November 14, 2018

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

Re: Docket No. FDA-2018-D-2173: Long Term Follow-Up After Administration of Human Gene Therapy Products

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments regarding the draft guidance titled "Long Term Follow-Up After Administration of Human Gene Therapy Products".

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 members are involved in the research and development of innovative healthcare, agricultural, industrial, and environmental biotechnology products.

BIO applauds the FDA on the work done to develop this Draft Guidance along with its companion documents on the topic of Gene Therapies. The Draft Guidance is reflective of the Agency's experience gathered over the past decade on the evaluation of safety of gene therapy products. This important Draft Guidance is well written and provides instrumental recommendations on how to determine and develop long term follow-up after administration of human gene therapy products. Below we have provided general comments as well as detailed comments in the table attached.

General Comments

- The Draft Guidance appropriately describes the primary rationale of gene therapy (GT) product development being the offering of therapeutic effect through permanent or long-acting changes in the human body. However, the document assumes that long-term persistence of the GT product increases their safety risk, which BIO believes overstates the concern. The safety risk, whether short-term or long-term, will be different between the carrier (e.g., vector) or the protein encoded by the transgene.

- BIO believes the Draft Guidance should recognize some of the challenges associated with viral vector persistence and safety risk. With respect to the persistence of the

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viral vector in GT products, it should be noted that if the viral vector does not persist then the efficacy may wane. In such circumstances it may be necessary to re-administer the viral vector. This comes with the additional risk of immune-mediated toxicities (as described in the Human Gene Editing for Retinal Disorder Draft Guidance). Since repeated administration of the GT product that has limited persistence may result in a prolonged duration of exposure to a GT product, it does not seem appropriate to emphasize the persistence of the GT product after a single administration. With respect to safety risk, there may be safety concerns related to the presence of the viral vector, whether the vector contains a genome (i.e., full capsids) or does not contain a genome (i.e., empty capsids) through immune-mediated mechanisms. Since GT products often utilize naturally occurring viruses (e.g., AAV), it is possible that safety concerns can arise as a result of an infection with a naturally occurring viral infection. It is likely that the long-term safety risks of the presence of the GT viral vector/capsid are no greater than the safety risks of a naturally occurring infection with the source vector.

- In general, BIO welcomes the updated change in the Draft Guidance on LTFU periods of 5 to 15 year follow up, which affords flexibility upon clinical experience and are based on product type. BIO notes that LTFU periods can present unique logistical challenges for sponsors. For example, patients can choose not to participate in the LTFU, drop out of a program, or relocate geographically without giving notice to the gene therapy manufacturer. Similar concerns exist for the health professionals treating patients, for example, a study investigator or a patient's personal physician may retire from practice during a 15-year period. BIO encourages FDA to work along with Sponsors to explore and develop best practices to ensure that the maximum number of patients can be effectively tracked and engaged over the course of lengthy follow-up timeframes.

- The Draft Guidance discusses the conduct of the biodistribution study for the purpose of designing the LTFU study. However, the Draft Guidance on Human Gene Therapy for Retinal Disorders indicates that the biodistribution study is conducted in order to design the toxicology study. Additionally, the biodistribution study is often taken into consideration as part of the environmental impact assessment. Acknowledgement of all uses of the biodistribution study should be included in this and other relevant Draft Guidances. In addition, BIO believes the Agency should consider partner with multiple stakeholders to evaluate key biodistribution questions including whether a quantitative approach is required, if studies using *in vivo* imaging may be acceptable, or whether studies evaluating the distribution of the viral vector without a transgene (i.e., evaluating the distribution of empty capsids) may be acceptable.

- BIO encourages the Agency to continue its initiative to promote global harmonization across multilateral organization in this field. As new GT are developed, harmonization become increasingly critical to support efficient development of safe and effective therapies for patients. Harmonization efforts should include organizations such as the International Conference on Harmonisation (ICH), or the International Pharmaceutical Regulators Programme (IPRP).

BIO appreciates this opportunity to submit comments regarding FDA's draft guidance titled "Long Term Follow-Up After Administration of Human Gene Therapy Products". We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Sesquile Ramon, Ph.D.
Director, Science & Regulatory Affairs
Biotechnology Innovation Organization

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
General		
	The guidance is written with the assumption that the delivery system for GT products is a viral vector. As non-viral delivery systems (e.g., lipid nanoparticles) are developed, some of the topics in this guidance may not be applicable.	BIO suggest the FDA consider and discuss how this Draft Guidance would apply to non-viral delivery systems.
I. INTRODUCTION		
Line 18	Long-term follow up studies may not necessarily mean "long-term follow-up observational studies" in case of study-related assessments planned.	BIO suggests the following change: "(…) recommendation regarding the design of long-term follow-up ~~observational~~ studies", and also consider accordingly for Section D.
II. SCOPE		
Lines 58 – 65	It is unclear which modalities affecting gene expression, if any, are out of scope (e.g., siRNAs) of this Draft Guidance.	FDA should consider providing further clarity on which modalities affecting gene expression, if any, are out of scope.
III. BACKGROUND		
A. Potential Risks of Delayed Adverse Events Following Exposure to Human Gene Therapy Products		
Lines 76 – 83 and Lines 523 - 525	There seems to be no differentiation between risks associated with vectors derived from gammaretrovirus and lentivirus while there is a body of literature indicating that lentiviral vectors appear to be safer.	BIO believes the risks associated with each vector should be different for new generations lentiviral vectors
Lines 96 – 99	The Draft Guidance suggests that there is a concern for autoimmune-like reactions (to self-antigen) upon prolonged exposure to CART cells. Nevertheless, CART-mediated effects on normal tissues are typically observed rapidly and this theoretical risk may not justify, in of itself, a LTFU.	BIO suggest the FDA consider using a different example.
IV. PRECLINICAL DATA USED FOR ASSESSMENT OF DELAYED RISKS IN GENE THERAPY CLINICAL TRIALS		

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General	Sponsors would expect to find the most recent recommendations for preclinical study conduct in the existing preclinical guidance. It is unlikely that preclinical experts would be consulting what appears to be a clinical or safety focused guidance.	FDA should consider updating their existing guidance on Preclinical Assessment of Investigational Cellular and Gene and refer readers to this current document.
Lines 210-213	The definition of vector class is unclear. Vector class could be defined as broadly as AAV vectors or more narrowly as AAV-based vectors. It is also uncertain as to whether the previous experience must be generated by the Sponsor or whether information that is in the public domain (e.g., in literature publications or SBAs) can be used	BIO suggest the Agency clarify what vector class means and provide further thinking regarding what other acceptable sources of data would be (e.g., real world data).
Lines 214-218	Section IV.B describes the design and the conduct of biodistribution studies. Inherent in this statement is the assumption that the biodistribution species as is used for the toxicology study. This may not be the true. For example, Sponsors are encouraged in the Draft Guidance for Human Gene Therapy for Retinal Disorders to perform toxicology studies in larger animals (e.g., primates). Conducting a biodistribution study in the primate could be regarded as being unethical since a large number of animals (3-5 per timepoint; both genders) would be required for the conduct of such a study and it is likely that a greater number of animals would be used in the conduct of the biodistribution study compared to the number used in the toxicology study of the GT vector is determined in the same BIO believes that persistence of the GT product or continued expression of the protein encoded by the transgene is not, in and of itself, a safety concern absent of any overt safety signals. This concept is similar to that accepted regarding the development of anti-drug antibodies (ADA) – the presence of ADA isn't itself a safety signal although there is the theoretical possibility of safety concerns arising from the generation of an ADA response.	BIO suggest deletion of following language: "However, for novel products such information may not be available or pertinent, or may be limited, in which case data from well-designed preclinical studies ~~(as described in section IV.B of this document)~~ should be used in assessing the risk of delayed adverse events."
Line 254	As previously defined, the GT product consists of the vector and transgene. Therefore, this question can be read as only relating to the presence of the	FDA should clarify whether this statement applies to the administered GT

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	vector and not the expression of the transgene that gives rise to the protein.	or the expression of the protein (or both).
Lines 260-275	There are several points in this text that would benefit from clarification. These include: *"relevant species"* is an ambiguous terminology as it is unclear what determines the relevance of a specie. *"threshold level"* is only used in this paragraph and is not used in Section IV.B. If the threshold level is 50 copies/µg DNA, then stating that level in this section would add clarity. It is unclear how many timepoints would suffice for *"several timepoints"*. Clarity on this point would be helpful. *"Downward trend"* It is unclear what constitutes a downward trend. Since it is not possible to determine a priori how many timepoints will be required to show a downward trend that would be acceptable to the FDA, the Sponsor may include a large number of timepoints in order to be able to show a downward trend. This would be counter to the objectives of the 3Rs which are described in this draft Guidance.	BIO suggest the agency provide further clarity the following terms: relevant specie, threshold level, several timepoints, and Downward trend.
Lines 297-302	This section provides sponsors the opportunity to leverage existing data on similar vectors to justify LTFU assessment or not. BIO supports the Agency on this approach and suggest it is made into its own section as it would elevate its value.	BIO suggest to break out language to an independent section. In addition, BIO request further clarity as to whether a Sponsor could leverage data from similar vectors to support not performing preclinical biodistribution studies as well.
A. Criteria to Assess Potential Delayed Risks of Gene Therapy Products		
B. Considerations for Preclinical Study Design to Assess Biodistribution and Persistence of Gene Therapy Product		
Lines 358-373	The first part of this paragraph relates to the distribution of the vector. However, at Line 367 the concept that "the animal species be biologically	BIO suggested edit: "If possible and applicable, we recommend that the

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	responsive to the specific transgene of interest." This may implies that the biodistribution study may need to be conducted in an efficacy species or in a large animal species (e.g. primate). "Biologically responsive to the transgene of interest" can be interpreted as meaning that the protein has a pharmacological effect in that species, although the statement does not mention the protein encoded by the transgene. The use of the efficacy species would better represent the target clinical population since efficacy studies are often conducted in animals in which the gene of interest has been knocked-out. In other species, the transgene would be expressed on top of endogenous levels of the protein encoded by the transgene and hence the levels of the protein may be "supratherapeutic".	studies employ an animal species that permits vector transduction and/or vector replication ~~and that the animal species be biologically responsive to the specific transgene of interest~~ or to therapeutic components in the product" (e.g., for products that may not contain transgenes and only genome editing components)."
Lines 375-376	It is unclear if a biodistribution study also be performed in the context of a pharmacology study in an animal model of disease.	BIO suggest FDA clarify if a biodistribution study can also be performed as a component of a pharmacology study
Line 379	Guidance should be provided to collect secreta/excreta in the relevant nonclinical model to assess risks to close contacts and the environment from patients over time. This will inform any special measures considered to protect close contacts, and the design of patient clearance studies. Taking these assessments over time will inform questions of latency (and risk of reactivation in the case of latent viral vectors) and the timeframe over which protective measures should be considered for patients and close-contacts. The risk of genetic material transfer to the fetus during pregnancy should be considered to inform pregnancy labeling and patient discussions. Conduct of a study to evaluate maternal-fetal transfer may be useful to inform this risk if appropriate and feasible.	FDA should provide guidance on collection of secreta/excreta in the relevant nonclinical model to assess risk to close contacts and the environment from patients over time. FDA should also provide guidance on a nonclinical study to evaluate the risk of genetic material transfer to the fetus during pregnancy and subsequently to inform pregnancy labeling.
Lines 381-383	BIO is unaware of examples where the components of a GT formulation have impacted the biodistribution of a viral-based GT. If examples exist, it	FDA should consider providing examples

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	would be helpful to the Sponsor if these examples could be added to the Guidance.	
Lines 381-383	Semantically, there is no such thing as a "final formulation proposed for the clinical study" since at the time of the IND the formulation will have been fixed (i.e., it isn't proposed). Additionally, the statement mentions "final formulation". As written, this statement could imply that each time the formulation is changed that a biodistribution study (and potentially a toxicology study) is required. We assume that this is not the FDA's intent and that a maximum of one biodistribution study per GT product is required unless there are clear and unequivocal reasons to conduct additional studies.	BIO proposed change: "Use the GT product in the final formulation that is identical, or highly similar, to the formulation that will be used in the initial clinical trial. Subsequent changes to the components of the formulation do not require the conduct of an additional biodistribution study unless there is clear scientific rationale for the change to the formulation to have an impact on the distribution of the vector. ~~proposed for the clinical study because changes in the final formulation may alter biodistribution pattern~~."
Line 384	The inclusion of both genders to assess distribution of the GT to the gonads is acknowledged. However, there is no scientific rationale for there to be a gender-related difference in the distribution of a viral vector to the tissues listed in this draft guidance. Therefore, BIO proposes that the default would be to include both genders in the study but to only analyze the full tissue set from one gender.	BIO proposed change: "Use both genders or justify the use of a single gender. Analysis of the full tissue set from one gender and only the gonads from the other gender may be an acceptable approach."
Lines 388-390	It is unclear how the animal's age and physiologic condition can change the GT distribution/persistence. BIO believes the scientific justification to this approach might be limited.	BIO suggest deleting this statement
Lines 393-397	The benefit of evaluating multiple dose levels in the biodistribution study needs to be weighed against the additional animal usage (i.e., inconsistent with the 3Rs), the impact on the Sponsor's ability to bring a GT into the clinic (time and opportunity cost) and add to the cost of drug development for GT products.	Proposed change: "Assess GT product biodistribution in a vehicle control group and a group of animals that receives the maximum feasible dose (MFD) or clinically relevant dose (defined in section

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	As currently written, this section could imply that a control group of animals is required at each and every timepoint. The control group of animals provides a set of tissues that can be used to show that the assay used in the study does not generate false-positive results and that there are no interfering substances that would quench the response in the assay (false-negative results). Animals collected at one timepoint (selected at the Sponsor's discretion) is sufficient for this purpose and would be consistent with the 3Rs. The Sponsor can also justify the use of un-injected animals instead of dosing animals with the dose vehicle	VIII). Only one timepoint is required for the control animals ~~Studies at additional dose levels might provide information on dose-dependent effects of your product."~~
Lines 398-405	The document suggests that a standalone biodistribution study would need to include all the typical endpoints of a standard toxicology study, which subtracts from the benefits of performing a standalone study. It is worth noting that, especially in rodents, tissues often cannot be used both for DNA/RNA harvest as well as histopathology given tissue size limitations.	BIO suggest to allow sponsors to obtain only biodistribution data in standalone biodistribution studies, and allow extrapolations between studies and species for implications on safety relevance.
Line 412	FDA should consider a precaution to perfuse the animal after the sacrifice to both preserve the integrity of the samples and to remove residual blood in tissues that may confound the analysis.	Suggest to add to Section 2 Tissue Collection and Analysis the following: "Perfuse the animal after the sacrifice to both preserve the integrity of the samples and to remove residual blood in tissues that may confound the analysis".
Lines 422-429	In-life conduct of the biodistribution study should not have to be GLP-compliant but should follow the principles of GLP. This will allow for the conduct of such studies in animal models of disease that may only be available in academic institutes (i.e., the study may not be performed in a GLP-compliant facility). Additionally, the bioanalytical methodology should be "fit for purpose" rather than having to be validated and compliant with the FDA's guidance on Bioanalytical Method Validation.	BIO suggest clarification on the FDA's requirements for GLP compliance is provided.

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	It should be noted that the methodology used for the detection of the GT product by PCR may differ slightly between animal and human tissues due to the presence of different interfering substances in the tissues of these species.	
Lines 422-426	Although human tissues are mentioned, there is no mention of human secretions/excreta which would be collected in order to assess the "shedding" of the GT product. The concept of shedding is not clearly addressed in this draft guidance.	BIO suggest the FDA provide clarity on this issue.
Lines 426-428	We welcome the opportunity to have an open and continuous discussion with the Agency on this, and other, topics throughout the development of GT products, especially prior to the initiation of the animal biodistribution and toxicology studies. The flexibility of the FDA regarding these discussions outside of the context of an IMPACT or pre-IND meeting is greatly appreciated.	No proposed change.
Lines 431-433	This LOQ has been described in previous guidances, although the origin and relevance of this "threshold" is uncertain. It would be informative to Sponsors to understand how this "threshold" was determined. The PCR results are reported as copies/µg DNA. In some cases (e.g., ocular tissues such as vitreous humor) the tissue may contain very low levels of DNA and hence the expression of the number of copies relative to DNA content may be misleading. It should be noted that techniques to distinguish between genomic DNA and non-genomic DNA (e.g. the GT product) are not widely available, if available at all. The measurement of genomic DNA may be highly accurate and precise which will reduce the information that can be obtained from the study.	It would be informative to Sponsors to understand how this "threshold" was determined.
Line 434	The text could be interpreted as meaning that 3 samples are required from each tissue collected from each animal (i.e., 15 samples/gender/timepoint) or could be interpreted as meaning that a minimum of 3 samples are required per timepoint.	BIO suggest FDA provide clarification.

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	For some tissues, and/or species, it may not be feasible to harvest a sufficient amount of DNA from each tissue collected from an individual animal (i.e. DNA may need to be pooled across animals). Guidance on the acceptability of this approach would be appreciated.	
Line 444	Based on the Draft Guidance, the duration of the study could be open ended if the intent was to determine the persistence of the GT product. BIO proposes that FDA consider providing some parameters, for example the duration of the biodistribution study could be no longer than 3 months with timepoints at an early time (e.g., 1 week), a mid-time (e.g., 1 month) and at a later timepoint (e.g. 3 months). Although this design may not, in and of itself, define the duration of persistence, this information coupled with data from other preclinical (efficacy and toxicology) studies may provide information to design the Clinical long-term follow-up study.	BIO suggest FDA provide additional information regarding during od the biodistribution study
Line 444	In some tissues the concentrations of GT product may be close to the LOQ in the majority, but not all, of the animals and the concentrations may be highly variable. The values that are < LOQ could be handled as "missing", "0" or "1/2 LOQ". These approaches would yield different mean or median results. In addition to the calculation of the median or mean value, the calculation of the number (%) of animals with detectable vector would be of interest.	BIO requests the FDA to provide guidance on their requirements for how the data should be analyzed.
V. RECOMMENDATIONS FOR PROTOCOLS FOR LONG TERM FOLLOW-UP 560 OBSERVATIONS: CLINICAL CONSIDERATIONS		
A. Goals of the Long Term Follow-up Observations		
B. Clinical Trial Populations for Long Term Follow-up Observations		
Line 588-592	The Draft Guidance is unclear as to how to best design a follow-up in a patient population with multiple co-morbidities as potential confounding factor of the long-term follow up, and ways to mitigate the potential reduced utility in assessing long-term risks (e.g. by comparison to disease registry data?)	The FDA should consider providing additional guidance on this topic.
C. Assay Duration of Long Term Follow-up Observations		

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Lines 617-624	Information in this section should align with data presented in Table 1.	FDA should consider aligning with data presented in Table 1, and herpes virus should be added to Line 620.
Lines 620-621	Irrespective of whether sequences are integrated into the host genome, if the manufacturer can demonstrate (non-clinically or clinically), that the modified cells do not persist, then LTFU should not be absolutely required, or at least the follow up period should be limited to a timepoint that "comfortably" exceeds (e.g., 2X) the persistence of the modified cells (See V.D.6 regarding recommended guidance to test until sequences become undetectable).	BIO suggested text: **"**Up to 15 years for integrating vectors such as gammaretroviral and lentiviral vectors and transposon elements. A follow-up of up to 15 years after administration may be expected; however, a shorter duration of follow-up may be considered based on the specifics of the construct and characteristics of the product."
Line 634	To date, no cases of malignant transformation have been reported following infusion of genetically modified T cells. A decade-long review of retroviral CAR T cell safety and function revealed no evidence of vector-induced immortalization of cells, no evidence of clonal expansion, and no enrichment for integration sites near genes implicated in growth control or transformation [Scholler et al. (2012) Science Translational Medicine, 4:132ra53]. Given the absence of emergent risk to date with some of these technologies, it is unclear how much data will be required to mitigate the need for long-term follow-up. To what degree of risk are we trying to achieve with these measures? Will each of these technologies be indefinitely required to conform to this guidance, or will the FDA be satisfied with a low risk-based argument (e.g., lower than 1 case in 10,000 patient years of use)? Given that multiple different therapies may be based on a common transduction method, FDA should consider the aggregated risk across these products for a pooled risk-based assessment, or assessment based on an aggregated assessment across the industry for a particular transduction	FDA should provide additional guidance on the data needed to mitigate the need or modify the duration of the LTFU observation study.

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	method (e.g., lentiviral transduction) to be recognized for informing a risk-based assessment.	
D. Elements of Long Term Follow-up Observations		
Lines 651-690	It is unclear if the study investigator needs to remain involved with a patient for a minimum of five and a maximum of fifteen years in. Acknowledging the text in lines 713-722, the guidance might benefit from further clarification of specific responsibilities and roles (e.g., patient education) by the different parties (e.g., HCP).	The Draft Guidance should provide clarity regarding responsible parties for LTFU observations.
Lines 658-661	The use of template to facilitate collection of case histories is suggested.	FDA should consider providing a template.
Lines 669-690	This section of the guidance provides a list of issues the investigators should monitor. It does not include infection which was referenced earlier in the document as being of specific concern for MVGT.	BIO suggest FDA provide clarity on whether infection should be monitored
Lines 677-682	All protocols already have a method for investigators to record the emergence of new clinical disorders. It is unclear why neurologic, rheumotologic, autoimmune, and hemotologic disorders are specficailly included here. BIO believes that depending on ex-vivo vs in-vivo administration of the GT, as well as distribution of the GT and/or GT product, it may be anticipated that the GT does not increase the risk of one or more of these categories of disorders.	Clarification whether active, directed interrogation/ investigation for neurologic and rheumotologic and autoimmune and hematologic disorders is recommended for all LTFUs.
Line 676	The draft guidance discusses investigators to record the emergence of new clinical conditions, including but not limited to: "new incidence or exacerbation of a pre-existing neurologic disorder", "a "new incidence of a hematologic disorder" and others.	BIO asks Agency to provide definition/specification of "neurologic disorder" and "hematologic disorder".
Line 682	"incidence of a hematologic disorder" in a LTFU study is too vague. Suggest more clarification	BIO suggested change: "incidence of a ~~hematologic disorder~~ malignant hematologic disorder, for example, MDS,

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		AML/ALL/CML/CLL, lymphoma, or plasma cell dyscrasia."
Lines 692-703	The draft guidance seems to indicate that the first 5 years of LTFU should be a clinical study, and years 6-15 may be accomplished by a registry. In some cases, a 15-year registry could potentially be appropriate.	BIO asks the Agency to clarify circumstances under which a registry may be acceptable for LTFU.
Lines 712-721	BIO suggest the Agecnny provide further clarity as to what is meant by "the LTFU protocol identify suitable HCPs". It is unclear if this means the protocol should identify by role relative to the subject, e.g.. "the subject's primary healthcare provider," or "the subject's primary hematologist". In addition, it si unclear what it means to "arrange to have such individuals notified to provide prompt reports of adverse events to investigators", as it could be interpreted that the contact information for these HCPs be entered into the TMF and that the Sponsor contact them and instruct them on AE reporting.	BIO suggest further clarification be provided on recommendations/expectations around which HCPs should be identified and how they should be involved considering they are not investigators.
Line 734 & 738	Patients may also be non-adults or cognitively impaired	BIO suggest adding: "study subjects, relatives, or guardians"
Lines 744-763	It is unclear what the expectations for transitioning to marketed status. For example, it is unclear if adverse events be reported to both the IND and BLA going forward, or if the BLA submissions would replace IND submissions.	BIO suggest clarifying the expectations for transitioning to marketed status.
Line 744	It would appear that the information being requested in the proposed LTFU report section of the IND Annual Report/DSRU is duplicative of information that would already be provided (i.e., preclinical information, clinical information).	FDA should consider whether a separate "report section" is needed or whether existing IND/DSUR subsections (preclinical and clinical updates) could provide the information of interest.
Line 794	Recommendation for annual physical exams (or more frequently) may not be practical for all patients (e.g., patient distance from the medical center)	BIO recommends that physical exam should be recommended if practical, but allow for yearly contact by telephone if needed.

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Line 804	Observations should be perform on a semi-annual or quarterly basis, or as clinically indicated.	BIO suggested change: "(…) and there is a reasonable possibility that the event may have been caused by the product, it may then become advisable to perform observations on a semi-annual or quarterly basis, or as clinically indicated."
Lines 813-817	It is unclear whether this statement refers to the collection of excreta/secreta or only refers to collection of tissues where feasible. Clarification would be welcomed. It should be noted that subjects will have been enrolled in a Clinical trial before entering a LTFU study. In the original study, excreta/secreta would have been collected and the collection stopped once viral vector was no longer detected in those samples. If the collection of samples had been discontinued under the original clinical protocol, then collection of such samples in the LTFU study is unnecessary.	BIO suggested text: "(..) they become undetectable. If the study subject was previously enrolled in a clinical trial and the samples collected from that subject did not show the presence of viral vector, the collection of additional samples in the LTFU is not required."
E. Informed Consent in Trials Involving Long Term Follow-up Observations		
F. Special Considerations Regarding Integrating Vectors		
Line 920	Two citations are made to support the statement "While we recognize that oligoclonality or even monoclonality itself will not a priori result in malignancy". A third citation should be considered: Fraietta et al. (2018) Disruption of TET2 promotes the therapeutic efficacy of CD19-targeted T cells. Nature. 558(7709):307-312. Fraietta and colleagues evaluated the clinical response in a patient with CLL treated with CD19 CAR T-cell therapy who achieved an exceptional response. After the second adoptive transfer of autologous CD19-targeted CAR T cells, there was a delayed expansion of CAR T cells in the peripheral blood, followed by a contraction, and the patient achieved a complete response that has been sustained for more than five years. Deep sequencing of the T-cell receptor beta repertoire revealed that, at the peak of the response, 94% of the CD8+ CAR T cells were derived from a single clone that demonstrated massive in vivo expansion. In this clone, the	Suggest to add additional reference in line 924.

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	lentiviral vector-mediated insertion of the CAR transgene disrupted the TET2 gene, and the patient exhibited a hypomorphic mutation in the second TET2 allele. These TET2-disrupted CAR T cells displayed a central memory phenotype at the peak of in vivo expansion and had an epigenetic profile that indicated altered T-cell differentiation that enhanced the proliferative capacity and cytokine production of CAR T cells. Taken together, these findings suggest that the antitumor response achieved in a patient with CLL was due to expansion of a single CAR T-cell clone with disruption of the TET2 locus. In this specific case, insertional mutation of the lentiviral vector productively altered CAR T cell differentiation and yielded a dominant T cell clone that resulted in protective and lasting anti-tumor immunity.	
Line 998	Reference in Section d to clinical studies conducted in France and the UK is made. While the risk of delayed adverse-events, e.g., leukemia-like malignancies exist, the specific examples of the UK and French studies where leukemia-like malignant diseases were reported should be removed. This is not informative outside the context nor is representative of all the studies conducted with gene therapy.	Suggest to remove reference to the studies conducted in United Kingdom and France.
G. Special Considerations Regarding Product Involving Genome Editing		
Lines 1021-1052	The draft guidance provides special considerations regarding products involving genome editing. These special considerations raise questions about what suitable controls would be given additional DNA damage and exposure to mutagenic agents.	Provide additional details regarding controls for LTFU observations of genome editing products.
Lines 1042-1045	The draft guidance recommends that sponsors of gene therapies involving genome editing consider quantiating "the relationship between the off-target and on-target activities." In practice, this may be challenging, as this presumes that off-target effects can be observed and measured.	Clarify how this may apply in the absence of observable and quantifiable off-target effects, and other general considerationsn for how this may be achieved in approrpiate circumstances.
VI. GENERAL CONSIDERATIONS FOR POST-MARKETING MONITORING 1054 PLANS FOR GENE THERAPY PRODUCTS		

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1078-1082	It is unclear what specific recommendation the FDA had in mind regarding the registry approach (e.g., is this seen as an additional tool to collect data, are there recommended ways to combine with LTFU study?)	BIO suggest the FDA provide examples
Section VI	FDA is requesting to include in the BLA submission the study protocol for the registry, no guidance is given on the expected number of subjects to be included or length of enrolment after marketing authorization.	Please provide some high-level guidance in this document on the expected number of subjects and the expected duration of enrolment after marketing authorization in order to meet FDA expectations at time of BLA submission.
VII. LONG TERM FOLLOW-UP UNDER SPECIAL CIRCUMSTANCES		
Lines 1100-1104	It is unclear what the general approach to complete of an LTFU observation would be under special circumstances.	BIO suggest the FDA provide additional general parameters for said special circumstances.
VIII. DEFINITIONS		
IX. REFERENCES		
Reference 3	We support the approach of customizing the preclinical program for each compound and the use of the 3Rs in the development of GT products. However, it is unclear as to how in vitro or in silico studies of GT products can be used to complement or replace animal studies. Other opportunities to comply with the 3Rs is for the acceptance of the use of a biodistribution study from one GT product (e.g. AAV8) administered by a defined route of administration (e.g. subretinal) to be used in lieu of conducting a biodistribution for another GT product that uses the same vector and same route of administration.	Please provide examples of in vitro or in silico studies that can be used in lieu of in vivo animal studies.