
Line 388	"The safety assessment should include identification and characterization of off-target activity, chromosomal rearrangements, and their biological consequences, as feasible."	BIO recommends the following edit: "The safety assessment should include identification and characterization of off-target activity, chromosomal rearrangements, and their biological consequences to the human genome, and if derived from pluripotent stem and progenitor cells, assessment of these residual contaminants in the final DP as feasible."
Lines 400- 404	The relevance of the recommendation of biodistribution studies for the GE product for ex vivo GE cells is not clear.	BIO requests that FDA describe an option for ex vivo GE cells where these studies may not be needed.
Lines 400- 404	"We recommend biodistribution studies be conducted to characterize the distribution, persistence, and clearance of the GE product, as well as any expressed GE components in vivo. Evaluation of the biodistribution profile of the edited genetic sequence and persistence of the gene product may provide additional information on the extent of editing activity in target and non-target tissues."	We request the Agency acknowledge that biodistribution can be conducted within the context of pharmacology and toxicology studies, consistent with the current draft of ICH S12.
Lines 400-401	"We recommend biodistribution studies be conducted to characterize the distribution, persistence, and clearance of the GE product, as well as any expressed GE components in vivo." "Clearance" is not applicable to the expressed GE components which would be considered as biomarker not the drug product.	Please define "any expressed GE components". We suggest revising as - We recommend biodistribution studies be conducted to characterize the distribution, persistence, and clearance of the GE product, as well as the distribution and persistence of any expressed GE components in vivo."

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A. Product Evaluated in Preclinical Studies		
Line 411	"The investigational human GE product should be evaluated in the definitive POC and safety studies, when feasible." Given manufacturing volumes and potentially limited stability information, it is not practical to use the same material in safety studies and clinical studies.	It would be helpful if the agency provided examples of stable long term expression studies or clearance of GE components, both in vitro and in vivo. We also suggest revising as – "Materials representative of the investigational human GE product should be evaluated..."
Lines 414-419	Does the Agency believe the surrogate GE data is acceptable for efficacy and/or safety evaluations?	BIO requests that FDA provide guidance on how to use surrogate data.
Lines 423-425	"For ex vivo-modified GE products, the clinical cell source should be used for the definitive preclinical studies." - This may be challenging for ex vivo GE human cells administered into animals.	To allow for alternatives when no good animal models are available and encourage sponsors to take advantage of opportunities for reducing, refining and replacing animal use during the process of designing a preclinical development program, we recommend FDA replace "clinical cell source" with "target human cell" to allow healthy volunteer samples.
B. Assessment of Activity		
Lines 432-446		Given the central role of the dose-response relationship in establishing treatment-related effects, BIO recommends adding a bullet point to this list stating: "The dose-response relationship of the GE component and the intended edit".
Line 436	"Specificity and efficacy of editing in target and non-target cells".	BIO recommends the following edit: "Specificity and efficacy of editing in target and non-target cells that will depend on the biodistribution of the GE product."
Line 444	Durability is a 'relative' measure when performed preclinically, limited by the length of the study. In vitro studies by nature are short (days to weeks) and in vivo	BIO requests clarification on the minimum requirements for assessing durability. If only an in vitro model exists, is durability of a few days sufficient? The reader would benefit

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	these can be short (weeks) or long (months. In either case the preclinical work will not predict the long-term durability of edits beyond the limits of the models and true durability will only be informed by clinical experience.	from clarification or recognition that durability preclinically may not be feasible to assess potential clinical durability. We suggest revising as – "Durability of the genomic modification and resulting biological response depending on cell type and function; and…"
Line 446	It is unclear what is meant by assessing "Effects of 'genetic variation' on editing activity across the target population". What are the expectations for how to assess this preclinically?	BIO requests the following clarification: is there an expectation to obtain samples from the target patient population for in vitro assessment of variation of editing activity? If this was an in vivo delivery of a GE therapeutic injected into the eye or brain, would eye or brain samples from the target patient population need to be tested 'a priori'? This might be prohibitive for some diseases and therapeutics but may be simpler for something like a (CAR) T. As this Guidance would be applicable to any GE therapy the language may need to be opened and the addition of "If feasible" be added to the sentence.
Line 446	"Effects of genetic variation on editing activity across the target population."	BIO suggests that effects of genetic variation on "off target" editing should also be mentioned in the Guidance on the assessment of safety (section IV- C). An example here would be useful.
C. Assessment of Safety		
Lines 456-458	Many methods of variable sensitivity are currently used to determine off-target effects.	BIO requests that FDA clarify how whole genome sequencing and next generation sequencing technologies can or should be used to support this characterization.
Lines 456-458	"The use of multiple orthogonal methods (e.g., in silico, biochemical, cellular-based assays) that include an	BIO suggests the following edit:

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	unbiased genome-wide analysis is recommended for identification of potential off-target sites." All methods used for the detection of off-targets have an inherent bias due to the technology. BIO suggests rephrasing the sentence to make clear that the goal is reduce bias.	"The use of multiple orthogonal methods (e.g., in silico, biochemical, cellular-based assays) that include an unbiased genome-wide analysis to reduce bias is recommended for identification of potential off-target sites."
Lines 458-460	"When possible, the analysis should be performed using the target human cell type(s) from multiple donors."	BIO suggests the following edit: "When possible, the analysis should be performed using the target human cell type(s) from multiple donors with appropriate justification." It would be helpful for the agency to provide examples of target and non-target human cell types for specificity of GE for on and off-target editing capabilities
Lines 471-472	"Assessment of genomic integrity, including chromosomal rearrangements, large insertions or deletions, integration of exogenous DNA, and potential oncogenicity or insertional mutagenesis." Assessments may be warranted on a case-by-case basis as not all assessments recommended may in scope or appropriate.	BIO suggests the following edit: Consideration of risk-benefit for each GE product should determine the extent of GE risk identification/characterization needed at the time of the IND. BIO suggests the following edit: "In vitro assessment in human donor cells of genomic integrity, including chromosomal rearrangements, large insertions or deletions, integration of exogenous DNA, and potential oncogenicity or insertional mutagenesis."

Biotechnology Innovation Organization
1201 New York Avenue, NW, Suite 1300
Washington, DC 20005
202-962-9200

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		BIO also requests that FDA include examples of assessment assays (i.e., sequencing of targeted cells, chromosomal spreads, karyotyping).
Lines 471-474	"Assessment of genomic integrity, including chromosomal rearrangements, large insertions or deletions, integration of exogenous DNA, and potential oncogenicity or insertional mutagenesis. For ex vivo-modified cells, this may include assessment for clonal expansion and/or unregulated proliferation."	BIO requests additional guidance on expectations related to in vitro and in vivo testing strategies.
Line 472-473	"…large insertions or deletions…"	BIO suggests the following edit: "…large insertions or deletions or those associated with tumor suppressor or oncogenes…,"
Line 479	Bullet misses the distinction between in vivo and ex vivo GE. Guidance reference needed.	BIO suggests replacing the bullet "Immunogenicity of the GE components and gene product expressed" with the following: "Immunogenicity: • For in vivo GE products: immunogenicity of the GE components and gene product expressed. • For ex vivo GE products: Immunogenicity of the GE product. Exclusion of immunogenicity of GE components should be justified in a risk assessment " To ensure the reader understands the composition of an appropriate immunogenicity assessment we recommend referring to the FDA's Guidance for Industry Immunogenicity Assessment for Therapeutic Protein Products, 2014.

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Line 481	Are kinetics of editing required for ex-vivo modified cells? Is this more relevant to an in vivo delivered editing product?	As this Guidance would be applicable to any GE therapy, BIO suggests the addition of "If delivered directly in vivo"
Line 484	"Assessment of viability and any selective survival advantage of the edited cells…"	BIO recommends the following edit: "Assessment of viability and any selective survival advantage of the edited human cells.."
Line 489	"Evaluation of the potential for inadvertent germline modification." We interpret the above to be necessary depending on biodistribution of the GE product and the patient population.	BIO recommends the following edit: "Evaluation of the potential for inadvertent germline modification if necessary."
Line 489	Potential addition to the list in Sec. IV.C	BIO suggests the following addition: "If derived from pluripotent stem and progenitor cells, the final DP should be evaluated for the potential of contaminating residual stem progenitor cells."
V. CONSIDERATIONS FOR CLINICAL STUDIES		
Entire section	No distinction is made between ex vivo GE and in vivo GE.	BIO requests clarification from FDA on what is needed in both cases (in vivo and ex vivo GE) separately.
Line 500	Duration of long-term follow-up not specified; however, it is specified in Line 588 and should be cross referenced	BIO suggests a cross reference to Line 588.

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Lines 500-501	"Additionally, long term follow-up is recommended for clinical trial subjects receiving human GE products for evaluation of clinical safety." Although long-term follow up (LTFU) in clinical development is primarily designed to identify and mitigate risks to patients receiving a GE product, LTFU also allows for assessment of other elements such as durability of effect but could be discretionary. This maintains constancy with the FDA LTFU Guidance for human gene therapy products.	We suggest revising as - Additionally, long term follow-up is recommended for clinical trial subjects receiving human GE products for evaluation of clinical safety. Inclusion of assessments of long-term efficacy and durability of clinical effect may also be considered at the sponsor's discretion."
Line 504	Reference is made to ref 8 (Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products; Guidance for Industry, June 2015).	BIO requests a greater focus on the specific requirements for GE products.
A. Study Population		
Lines 513-515	"[F]irst-in-human trials involving such products generally should be designed to enroll only subjects for whom no other treatment options are available or acceptable. Factors to consider in determining the study population include… The availability and effectiveness of alternative therapeutic options for the patient population…" Safety and tolerability of available therapies should also be considered.	BIO suggests the following edit: "The availability, safety, tolerability, and effectiveness of alternative therapeutic options for the patient population…"
Line 513-515	The language used in the Draft Guidance document appears very restrictive with respect to clinical enrollment for GE trials.	BIO suggests editing the text to read: "Therefore, first-in-human trials involving such products generally should be designed to enroll preferentially ~~only~~

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		subjects for whom no other treatment options are available or acceptable or adequate."
Lines 525-526	"Subjects with severe or advanced disease may be more willing to accept the risks of an investigational human GE product."	BIO suggests the following edit: "Subjects with severe or advanced disease may be more willing to accept the potential risks of an investigational human GE product."
C. Treatment Plan		
Lines 547-553	"We recommend that any risk(s) anticipated in association with the GE product be mitigated by staggered subject enrollment, with a specified time interval between product administration to sequential subjects within and between cohorts." Staggering of enrollment and dosing applies to early phase studies and therefore we suggest this language be updated to reflect that.	BIO requests that FDA provide additional clarification on the scope of the recommendations on staggered enrolment. As written, it suggests a blanket approach that would apply to FTIH/initial cohorts as well as later clinical trial stages. BIO does not expect that this is a blanket recommendation and additional clarification on this issue would be helpful. BIO also suggests editing the text to read: "…In early-phase studies, we recommend that any risk(s) anticipated in association with the GE product be mitigated by staggered subject enrollment, with a specified time interval between product administration to sequential subjects within and between dose cohorts."
Lines 552-553	Clarity is needed regarding duration of the staggering interval. We interpret the recommendation as the interval will depend on the duration of activity of the human GE enzyme (not the human GE product); as written currently, the interval would be highly protracted and raise significant challenge to study conduct.	BIO requests that FDA expand upon the meaning of this sentence, "The staggering interval should also take into account the expected duration of activity of the human GE product." and consider the following edit: "The staggering interval should also take into account the expected duration of activity of the human GE ~~product~~ enzyme."

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D. Monitoring and Follow-Up		
a. Assessment of Product-Related Adverse Events		
Lines 568-570	"Specific consideration should be given for adequate monitoring of any off-target editing and adequate assessment of the outcomes of unintended consequences of on- and off-target editing." – relevance for ex vivo GE cells	BIO requests that FDA specify that this may not be needed for ex vivo GE cells when justified.
Lines 568-574	"Specific consideration should be given for adequate monitoring of any off-target editing and adequate assessment of the outcomes of unintended consequence of on- and off-target editing. Additional monitoring should capture AEs related to aberrant cellular proliferation, immunogenicity, and tumorigenicity. Such AEs should be anticipated from pre-clinical studies, if possible, and toxicity grading and management strategy should be outlined in the clinical protocol."	BIO suggests the following edit: "Specific consideration should be given for adequate monitoring of any off-target editing and adequate assessment of the outcomes of unintended consequence of on- and off-target editing, anticipated from preclinical studies. ~~Additional monitoring should capture AEs related to aberrant cellular proliferation, immunogenicity, and tumorigenicity.~~ Such AEs should include immunogenicity, cellular proliferation, and potential tumorigenicity. If possible, toxicity grading and management strategy should be outlined in the clinical protocol."
b. Long Term Follow-Up		
Lines 587-590	"Therefore, we recommend that sponsors conduct LTFU at least 15 years after product administration, as outlined in FDA's Long Term Follow-Up After Administration of Human Gene Therapy; "Guidance for Industry (Ref. 10)." – for ex vivo GE cells such a long follow-up may not be needed	BIO requests that FDA specify the needed follow-up for the different options ex-vivo GE or in vivo GE or give the option to deviate from this requirement and specify the requirements.
E. Study Endpoints		
Lines 594-596	Efficacy endpoints should represent clinical benefit. For traditional approval, the endpoint should reflect direct clinical benefit or a validated surrogate endpoint. For	BIO suggests editing the text in this section to read:

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	accelerated approval, a reasonably likely surrogate can be used. There is no reason for GE products not to benefit from accelerated approval mechanisms.	"We recommend that study endpoints be based on the proposed indication. For efficacy studies aiming for traditional approval, the primary endpoint should also reflect a clinically meaningful effect of the GE product or an effect on a validated surrogate endpoint. For accelerated approval, substantial evidence should be provided on an effect on a reasonably likely surrogate endpoint (source: BEST (Biomarkers, Endpoints and Other Tools) Resource." BIO also requests that FDA please consider adding a section on considerations for scientifically justified and clinically relevant surrogate endpoints in diseases that are slow progressing.