Alliance for Regenerative Medicine

Comments on the FDA's Six Draft Guidances for Gene Therapy

Filed December 2018

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Alliance for Regenerative Medicine

December 7, 2018

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

Re: FDA Docket No. Docket No. FDA–2018-D-2238: FDA Draft Guidance, Human Gene Therapy for Hemophilia

The Alliance for Regenerative Medicine (ARM) is an international multi-stakeholder advocacy organization that promotes legislative, regulatory and reimbursement initiatives necessary to facilitate access to life-giving advances in regenerative medicine worldwide. ARM is comprised of more than 300 leading life sciences companies, research institutions, investors, and patient groups that represent the regenerative medicine and advanced therapies community. Our life science company members are directly involved in the research, development, and clinical investigation of cell and gene therapy products, as well as the submission of investigational new drug (IND) applications, and Biologics License Applications (BLA) for such products to the FDA. Many of our member companies have gene therapy products under development covering a broad range of conditions. ARM takes the lead on the sector's most pressing and significant issues, fostering research, development, investment and commercialization of transformational treatments and cures for patients worldwide.

ARM commends the Food and Drug Administration (FDA) for the development of the recently released six gene therapy draft guidances. They are a good compliment to the four-cell therapy product guidance documents the Agency published last year and are helpful because they cover a broad spectrum of topics, from manufacturing to nonclinical, clinical and long-term follow-up as well as rare diseases and specific diseases; and demonstrate support for innovation in this field.

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ARM is providing comments for each of the six gene therapy guidances. However, below is a list of general recommendations and concerns we would request the Agency consider in addition to the specific guidance comments:

- ARM encourages the FDA to select a definition for gene therapy, such as the one listed on FDA's website, and to use this definition consistently throughout the guidance documents.

- The Agency should consider creating a new version of the Common Technical Document (CTD) with examples for gene therapy, as the Chemistry, Manufacturing and Controls (CMS) guidance is quite detailed. Providing additional guidance on comparability would be helpful for all sponsors, including for when sponsors are improving the safety or efficacy of their products through manufacturing changes.

- Several of the draft guidances contain information on CMC, nonclinical and clinical development. It may be challenging for new sponsors to determine where to find relevant information for one of the disciplines if the information is spread throughout several guidance documents. The Agency may want to consolidate discipline specific guidance in the future for life-cycle management purposes.

- The FDA may also want to consider cross-referencing between the guidelines when appropriate.

- Long-term follow-up of patients treated with gene therapy will need to evolve as the field matures and we anticipate the maximum duration of recommended long-term follow-up will eventually be limited to 10 years or less, instead of 15 years. We encourage FDA to consider follow-up duration based on gene therapy specificity in vivo vs ex vivo and whether the vector is episomal or integrative.

- Whether transgene expression, or expression of the modified gene, can be used as a surrogate endpoint should be clarified, and if yes, the FDA should clarify how to use the surrogate endpoints (as primary or secondary?). It may be helpful to refer to ICH E8: "A surrogate endpoint is an endpoint that is intended to relate to a clinically important outcome but does not in itself measure a clinical benefit. Surrogate endpoints may be used as primary endpoints when appropriate (when the surrogate is reasonably likely or well known to predict clinical outcome).

- We would encourage the Agency to clarify how patient preference and willingness can be better incorporated into the risk benefit consideration.

In conclusion, ARM appreciates the opportunity to continue the dialogue with the Agency. Responding to draft guidances provide a significant opportunity to foster development of gene therapies for conditions with significant unmet medical need. Additionally, ARM hopes that the Agency will consider our August 3, 2018 letter which recommended "guiding principles that may be helpful to determining approaches to other disease-specific guidance as well as finalizing the recently published guidances."

Below are comments and recommend changes to the *Human Gene Therapy for Hemophilia Draft Guidance.*

Sincerely,

Director, U.S. Policy and Advocacy

Alliance for Regenerative Medicine

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

Section/ Line	Guidance Text	Comment	Proposed Change
I.	**INTRODUCTION**		
Lines			
II.	**BACKGROUND**		
Lines			
III.	**CONSIDERATIONS FOR PRODUCT DEVELOPMENT**		
69-72	Guidance text: "Sponsors developing GT products for hemophilia are strongly encouraged to contact the Office of Tissues and Advanced Therapies (OTAT) in the Center for Biologics Evaluation and Research (CBER) early in product development to discuss product-specific issues."	We recommend that FDA consider referencing the INTERACT program and section VIII of the guidance. Additionally, it is not clear when FDA may grant such meetings early in development to discuss product-specific issues or what type of meeting may be appropriate i.e. whether a pre-IND or an INTERACT meeting. This lack of clarity may result in delays in development programs. Therefore, we recommend providing some clarity on what types of product-specific issues may be discussed and the stage of development FDA may consider granting such meetings.	
IV.	**CONSIDERATIONS FOR FACTOR VIII/FACTOR IX ACTIVITY MEASUREMENT ASSESSED BY DIFFERENT CLINICAL LABORATORY ASSAYS**		
Section IV	N/A	We recommend streamlining this section if possible. For example, it would be helpful to clarify what is meant by "these" results in line 100—whether it means results from the	

		assay used in clinical studies or the results of analyzing the discrepancies between assay types to inform assay selection for clinical studies. Also for example, the information provided in bullet points following lines 100 (lines 100-107) & 124 (lines 124-130) both discuss how data from preclinical studies may inform assay selection for clinical studies. We recommend streamlining this information for better flow.	
102-107	Guidance text: "Performing animal or in vitro preclinical studies that compare the performance of OC and CS assays. Both assays should be calibrated in International Units (IU) of factor activity and should use a reference standard analogous to the expressed transgene, if available." "Using various clinical laboratory assays in preclinical animal studies and, where feasible, assays intended for human use."	Consider whether sponsors can bridge the assay for vector titer determination of the preclinical lots to assay used for clinical lots.	
Line 104 FN 4	Line 104 includes a reference to footnote 4 which states "We encourage sponsors to explore opportunities for reducing, refining, and replacing animal use in the preclinical program. For example, it may be	The footnote includes important concepts and recommendations for streamlining the preclinical program. Therefore, we recommend elevating the footnote into the main text of section V so that the recommendation in footnote regarding animal use in	

	appropriate to use *in vitro* or *in silico* testing to complement or replace animal studies."	preclinical program is appropriately provided in the main text in the relevant section on preclinical studies. This important recommendation may lose prominence as placed in footnote. Additionally, we recommend including examples of the use of in silico testing to complement or replace animal studies.	
V.	**CONSIDERATIONS FOR PRECLINICAL STUDIES**		
134-135	Guidance text: "Performing a comparative field study with patient plasma samples using assays routinely performed in clinical laboratories to evaluate the range of discrepancies."	It would be helpful to provide more guidance on what a "comparative field study" should look like. There may be feasibility issues with collecting adequate amounts of patient plasma samples for a large field study.	
166-167	Guidance text: "These data encompass the distribution, persistence, and clearance of the vector and possibly the expressed transgene product in vivo, from the site of administration to target and non-target tissues, including biofluids (e.g., blood, lymph node fluid)."	It is challenging to collect adequate volumes of lymph node fluid in certain animal models, e.g. rodents. We recommend that FDA consider deleting the example in parenthetical for lymph node fluid.	Proposed text: "These data encompass the distribution, persistence, and clearance of the vector and possibly the expressed transgene product in vivo, from the site of administration to target and non-target tissues, including biofluids (e.g., blood~~, lymph node fluid~~)."
177-181	Guidance text: "To support translation of effective and safe dose levels determined in preclinical studies to clinical trials, the assay for vector titer determination of the preclinical lots should be	The recommendation for an "identical" assay is challenging because there are species specific features that preclude the use of "identical" assays in preclinical and clinical lots. For example, the volume of sample requirements would differ by species	Proposed text: "To support translation of effective and safe dose levels determined in preclinical studies to clinical trials, the assay for vector titer determination of the preclinical lots should be consistent with ~~identical to~~ the assay used for

	identical to the assay used for clinical lots. The assays for measuring factor activity in animals administered the GT product should be consistent to the assays used in humans. The factor activity assays are discussed in detail under section IV. of this document."	for use in assays and the assay readout may differ as well. Accordingly, we recommend that FDA consider changing the recommendation from an "identical" assay for use between preclinical and clinical lots to a "consistent" assay.	clinical lots. The assays for measuring factor activity in animals administered the GT product should be consistent to the assays used in humans. The factor activity assays are discussed in detail under section IV. of this document."
185-186	As the clinical development program for an investigational GT product progresses to late-phase clinical trials and possible marketing approval, additional nonclinical studies may need to be considered to address: 1) "the potential for reproductive/developmental toxicity"	It would be helpful to clarify what additional nonclinical studies may need to be considered to address the potential for reproductive/developmental toxicity distinguishing between the type of gene therapy and vector, e.g. considerations may vary depending on whether AAV or lentivirus is used.	
VI. CONSIDERATIONS FOR CLINICAL TRIALS			
Lines			
A. Efficacy Endpoints			
221-224	Guidance text: "Resolve discrepancies in factor assay results from various assay methods prior to considering a target factor activity as a surrogate endpoint for primary efficacy assessment. "	The discrepancies referenced are not unique to gene therapy products and are also present with recombinant products. The discrepancies are inherent and should be explained by the sponsor, not "resolved."	Proposed change: "Explain ~~Resolve~~ discrepancies in factor assay results from various assay methods prior to considering a target factor activity as a surrogate endpoint for primary efficacy assessment."
224-225	Guidance text: "Determine a target factor activity level within the range of factor activity of normal population."	We recommend that FDA provide additional context regarding the factor activity level considered to be within the "range of factor activity of normal population."	
B. Study Design			

234-236	Guidance text: "Enrolling patients who have not required dose adjustments to their prophylactic replacement therapy for at least 12 months as this may best facilitate efficacy determinations following administration."	It would be helpful to provide flexibility by recommending a well-controlled or well-managed treatment plan instead of the recommendation of no dose adjustments for 12 months.	Proposed change: "Enrolling patients who are managed by a well-controlled treatment plan ~~have not required dose adjustments to their prophylactic replacement therapy~~ for at least 12 months as this may best facilitate efficacy determinations following administration."
C. Study Population			
Lines			
D. Statistical Consideration			
298	N/A	This section provides recommendations on statistical evaluations to support a marketing application for traditional approval with ABR as the primary efficacy endpoint. It would be helpful for the section to also provide information on statistical evaluation of the surrogate endpoint.	We recommend FDA to consider adding new language or bullet points in this section on statistical considerations for using factor activity levels for accelerated approval.
303-305	Guidance text: "Developing a NI margin (M) for comparing ABR of the investigational GT product to that of current prophylaxis therapies in the within-subject comparison trial."	It would be helpful to recommend that the weight of proof should be on prophylaxis group.	
E. Study Monitoring			
320-364	Guidance text following line 325: "Short-Term Monitoring (first 2 years following GT product administration)" and following line 346: "Long-	As written, it is not entirely clear when short or long-term follow-up must begin and whether initiation of follow-up begins within the study or upon study completion.	We recommend clarifying FDA's expectations on the conduct, structure, and timing of long term follow up studies, per the concerns noted here.

	Term Monitoring (≥2 years following GT product administration)"	Additional clarity is needed for FDA's expectations.	
350-352	Guidance text: "Monitoring for adverse events for at least 5 years after exposure to non-integrating GT products and 15 years for integrating GT products. (Ref. 16)"	We recommend ensuring consistency with the recommendations in the draft guidance for industry *Long Term Follow-Up After Administration of Human Gene Therapy Products* i.e. the LTFU for AAV vectors should be 2-5 years. Alternatively, if FDA intends to always require 5 years LTFU for Hemophilia regardless of the vector, it would helpful to clarify that.	
325	Guidance text: "Short-Term Monitoring (first 2 years following GT product administration)"	Based on the recommended short-term monitoring duration being 2 years, it appears that the 2-year short term monitoring data may be expected at the time of BLA approval. It would be helpful if the guidance clarifies this interpretation.	
354-356, 360-362	Guidance text: "Monitoring for adverse events to include: eliciting history of and non-invasive screening for hepatic malignancies; physical examination; and laboratory testing for hepatic function." "Monitoring for the emergence of new clinical conditions, including new malignancies and new incidence or exacerbation of pre-existing neurologic, rheumatologic, or autoimmune disorders."	As written, it is not clear whether active or passive monitoring for malignancies is recommended. An expectation for active monitoring for malignancies would be challenging. Passive monitoring for malignancies would be acceptable and should be specified.	Proposed change: "Monitoring for adverse events to include: eliciting history of and non-invasive passive screening for hepatic malignancies; physical examination; and laboratory testing for hepatic function." "Passive monitoring for the emergence of new clinical conditions, including new malignancies and new incidence or exacerbation of pre-existing neurologic, rheumatologic, or autoimmune disorders."

358	Guidance text: "Monitoring for inhibitor antibodies to factor VIII or factor IX."	More detailed guidance on what levels would create a safety concern would be helpful.	
F. Patient Experience			
Lines			
VII.	**EXPEDITED PROGRAMS**		
Lines			
VIII.	**COMMUNICATION WITH FDA**		
Lines			
IX.	**REFERENCES**		
Lines			

Alliance for Regenerative Medicine

December 7, 2018

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

Re: Specific Comments for FDA Docket No. FDA–2018-D-2258: Human Gene Therapy for Rare Diseases; Draft Guidance for Industry

The Alliance for Regenerative Medicine (ARM) is an international multi-stakeholder advocacy organization that promotes legislative, regulatory and reimbursement initiatives necessary to facilitate access to life-giving advances in regenerative medicine worldwide. ARM is comprised of more than 300 leading life sciences companies, research institutions, investors, and patient groups that represent the regenerative medicine and advanced therapies community. Our life science company members are directly involved in the research, development, and clinical investigation of cell and gene therapy products, as well as the submission of investigational new drug (IND) applications, and Biologics License Applications (BLA) for such products to the FDA. Many of our member companies have gene therapy products under development covering a broad range of conditions. ARM takes the lead on the sector's most pressing and significant issues, fostering research, development, investment and commercialization of transformational treatments and cures for patients worldwide.

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- ARM encourages the FDA to select a definition for gene therapy, such as the one listed on FDA's website, and to use this definition consistently throughout the guidance documents.

- The Agency should consider creating a new version of the Common Technical Document (CTD) with examples for gene therapy, as the Chemistry, Manufacturing and Controls (CMS) guidance is quite detailed. Providing additional guidance on comparability would be helpful for all sponsors, including for when sponsors are improving the safety or efficacy of their products through manufacturing changes.

- Several of the draft guidances contain information on CMC, nonclinical and clinical development. It may be challenging for new sponsors to determine where to find relevant information for one of the disciplines if the information is spread throughout several guidance documents. The Agency may want to consolidate discipline specific guidance in the future for life-cycle management purposes.

- The FDA may also want to consider cross-referencing between the guidelines when appropriate.

- Long-term follow-up of patients treated with gene therapy will need to evolve as the field matures and we anticipate the maximum duration of recommended long-term follow-up will eventually be limited to 10 years or less, instead of 15 years. We encourage FDA to consider follow-up duration based on gene therapy specificity in vivo vs ex vivo and whether the vector is episomal or integrative.

- Whether transgene expression, or expression of the modified gene, can be used as a surrogate endpoint should be clarified, and if yes, the FDA should clarify how to use the surrogate endpoints (as primary or secondary?). It may be helpful to refer to ICH E8: "A surrogate endpoint is an endpoint that is intended to relate to a clinically important outcome but does not in itself measure a clinical benefit. Surrogate endpoints may be used as primary endpoints when appropriate (when the surrogate is reasonably likely or well known to predict clinical outcome).

- We would encourage the Agency to clarify how patient preference and willingness can be better incorporated into the risk benefit consideration.

In conclusion, ARM appreciates the opportunity to continue the dialogue with the Agency. Responding to draft guidances provide a significant opportunity to foster development of gene therapies for conditions with significant unmet medical need. Additionally, ARM hopes that the Agency will consider our August 3, 2018 letter which recommended "guiding principles that may be helpful to determining approaches to other disease-specific guidance as well as finalizing the recently published guidances."

Below are comments and recommend changes to the *Human Gene Therapy for Rare Diseases; Draft Guidance for Industry.*

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Re: Specific Comments for FDA Docket No. FDA–2018-D-2258: Human Gene Therapy for Rare Diseases; Draft Guidance for Industry

Lines	Guidance Text	Comment	Proposed Change
I.	INTRODUCTION		
II.	BACKGROUND		
III.	CONSIDERATIONS FOR PRODUCT DEVELOPMENT		
49-61	"The general chemistry, manufacturing and control (CMC) considerations for product manufacturing, testing and release of GT products for rare diseases are the same as those described for other GT products (Ref. 2). However, some aspects of the development programs for rare diseases, such as limited population size and fewer lots manufactured, may make it challenging to follow traditional product development strategies. In traditional product development, critical quality attributes (CQA) of the product are evaluated during each phase of clinical development, and	The paragraph would benefit from restructuring of the information to help with communicating the key concepts. As written, there is a mix of information regarding CQA followed by population and again, quality information specific to gene therapies.	

Lines	Guidance Text	Comment	Proposed Change
	characterization data from many product lots are correlated to clinical outcomes. In addition, GT products may have CQA with higher variability than drugs or well-characterized biologics, which can add to CQA uncertainty. Smaller study populations may result in the need for fewer manufacturing runs, which can make it difficult to establish the critical process parameters (CPP) necessary for ensuring CQA. However, demonstrating process control to ensure a consistent product with predefined CQA for potency, identity and purity is required to demonstrate compliance with licensure and regulatory requirements.		
63-66	"These factors make it even more critical that a sponsor of a GT product for a rare disease establish a well-controlled manufacturing process along with suitable analytical assays to assess product CQA as early in development as possible,	We recommend that FDA clarify and explain expectations regarding the need for a "well-controlled manufacturing process." Additionally, it is important to note in the guidance that the manufacturing process may continue to be refined after the administration to the first subject as more	"These factors make it even more critical that a sponsor of a GT product for a rare disease establish a well-controlled manufacturing process along with suitable analytical assays to assess potential product CQA (e.g. for potency, identity, and

Lines	Guidance Text	Comment	Proposed Change
	optimally before administration of the GT product to the first subject."	experience is gained and technology advances. In addition, acknowledging the difficulty of confirming product CQA early in the process, the specific attributes should be noted. Preclinical studies also may be able to be leveraged, in the early processes of determining product CQA.	purity) as early in development as possible, optimally before administration of the GT product to the first subject. Importantly, as the phase 1 study may provide evidence of safety and effectiveness, characterization of product CQA and manufacturing CPP should be implemented during early clinical development, and innovative strategies, such as using nonclinical study data to help inform the beginning basis for characterization of product CQA, and the production of multiple small lots versus a single large product lot, may be considered. Sponsors developing GT products for rare diseases are strongly encouraged to contact the Office of Tissues and Advanced…"
66-69	"Importantly, as the phase 1 study may provide evidence of safety and effectiveness, characterization of product CQA and manufacturing	The recommendation for characterization of product CQAs and CPPs during early clinical development may not always be possible or appropriate considering that there will be continued refinement of the manufacturing process.	Proposed change: "Importantly, as the phase 1 study may provide evidence of safety and effectiveness, characterization of product

Lines	Guidance Text	Comment	Proposed Change
	CPP should be implemented during early clinical development, and innovative strategies such as the production of multiple small lots versus a single large product lot may be considered."		CQA and, when feasible, manufacturing CPP, should be implemented during early clinical development, and innovative strategies such as the production of multiple small lots versus a single large product lot may be considered."
69-74	"Sponsors developing GT products for rare diseases are strongly encouraged to contact the Office of Tissues and Advanced Therapies (OTAT) in the Center for Biologics Evaluation and Research (CBER) prior to investigational new drug application (IND) submission to discuss their product-specific considerations,"	We recommend providing a mechanism for such contact. We recommend highlighting that the INTERACT meeting discussed in section VII may be considered as a forum for such discussions.	
87-88	"we recommend that a potency test that measures a relevant biological activity be qualified for suitability"	Is there a particular distinction in this recommendation as applied to rare diseases? If so, it would be helpful for the Agency to clarify.	
98-99	"Importantly, if product comparability cannot be demonstrated, additional clinical studies may be needed."	We recommend clarifying FDA's expectation for product comparability for GT products, including circumstances when analytical comparability will be sufficient and when additional data such as from preclinical studies, will be needed. Also, any existing FDA or ICH guidance on comparability for	

Lines	Guidance Text	Comment	Proposed Change
		biological products that the sponsors can rely on for recommendations for comparability for GT products should be referenced.	
IV.	CONSIDERATIONS FOR PRECLINICAL STUDIES		
123	"Preclinical in vitro and in vivo proof-of-concept (POC) studies are recommended to establish feasibility and support the scientific rationale for administration of the investigational GT product in a clinical trial."		We suggest replacing "preclinical in vitro and in vivo POC studies" with "preclinical in vitro and/or in vivo POC studies". Indeed, when there is no animal model to the disease, in vitro data are sometimes more relevant.
132-137	"These data encompass the distribution profile of the vector from the site of administration to target and non-target tissues, including biofluids (e.g., blood, lymph node fluid, cerebrospinal fluid (CSF)) as applicable."	Collecting adequate volume/quantities of lymph node fluid and CSF is particularly challenging and may not be practical, especially in rodents. E.g. in mice, it is near impossible to collect adequate quantities without pooling, and pooling is not appropriate in such studies in general.	We recommend deleting lymph node fluid and CSF, from the examples provided. Recommended text: "These data encompass the distribution profile of the vector from the site of administration to target and non-target tissues, including biofluids (e.g., blood ~~lymph node fluid, cerebrospinal fluid (CSF)~~) as applicable."
149 - 152	"The conduct of additional nonclinical studies may be needed to address such factors as: 1) the potential for developmental and	Consistent with the above comment to lines 63-66, note that preclinical studies can inform the early processes of determining product CQA.	"The conduct of additional nonclinical studies may be needed to address such factors as: 1) the potential for developmental and

Lines	Guidance Text	Comment	Proposed Change
	reproductive toxicity; and 2) significant changes in the manufacturing process or formulation that may impact comparability between the product administered in clinical trials and the product intended for licensure."		reproductive toxicity; and 2) significant changes in the manufacturing process or formulation that may impact comparability between the product administered in clinical trials and the product intended for licensure. Nonclinical studies may also be useful to further characterize the CQA.
149 (FN 4)	"The preclinical program for any investigational product should be individualized with respect to scope, complexity, and overall design, to maximize the contribution and predictive value of the resulting data for clinical safety and therapeutic activity. We encourage sponsors to explore opportunities for reducing, refining, and replacing animal use in the preclinical program. For example, it may be appropriate to use in vitro or in silico testing to complement or replace animal studies. Sponsors are encouraged to submit proposals and justify any potential alternative	Language on four Rs in footnote 4 is important and loses emphasis as a footnote.	Footnote 4 should be elevated into the main text as a separate sub-bullet in the same section where it is referenced. Further, we recommend that FDA expand on *in silico* testing and provide guidance on how to conduct such testing and where, and when it is acceptable and appropriate.

Lines	Guidance Text	Comment	Proposed Change
	approaches, which we will evaluate for equivalency to animal studies."		
Lines 182 - 191	"If the disease is caused by a genetic defect, the sponsor should perform genetic test(s) for the specific defect(s) of interest in all clinical trial subjects. This information is important to ensure correct diagnosis of the disorder of interest. In addition, since many of these disorders can involve either deletions or functional mutations at any of several loci within a specific gene, safety and effectiveness may be linked to genotype in unpredictable ways. Given this, early understanding of such associations may help in planning future clinical trials. Therefore, if there are no readily available, reliable means of obtaining the needed genetic diagnosis, a companion diagnostic may be needed and therefore should be considered early in development.	FDA should consider scenarios where there is no available genetic testing for the disease. As such we suggest including the possibility of confirming the disease by other means. Additionally, there are instances where the genetic test has already been performed and the sponsor just collects the information.	Proposed wording "the sponsor should perform genetic test(s) for the specific defect(s) of interest or if already performed collect the information, in all clinical trial subjects."

Lines	Guidance Text	Comment	Proposed Change
193	"Pre-existing antibody to the GT product may limit its therapeutic potential. Sponsors may choose to exclude patients with pre-existing antibodies to the GT product. In such cases, the sponsor should strongly consider contemporaneous development of a companion diagnostic to detect antibodies to the GT product"	Not only "pre-existing antibody to the GT product may limit its therapeutic potential" but also re-administration; immunogenicity should be addressed (in case of re-administration of the GT)	
V. CONSIDERATIONS FOR CLINICAL TRIALS			
		We recommend that FDA include language encouraging sponsors to engage in early dialogue with the agency regarding the acceptability and use of data from compassionate use programs to support licensure due to the limited overall clinical dataset available.	
a. Study Population			
203-208	"Severity of disease should be considered in designing clinical GT trials (Ref. 8), as well as the anticipated risk and potential benefits to subjects. Subjects with severe or advanced disease might experience confounding adverse events that are related to the underlying disease rather than to the GT product	The language could be interpreted in several different ways, e.g. it appears to convey FDA's intent to use reasonableness in their review of confounding adverse events that are related to the underlying disease rather than to the GT product itself; also it appears to convey FDA's recommendation to take patient preference or willingness for acceptance of risk of an investigational GT product into account. Further clarity is needed.	The recommendation and consideration should be clarified. Specifically, we request that the agency clarify how patient preference and willingness can be incorporated into the risk benefit consideration.

Lines	Guidance Text	Comment	Proposed Change
	itself; however, they may be more willing to accept the risk of an investigational GT product in the context of the anticipated clinical benefit."		
216	"the administration of an investigational drug in children must offer a prospect of direct clinical benefit to individually enrolled patients, the risk must be justified by the anticipated benefit, and the anticipated risk-benefit profile must be at least as favorable as that presented by accepted alternative treatments (21 CFR 50.52)."	Certain edits change the original meaning of the cited regulation, e.g. 21 CFR 50.52 states "direct benefit" and not "direct *clinical* benefit."	We recommend that this language be consistent with the cited regulation. Recommended language: "the administration of an investigational drug in children must offer a prospect of direct ~~clinical~~ benefit to individually enrolled patients, the risk must be justified by the anticipated benefit, and the anticipated risk-benefit profile must be at least as favorable as that presented by accepted alternative treatments (21 CFR 50.52)."
b. Study Design			
278	"Ideally, utilizing as an endpoint a treatment outcome that virtually never occurs in the natural course of the disease would greatly facilitate the design and cogency of small trials."	The language "virtually never occurs" is limiting and confusing.	We recommend the following changes: "Ideally, utilizing as an endpoint a treatment outcome that would not be expected to occur spontaneously in the natural course of the disease would greatly

Lines	Guidance Text	Comment	Proposed Change
			facilitate the design and cogency of small trials."
c. Dose Selection			
298-300	"For early-phase studies, clinical development of GT products should include evaluation of two or more dose levels to help identify the potentially therapeutic dose(s). Ideally, placebo controls should be added to each dose cohort."	Placebo controlled studies to support dose selection may not be feasible when evaluating treatment for a rare disease. We recommend FDA consider the unique limitations and continue to adopt a few that dose-finding can be supported through a number of different study designs. This would also be consistent with regulatory precedent.	"For early-phase studies, clinical development of GT products should include evaluation of two or more dose levels to help identify the potentially therapeutic dose(s). ~~Ideally~~ Placebo controls ~~should~~ may be added to each dose cohort, if feasible."
306-308	"Efforts should be made early in the GT product development program to identify and validate biomarkers and to leverage all available information from published investigations for the disease of interest (or related diseases)."	Validation of biomarkers is a high bar. Biomarker validation at an early stage presents significant challenges for rare diseases where there is no established regulatory precedent or natural history. Use of validated biomarkers should be expected 'when feasible'. We recommend that FDA allow more flexibility regarding use of biomarkers, including exploratory endpoints, which are appropriate for the condition under investigation. Further, FDA should acknowledge the challenges with rare disease drug development, including limited patient population, when evaluating the use of biomarkers, including their potential validation and qualification, for rare disease drug development.	"Efforts should be made early in the GT product development program to identify ~~and validate~~ biomarkers with available data or literature supportive of a clinical benefit, and to leverage all available information from published investigations for the disease of interest (or related diseases)."
308-312 (also 377-382)	"Some biomarkers or endpoints are very closely linked to the underlying pathophysiology of the	If MOA is understood and elucidated based on underlying disease pathology, long-term transgene expression should be predictive of clinical benefit.	This recommendation is welcome and considers the unique qualities of gene therapy products. We

Lines	Guidance Text	Comment	Proposed Change
	disease (e.g., a missing metabolite in a critical biosynthetic pathway). In this case, total or substantial restoration of the biosynthetic metabolic pathway may generally be expected to confer clinical benefit."		recommend including similar considerations in Section IV.E "Efficacy Endpoints." Such considerations are important for dose selection as for selection of efficacy endpoints.
d. Safety Considerations			
e. Efficacy Endpoints			
377-382 (also 310-312)	"For sponsors that are considering seeking accelerated approval of a GT product for a rare disease pursuant to section 506(c) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) based on a surrogate endpoint, it will be particularly important to understand the pathophysiology and natural history of the disease in order to help identify potential surrogate endpoints that are reasonably likely to predict clinical benefit."	In line with line 308-312, substantial restoration of the biosynthetic metabolic pathway should generally be expected to confer clinical benefit.	Recommendations should note that total or substantial restoration of the biosynthetic metabolic pathway may generally be expected to confer clinical benefit.
f. Patient Experience			
393-395	Patient experience data may provide important additional information about the clinical benefit of a GT product. FDA	If possible, FDA should expand on, and/or add examples around, how FDA might use and consider patient experience data in the	

Lines	Guidance Text	Comment	Proposed Change
	encourages sponsors to collect patient experience data during product development, and to submit such data in the marketing application.	context of reviewing and approving a rare disease gene therapy.	
VI.	EXPEDITED PROGRAMS		
VII.	COMMUNICATION WITH FDA		
413-420	"FDA recommends communication with OTAT early in product development, before submission of an IND. There are different meeting types that can be used for such discussions, depending on the stage of product development and the issues to be considered. These include pre-IND meetings and, earlier in development, INitial Targeted Engagement for Regulatory Advice on CBER producTs (INTERACT) meetings. Early nonbinding, regulatory advice can be obtained from OTAT through an INTERACT meeting, which can be used to discuss issues such as a product's early preclinical program, and/or through a pre-IND	Referring to both pre-IND meetings and INTERACT meetings, the guidance suggests sponsors meet with FDA prior to conducting the nonclinical IND enabling studies. It is unclear whether this first meeting would be required to be an INTERACT meeting, or whether FDA would permit a second pre-IND meeting to be held. It would be useful for sponsors to have an opportunity to have a second, formal, pre-IND meeting—1 before IND enabling, and one after the studies are conducted) to allow for discussion of both preclinical and FIH/pivotal study design, in light of preclinical data. FDA also recently issued a SOPP on the INTERACT program, which is not referenced in the draft guidance. We recommend including a reference to the recently issued SOPP on the INTERACT program.	Please clarify whether FDA would permit a second formal pre-IND meeting (Type B or Type C), meeting (if needed,) after the data from the IND enabling studies, to discuss the clinical study design. The guidance suggests (247-249) that sponsors consider designing their FIH as an adequate and well-controlled study that could provide evidence of effectiveness depending on the results to support a marketing authorization. Given that there may be a considerable amount of time between the pre-IND meeting and the IND submission, it may would be beneficial to have the opportunity for an additional interaction with

Lines	Guidance Text	Comment	Proposed Change
	meeting prior to submission of the IND (Ref. 13)."		the FDA (if needed) prior to the IND submission. We also recommend including a reference to the recently issued SOPP on the INTERACT program
413-420		In this section of the draft guidance, FDA may ask a note on the possibility to have platform or pipeline meetings with CBER/OTAT to discuss a portfolio of products development of advanced therapies (anticipated once a year, or once every other year). This type of meeting may be helpful to discuss challenges across development of several ultra-rare diseases or to leverage platform technologies across several programs.	When appropriate the Agency can meet with companies developing several advanced therapies products to discuss their portfolio of products for rare or ultra-rare diseases.
VIII. REFERENCES			

Alliance for Regenerative Medicine

December 7, 2018

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

Re: FDA Docket No. FDA–2018-D-2236: FDA Draft Guidance, Human Gene Therapy for Retinal Disorders

The Alliance for Regenerative Medicine (ARM) is an international multi-stakeholder advocacy organization that promotes legislative, regulatory and reimbursement initiatives necessary to facilitate access to life-giving advances in regenerative medicine worldwide. ARM is comprised of more than 300 leading life sciences companies, research institutions, investors, and patient groups that represent the regenerative medicine and advanced therapies community. Our life science company members are directly involved in the research, development, and clinical investigation of cell and gene therapy products, as well as the submission of investigational new drug (IND) applications, and Biologics License Applications (BLA) for such products to the FDA. Many of our member companies have gene therapy products under development covering a broad range of conditions. ARM takes the lead on the sector's most pressing and significant issues, fostering research, development, investment and commercialization of transformational treatments and cures for patients worldwide.

ARM commends the Food and Drug Administration (FDA) for the development of the recently released six gene therapy draft guidances. They are a good compliment to the four-cell therapy product guidance documents the Agency published last year and are helpful because they cover a broad spectrum of topics, from manufacturing to nonclinical, clinical and long-term follow-up as well as rare diseases and specific diseases; and demonstrate support for innovation in this field.

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ARM is providing comments for each of the six gene therapy guidances. However, below is a list of general recommendations and concerns we would request the Agency consider in addition to the specific guidance comments:

- ARM encourages the FDA to select a definition for gene therapy, such as the one listed on FDA's website, and to use this definition consistently throughout the guidance documents.

- The Agency should consider creating a new version of the Common Technical Document (CTD) with examples for gene therapy, as the Chemistry, Manufacturing and Controls (CMS) guidance is quite detailed. Providing additional guidance on comparability would be helpful for all sponsors, including for when sponsors are improving the safety or efficacy of their products through manufacturing changes.

- Several of the draft guidances contain information on CMC, nonclinical and clinical development. It may be challenging for new sponsors to determine where to find relevant information for one of the disciplines if the information is spread throughout several guidance documents. The Agency may want to consolidate discipline specific guidance in the future for life-cycle management purposes.

- The FDA may also want to consider cross-referencing between the guidelines when appropriate.

- Long-term follow-up of patients treated with gene therapy will need to evolve as the field matures and we anticipate the maximum duration of recommended long-term follow-up will eventually be limited to 10 years or less, instead of 15 years. We encourage FDA to consider follow-up duration based on gene therapy specificity in vivo vs ex vivo and whether the vector is episomal or integrative.

- Whether transgene expression, or expression of the modified gene, can be used as a surrogate endpoint should be clarified, and if yes, the FDA should clarify how to use the surrogate endpoints (as primary or secondary?). It may be helpful to refer to ICH E8: "A surrogate endpoint is an endpoint that is intended to relate to a clinically important outcome but does not in itself measure a clinical benefit. Surrogate endpoints may be used as primary endpoints when appropriate (when the surrogate is reasonably likely or well known to predict clinical outcome).

- We would encourage the Agency to clarify how patient preference and willingness can be better incorporated into the risk benefit consideration.

In conclusion, ARM appreciates the opportunity to continue the dialogue with the Agency. Responding to draft guidances provide a significant opportunity to foster development of gene therapies for conditions with significant unmet medical need. Additionally, ARM hopes that the Agency will consider our August 3, 2018 letter which recommended "guiding principles that may be helpful to determining approaches to other disease-specific guidance as well as finalizing the recently published guidances."

Below are comments and recommend changes to the *Human Gene Therapy for Retinal Disorders.*

Sincerely,

Director, U.S. Policy and Advocacy

Alliance for Regenerative Medicine

Re: Specific Comments for FDA Docket No. FDA–2018-D-2236: FDA Draft Guidance, Human Gene Therapy for Retinal Disorders

Section/ Lines	Guidance Text	Comment	Proposed Change
I.	**INTRODUCTION**		
Lines			
II.	**CONSIDERATIONS FOR PRODUCT DEVELOPMENT**		
59-60	The endotoxin limit for intraocular delivery is not more than(NMT) 2.0 Endotoxin Unit(EU/dose/eye or NMT 0.5/EU/mL	We recommend clarifying whether this recommendation is "for consideration" only. For example, if the dose is 300uL per eye, it is not clear which spec should be used— 2.0 EU or 1.7EU.	
67	Compatibility of the GT product and the delivery system should be evaluated	We recommend highlighting the importance of also taking into account the local site of administration and appropriate formulation.	
III.	**CONSIDERATIONS FOR PRECLINICAL STUDIES**		
95-101	Biodistribution studies should be conducted to assess the pharmacokinetic profile of a GT product (Ref. 3). These data encompass the distribution, persistence, and clearance of the vector and possibly the expressed transgene product in vivo, from the site of administration to target ocular and non-ocular tissues, intraocular fluids, and blood. These data can determine extent of tissue transduction and transgene expression,	These studies are not routinely needed or conducted. We recommend that the guidance should acknowledge the flexibility.	Proposed text: "Biodistribution studies should be conducted to assess the pharmacokinetic profile of a GT product when appropriate (Ref. 3). These data encompass the distribution, persistence, and clearance of the vector and possibly the expressed transgene product in vivo, from the site of administration to target ocular and non-ocular tissues, intraocular

Section/ Lines	Guidance Text	Comment	Proposed Change
	evaluate whether expression is transient or persistent, and guide the design of the preclinical toxicology studies as well as the early-phase clinical trials.		fluids, and blood, when applicable. These data can determine extent of tissue transduction and transgene expression, evaluate whether expression is transient or persistent, and may guide the design of the preclinical toxicology studies as well as the early-phase clinical trials, when feasible.
125-127	Therefore, clinical data, rather than preclinical data, may provide the most relevant safety information for repeat product administration.	We suggest clarifying the statement, that clinical data (rather than preclinical) provide relevant safety information for repeat administration. It would be helpful to understand how this can be implemented before First-In-Human. Does this statement imply that repeat toxicity studies are not relevant?	
129-133	As the clinical development program for an investigational GT product advances to late-phase clinical trials and possible marketing approval, additional preclinical studies may be indicated. Further testing may be necessary to address factors such as any significant changes in the manufacturing process or formulation, which may affect comparability of the late-phase product to product administered in early-phase clinical trials.	The necessity and relevance of "further testing" to be performed in the case of significant changes in manufacturing process should be also included in the Section II. of the guidance	
IV.	**CONSIDERATIONS FOR CLINICAL TRIALS**		

Section/ Lines	Guidance Text	Comment	Proposed Change
Lines			
139-144	Early-phase trials of GT products should not only evaluate safety and feasibility, but also gauge bioactivity and preliminary efficacy. Later-phase trials should be designed as adequate and well-controlled studies that can provide substantial evidence of effectiveness to support an application for marketing. For further details of general considerations for gene therapy clinical trials, please refer to relevant FDA guidance documents.	In light of the fact that many retinal disorders are rare, it is suggested to include a reference the Human Gene Therapy for Rare Diseases Guidance with respect to the study design consideration for the first in human study. Additionally, this indicates that even First-In-Human studies shall not be performed in healthy volunteers (as usual for gene therapies). We recommend further emphasizing this in the guidance.	For rare retinal disorders, Sponsors should consider designing the FIH trials to be an adequate and well-controlled investigation that has the potential to provide evidence of effectiveness to support a marketing application (ref to Human Gene Therapy for Rare Disease Guidance).
A. Natural History Studies			
Lines			
B. Study Design			
164-167	In general, while intravitreal injection of the vehicle alone is often feasible as a placebo control, it may not be considered ethically acceptable unless the physical properties of an injection in a closed space have a potential therapeutic benefit.	The recommendation seems to relate to a specific paradigm. We suggest modifying the recommendation to be generally applicable to any administration procedure. We also request that FDA clarify, in the final guidance, whether and under what circumstances it is acceptable (from an ethical standpoint)	…as a placebo control, it may not be considered ethically acceptable unless some benefit is provided.

Section/ Lines	Guidance Text	Comment	Proposed Change
		to require a vehicle control, especially in the context of a pediatric trial.	
162-174	To facilitate interpretation of clinical data, inclusion of a randomized, concurrent parallel control group is recommended for clinical trials whenever possible. Administration of the vehicle alone may serve as a control. In general, while intravitreal injection of the vehicle alone is often feasible as a placebo control, it may not be considered ethically acceptable unless the physical properties of an injection in a closed space have a potential therapeutic benefit. When ethically acceptable, such a control is especially helpful early in clinical development, to evaluate bioactivity of the investigational GT product and possibly to provide initial evidence of its clinical efficacy. However, FDA acknowledges the risks associated with intravitreal and subretinal injection procedures and vehicles; without any prospect of direct benefit, these risks may not be acceptable under certain circumstances, such as for pediatric patients (21 CFR Part 50, Subpart D). Other possibilities to vehicle controls include alternative dosing regimens, alternative dose levels, and existing products approved for the indication being sought.	We recommend considering the following proposed changes, in light of the fact that many retinal disorders are rare and affect pediatric patients.	To facilitate interpretation of clinical data, inclusion of a randomized, concurrent parallel control group is generally preferred ~~recommended~~ for clinical trials whenever possible. Administration of the vehicle alone may serve as a control. In general, while intravitreal injection of the vehicle alone is often feasible as a placebo control, it may not be considered ethically acceptable unless the physical properties of an injection in a closed space have a potential therapeutic benefit. When ethically acceptable, such a control is especially helpful early in clinical development, to evaluate bioactivity of the investigational GT product and possibly to provide initial evidence of its clinical efficacy. However, FDA acknowledges the risks associated with intravitreal and subretinal injection procedures and vehicles; without any prospect of direct benefit, these risks may not be acceptable under certain circumstances, such as for pediatric patients (21 CFR Part 50, Subpart D). Other possibilities to vehicle controls include alternative dosing regimens, alternative dose levels, ~~and~~ existing

Section/ Lines	Guidance Text	Comment	Proposed Change
			products approved for the indication being sought, and historical controls (ref to Human Gene Therapy for Rare Disease Guidance).
172-174	Other possibilities to vehicle controls include alternative dosing regimens, alternative dose levels, and existing products approved for the indication being sought.	Many of these inherited retinal disorders are very rare. For example, the natural history of retinitis pigmentosa is relentless progression. FDA may consider discussing the possibility of using historical controls for such diseases, or refer to existing guidance for control groups in rare diseases.	Refer to existing FDA rare disease guidance and/or the draft guidance on gene therapy for rare diseases.
176-180	Measurement of certain efficacy and safety endpoints such as visual acuity is subjective, and results can be influenced by effort on the part of the patient, leading to a potential source of bias in the clinical trial. For trials intended to form the primary basis of an efficacy claim to support a marketing application, concurrent parallel group(s) should be used as a control (placebo or active) to decrease potential bias.	Other ways to decrease or address the bias from use of subjective endpoint such as visual acuity should be encouraged. Alternatives to placebo should be explored.	Proposed edits: "Measurement of certain efficacy and safety endpoints such as visual acuity is subjective, and results can be influenced by effort on the part of the patient, leading to a potential source of bias in the clinical trial. For trials intended to form the primary basis of an efficacy claim to support a marketing application, sponsors should consider and employ study designs to address and decrease potential bias, such as use of concurrent parallel group(s) ~~should be used~~ as a control (placebo or active) to decrease potential bias."
182-189	To further reduce potential bias, sponsors should include adequately-designed masking procedures.		~~To further reduce potential bias~~ In cases where a control group is included in a study, to reduce potential bias,

Section/ Lines	Guidance Text	Comment	Proposed Change
			sponsors should include adequately-designed masking procedures.
191-204	Although use of the contralateral eye to which the GT product is not administered as a control may potentially be considered, it is generally not recommended due to the following:…	The language should be softened to provide flexibility to use contralateral eye as a control, and acknowledge other considerations because otherwise trial design can be unduly burdensome. As many retinal disorders are rare, use of the contralateral eye as a control may be the best option. It is suggested to include examples in the guidance of circumstances that would allow for the contralateral eye to be used as a control, e.g when disease progression is similar between the two eyes.	~~Although use of the contralateral eye to which the GT product is not administered as a control may potentially be considered, it is generally not recommended due to the following~~ Sponsors should consider the following challenges when using the contralateral eye as a control:
164-168	In general, while intravitreal injection of the vehicle alone is often feasible as a placebo control, it may not be considered ethically acceptable unless the physical properties of an injection in a closed space have potential therapeutic benefit.	This statement should be clarified by providing an example of a placebo-controlled injection that would be considered to have potential therapeutic benefit, including necessary supportive data that establishes benefit.	

Section/ Lines	Guidance Text	Comment	Proposed Change
182-189	To further reduce potential bias, sponsors should include adequately-designed masking procedures…	This statement should be clarified by providing examples of masking procedures that may be considered appropriate. For example, sham surgical procedures may not be considered ethical or otherwise pose unacceptable risks to the subject (per lines 164-170). Furthermore, vehicle controls that incorporate only empty capsids may also pose unacceptable risks to the subject due to immunogenicity concerns and preclude the subject from future treatment with the investigational gene therapy.	
C. Study Population			
238	…the administration of an investigational drug in children must offer a prospect of direct clinical benefit to individually enrolled patients,…	Certain edits change the original meaning of the cited regulation, e.g. 21 CFR 50.52 states "direct benefit" and not "direct clinical benefit."	…the administration of an investigational drug in children must offer a prospect of direct ~~clinical~~ benefit to individually enrolled patients,…
D. Study Use			
261-263	For products intended for both eyes, the overall development plan prior to approval should include clinical trials in which both eyes receive the GT product.	Many patients only need one good eye to function on a daily basis. The current text suggests treatment must be assessed, with pre-approval,	We suggest adding the following sentence at the end of this section: "The need for bilateral treatment should be considered on a case by case basis based on the overall benefit risk assessment. This assessment may

Section/ Lines	Guidance Text	Comment	Proposed Change
		in both eyes when the disease is bilateral. Even in the presence of bilateral disease, the decision to treat one or two eyes will be dependent on the differences in vision in each eye, the disease being treated, the mechanism of action of the agent and overall benefit risk assessment (including surgical risk as described in lines 169-172).	be conducted in consultation with disease area experts and patient advocates, where appropriate." Examples and case studies may be helpful.
265-266	To ensure consistency across study sites, sponsors should include in the study protocol a detailed description of the product delivery procedure and devices used for delivery.	In the event that a new surgical procedure or device is being developed, materials outside of the protocol may be developed to communicate procedure or device information.	To allow for flexibility in the location of procedural and device information, we recommend the following revision: To ensure consistency across study sites, sponsors should include in the study ~~protocol~~ materials a detailed description of the product delivery procedure and devices used for delivery.
268-270	A single administration of a GT product in each eye may not always be sufficient for a variety of reasons. In such cases, careful studies, especially trials in humans, are recommended to explore the feasibility of repeat administration in the same eye	This section should be expanded to clarify circumstances in which it may be appropriate to enroll subjects previously administered the investigational GT product to explore the feasibility of repeat administration in the same eye in a subsequent trial.	

Section/ Lines	Guidance Text	Comment	Proposed Change
E. Safety Considerations			
278	Therefore, the procedure should be performed by individuals experienced in the method of planned delivery.	We agree that the procedure should be performed by individuals experienced in the method of planned delivery. The sponsor should ensure that investigators utilize the same device and that the product is delivered in a standardized, reproducible way.	We recommend adding to the end of this section: All participating investigators should agree to a standard delivery method and device and be trained (where necessary) in the use of that method to minimize patient-to patient variability in the delivery of the GT vector.
288-292	To minimize immune responses, immunosuppressants such as corticosteroids may be 288 considered before and after product administration. Immunosuppressant drugs may cause 289 increased intraocular pressure, cataracts, and other adverse events. Patients should be 290 closely monitored and treated as necessary to minimize the risk of developing glaucoma, 291 vision loss, and other complications.	This section of the guidance refers to the potential for immunosuppression to minimize immune responses. Since the eye has been described as an immune privileged location (at least in the absence of significant disease), it would be helpful if the Agency can provide additional direction on how the decision for instituting local or systemic immunosuppression should be made.	We recommend FDA consider adding information, in either the preclinical or clinical sections of the guidance, to assist sponsors in their evaluation of the need to include local or systemic immunosuppressive agents. As FDA acknowledges (at line 121) differences between the immune responses of animals and humans are important considerations when interpreting preclinical data.
F. Study Endpoints			
294		The section emphasizes clinical or functional endpoints but does not address the potential for surrogate endpoints. In line with recommendations included in other gene	We recommend including in this section a discussion on the potential use of surrogate endpoints.

Section/ Lines	Guidance Text	Comment	Proposed Change
		therapy guidances, we recommend that the guidance encourage the use of novel surrogate endpoints when feasible. For example, transgene expression can be considered as a valuable endpoint, and anatomical changes can be used as surrogate endpoints if they are quantifiable and related to the disease progression/recession. As the science evolves, there may be more surrogate endpoints to consider. For example, quantification of RNFL thickness or ganglion cell layer (GCL) volume measured by optical coherence tomography is considered as a meaningful measurement to quantify remaining ganglion cells and axons in patients affected with neuro-ophthalmic diseases. Preservation of remaining RNFL thickness and GCL volume is considered clinically meaningful as relationships between	

Section/ Lines	Guidance Text	Comment	Proposed Change
		structure and function have been described. In a conservative approach, a prevention of 4% loss of remaining GCL volume and RNFL thickness can be considered as clinically meaningful.	
G. Follow-Up Duration			
Lines			
H. Patient Experience			
353-355	Patient experience data may provide important additional information about the clinical benefit of a GT product. FDA encourages sponsors to collect patient experience data during product development and submit such data in a marketing application	This section should be expanded to clarify potential utility of patient experience data, such as circumstances in which inclusion of patient experience data in final product labeling may be appropriate.	
V.	**EXPEDITED PROGRAMS**		
VI.	**COMMUNICATION WITH FDA**		
373-380	FDA recommends communication with OTAT early in product development, before submission of an investigational new drug application (IND).) There are different meeting types that can be used for such discussions, depending on the stage of product development and the issues to be considered. These include pre-IND meetings and, earlier in development,	We note the recommendation in FDA's Draft Guidance on Human Gene Therapy for Rare Disease (lines 247-249) that sponsors consider designing their FIH as an adequate and well-controlled study that could provide evidence of effectiveness	Please clarify whether FDA would permit a second formal pre-IND meeting (Type B or Type C), meeting (if needed,) after the data from the IND enabling studies, to discuss the clinical study design. The guidance suggests (247-249) that sponsors consider designing their FIH as an adequate and well-controlled study

Section/ Lines	Guidance Text	Comment	Proposed Change
	INitial Targeted Engagement for Regulatory Advice on CBER producTs (INTERACT) meetings. Early nonbinding, regulatory advice can be obtained from OTAT through an INTERACT meeting, which can be used to discuss issues such as a product's early preclinical program, and/or through a pre-IND meeting prior to submission of the IND (Ref. 5).	depending on the results to support a marketing authorization. We agree that more frequent interactions with the FDA, particularly for products intended to treat rare diseases, would be beneficial. As INTERACT meetings focus on early nonclinical development, the option to have more than one formal meeting to discuss clinical trial design, manufacturing, etc prior to the initial IND submission would be helpful, particularly given that there may be a considerable amount of time between the pre-IND meeting and the IND submission.	that could provide evidence of effectiveness depending on the results to support a marketing authorization. Given that there may be a considerable amount of time between the pre-IND meeting and the IND submission, it may would be beneficial to have the opportunity for an additional interaction with the FDA (if needed) prior to the IND submission. Additional text suggestion: In addition to the pre-IND meeting for gene therapy products, the FDA will allow for an additional formal meeting prior to the submission of the initial IND submission.
VII.	**REFERENCES**		
		To assure that developers have a complete list of all applicable guidance in one location, footnotes (2, 4, 5, 6, 7, and 8) should be moved to the reference section.	List all FDA guidance as references

Alliance for Regenerative Medicine

December 7, 2018

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

Re: FDA Docket No. 2018-D-2173: Long-Term Follow-up After Administration of Human Gene Therapy Products; Draft Guidance for Industry

The Alliance for Regenerative Medicine (ARM) is an international multi-stakeholder advocacy organization that promotes legislative, regulatory and reimbursement initiatives necessary to facilitate access to life-giving advances in regenerative medicine worldwide. ARM is comprised of more than 300 leading life sciences companies, research institutions, investors, and patient groups that represent the regenerative medicine and advanced therapies community. Our life science company members are directly involved in the research, development, and clinical investigation of cell and gene therapy products, as well as the submission of investigational new drug (IND) applications, and Biologics License Applications (BLA) for such products to the FDA. Many of our member companies have gene therapy products under development covering a broad range of conditions. ARM takes the lead on the sector's most pressing and significant issues, fostering research, development, investment and commercialization of transformational treatments and cures for patients worldwide.

ARM commends the Food and Drug Administration (FDA) for the development of the recently released six gene therapy draft guidances. They are a good compliment to the four-cell therapy product guidance documents the Agency published last year and are helpful because they cover a broad spectrum of topics, from manufacturing to nonclinical, clinical and long-term follow-up as well as rare diseases and specific diseases; and demonstrate support for innovation in this field.

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ARM is providing comments for each of the six gene therapy guidances. However, below is a list of general recommendations and concerns we would request the Agency consider in addition to the specific guidance comments:

- ARM encourages the FDA to select a definition for gene therapy, such as the one listed on FDA's website, and to use this definition consistently throughout the guidance documents.

- The Agency should consider creating a new version of the Common Technical Document (CTD) with examples for gene therapy, as the Chemistry, Manufacturing and Controls (CMS) guidance is quite detailed. Providing additional guidance on comparability would be helpful for all sponsors, including for when sponsors are improving the safety or efficacy of their products through manufacturing changes.

- Several of the draft guidances contain information on CMC, nonclinical and clinical development. It may be challenging for new sponsors to determine where to find relevant information for one of the disciplines if the information is spread throughout several guidance documents. The Agency may want to consolidate discipline specific guidance in the future for life-cycle management purposes.

- The FDA may also want to consider cross-referencing between the guidelines when appropriate.

- Long-term follow-up of patients treated with gene therapy will need to evolve as the field matures and we anticipate the maximum duration of recommended long-term follow-up will eventually be limited to 10 years or less, instead of 15 years. We encourage FDA to consider follow-up duration based on gene therapy specificity in vivo vs ex vivo and whether the vector is episomal or integrative.

- Whether transgene expression, or expression of the modified gene, can be used as a surrogate endpoint should be clarified, and if yes, the FDA should clarify how to use the surrogate endpoints (as primary or secondary?). It may be helpful to refer to ICH E8: "A surrogate endpoint is an endpoint that is intended to relate to a clinically important outcome but does not in itself measure a clinical benefit. Surrogate endpoints may be used as primary endpoints when appropriate (when the surrogate is reasonably likely or well known to predict clinical outcome).

- We would encourage the Agency to clarify how patient preference and willingness can be better incorporated into the risk benefit consideration.

In conclusion, ARM appreciates the opportunity to continue the dialogue with the Agency. Responding to draft guidances provide a significant opportunity to foster development of gene therapies for conditions with significant unmet medical need. Additionally, ARM hopes that the Agency will consider our August 3, 2018 letter which recommended "guiding principles that may be helpful to determining approaches to other disease-specific guidance as well as finalizing the recently published guidances."

Below are comments and recommend changes to the *Long-Term Follow-up After Administration of Human Gene Therapy Products; Draft Guidance for Industry.*

Sincerely,

Director, U.S. Policy and Advocacy

GENERAL COMMENTS:

1. Overall, ARM welcomes this updated guidance document, and find that the illustrative examples as well as the Figure, Table, and Definitions provided are very helpful to the reader to understand the Agency's recommendations. The examples are also helpful to understand the guidance for the different types of gene therapy products, which is appreciated.
2. We also welcome the risk-based approach selected by the Agency to determine the nature and duration of the long-term follow-up (LTFU), and the Agency's flexibility in reassessing the design and duration of the LTFU as additional information on risk/benefit becomes available.
3. As the field of gene therapy matures, we anticipate that the recommendation for LTFU will evolve, and that the recommended duration for LTFU will be significantly reduced, particularly for products using integrating vectors as 15 years is quite burdensome for both patients and Sponsors and could hinder innovation. In the future, we anticipate the duration of LTFU post-approval will be driven by the rarity of the disease, rather than by the fact the product is a gene therapy product; and 10 years may be the maximum duration recommended (at least for adults).
4. As for the previous guidance on LTFU, it might be helpful to ask experts in the field of gene therapy to provide their input on the proposed revisions, and the Agency may consider hosting a public workshop or discussion to confirm certain aspects of the guidance, particularly with respect to more innovative gene therapy products. For example, experts could opine on Figure 1, Table 1 and on how best to adapt the guideline to novel or emerging gene therapy technology.
5. It might be helpful to add a section on recommended regulatory interactions throughout the lifecycle of a gene therapy product with regards to long-term follow-up. For example, the guidance could mention: INTERACT meeting for design nonclinical studies to inform duration of LTFU during clinical development, pre-IND meeting for nonclinical and clinical studies, etc.).
6. Lastly, there are a lot of recommendations on how to conduct nonclinical studies in this guidance, and given the title of the document, it may not be obvious to sponsors that this level of detail is included. Thus, the Agency may consider moving the details on nonclinical study design in a different guidance, such as for example the November 2013 Preclinical Assessment of Investigational Cellular and Gene Therapy Products, and simply refer to this updated guidance in the revised LTFU guidance. Cross-referencing between the appropriate guidance documents at the minimum would likely be useful for Sponsors developing gene therapy products for the first time.

SPECIFIC MAJOR COMMENTS

Page Number	Section/ Page/Line	Comment and Rationale	Proposed change (if applicable)
1	Section I. Introduction	In this section, the Agency may want to be more explicit about the fact that the guidance is organized into 3 major parts. This may help the reader understand the scope of the guidance better.	Insert the following text in line 41: Specifically, the guidance is organized in three major parts:

			1) Nonclinical risk assessment to determine whether long-term follow-up of subjects treated in clinical trials will be recommended in a LTFU clinical study and to inform the potential duration of this LTFU study. 2) Recommendations for LTFU clinical studies (i.e. LTFU of subjects treated in clinical trials) 3) Recommendations for additional LTFU of patients treated post licensure, if applicable.
Page 1	Section I. Introduction Line 17	"Human gene therapy product" is defined on lines 1124-1129 of the guidance. "What is Gene Therapy?" is currently described in an alternative way on the FDA website. Is it appropriate to broadly reference the administration of nucleic acids or genetically modified microorganisms as examples of gene therapy products when they may not mediate their effects by transcription or translation of transferred genetic material, or by specifically altering host (human) genetic sequences? Should the definition of gene therapy exclude products that do not have long lasting, durable, effects, i.e. gene therapy that have transient effect? (see lines 61-62). To date, siRNA products have not been considered gene therapy products for example. In the past, ARM has shared the following definition with FDA:	We recommend that the definition for "human gene therapy" and "human gene therapy product" be aligned across FDA resources. We recommend including the definition of gene therapy in the Introduction of all gene therapy guidance documents including the LTFU guidance. We recommend the Agency considers our proposed definition.

		"Gene therapy is defined as a medical intervention intended to prevent, treat, cure, or diagnose a disease or medical condition by regulating, repairing, replacing, adding, modifying, or deleting a genetic sequence or sequences, in somatic cells." In addition, the following recent publication may be helpful to update the definition: Dunbar *et al*., Gene therapy comes of age. *Science* 359, eaan4672 (2018).	
Page 20 Page 32	Line 764 (Appendix 1 Line 1252)	The recommendation to have a separate heading for long-term follow-up seems somewhat redundant with existing guidance for DSURs (FDA Guidance for Industry E2F Development Safety Update Report Guidance dated August 2011). Overall, the value of the template form provided in Appendix 1 seems to be primarily for when the development program is completed, and long-term follow-up is the only ongoing activity generating data for the Annual Report or DSUR. In this case, only the form could be provided as DSUR/Annual Report. The template provided in Appendix 1 is not helpful if a sponsor has ongoing clinical trials (in addition to the LTFU data collection effort) as in that case all the information requested in the form would already be planned to be provided in the DSUR or Annual Report in written text (not in tabular format) in part in other sections. Using the form would require redundancy.	Suggested edit page 20, line 767: It is recommended that the annual report contain a subtitle for Long Term Follow-Up ~~(See Appendix 1 of this document)~~. Suggested edit page 20, line 778: "In this case, you should provide the LTFU information **in Section 8.3 of the DSUR**. **If the development program is completed and long-term follow-up is the only ongoing activity generating data for the DSUR or Annual Report, using the form provided in Appendix 1 is recommended to summarize the available information since previous DSUR or Annual report.** **When the development program is completed, and long-term follow-up is the only ongoing activity generating data for the DSUR or Annual Report, the form could be the only section where new information is presented** (Ref. 28).

Page 1	Section II. Scope	The Agency clarifies that the scope of the guidance includes investigational gene therapy products in clinical studies as well as products that are on the market ("licensed"). It may be helpful to clarify that in addition to safety, the guidance discusses LTFU of efficacy. In this case, the LTFU study may not be "observational". In short, the scope of this guidance is for gene therapy products, pre and post BLA, for LTFU of safety, persistence and as applicable efficacy.	Consider merging some of the text in Section V.A. page 15 into the Scope section of the guidance. For example, the Agency could paste line 573 ("As a sponsor, you may consider designing the LTFU protocol to assess the long-term clinical efficacy, and durability of your product.") into the scope of the guidance.
Page 1	Section II. Scope	The Agency should make it explicit that the use of real word evidence for post-licensure LTFU is within the scope of this guidance.	For example, the Agency could add a reference to the use of a Registry (line 1078).
Page 1	Section II. Scope	The concept of LTFU may be confusing when a short follow-up period is recommended (such as 2 years for patients treated with an AAV gene therapy product for example). The Agency should clarify whether the duration described in the guidance is *after* the main study is completed or whether it is the total duration post drug product administration. For example, for AAV products, in the latter situation if the main study is a 2-year study, then once it is completed one would consider that no additional LTFU is required based on the draft guidance. In the former situation, a total of 4 years of follow-up would be needed (2 years in main study, and 2 years in LTFU study).	Consider adding clarification on where the LTFU starts (after main study, or after drug product infusion). This clarification could be added before Table 1 on page 14 as well.
Page 1	Section II. Scope	The Agency may wish to clarify that in general the complete data set from LTFU activities, regardless of	Suggested text to add at the end of the paragraph in this section:

		the duration of LTFU, would be expected to be provided post-licensure.	"In general, it is expected that the totality of the LTFU data would be provided post-licensure and that not all of the LTFU data would be provided at time of BLA submission."
Page 2	Section II. Scope	Related to the comments made in this document on gene therapy definitions and given the rapid evolution of the gene therapy field, it would be useful for this section to outline the types of gene therapy products this guidance is supposed to cover (genetically modified cells, as well as direct administration of vectors etc.). OTAT may consider including the definition of gene therapy in the "Scope" section of this guidance, and any other guidance refereeing to gene therapy. [See other comment on Definition of gene therapy below.]	
Page 5	Section IV.A.	Within this section, FDA suggests that sponsors can combine nonclinical and clinical experience to assess the risk of delayed adverse events to potentially revise the length/rigor of LTFU. The example criteria for using data from other products for risk evaluation refers to the same vector class, similar route of administration, or the same clinical indication. The Agency may wish to clarify whether LTFU would be required for the use of the same vector, same target cells for ex vivo genetic modification, with the same route of administration, for a second indication. The statements in this guidance suggest that the indication would not need to be the same to alleviate the	

		need for LTFU. Could the Agency clarify whether the indications need to be closely related or whether if the product has the same vector/route, then the indication does not need to be the same to alleviate need for LTFU? In other words, it would be helpful to clarify if there are specific cases that do not require LTFU either because there are enough data for the vector class or because there are enough data for that product for a previous indication. This may be applicable as the field matures. The FDA may wish to think about criteria for when that will be the case for a future update of this guidance.	
Page 6	Section IV.A. Line 218	The Agency may want to provide additional guidance on the type of data and information "relevant to the assessment of the risk of delayed events" that should be submitted to the INDs. Would the Agency consider a risk-based approach section in INDs to justify the development of gene therapy products and in particular the design of the LTFU study? It might be helpful to provide some guidance or cross reference on methodologies and format that could be used (Similar to Module 2.2 for European Marketing Authorization Applications for advanced therapies).	
Page 6	Section IV.A. Figure 1	Figure 1 is extremely helpful and clear.	
Page 6	Section IV.A. Figure 1	Guidance seems to be missing the criteria for LTFU of patients treated post licensure. Figure 1 is clear as to when LTFU is required for subjects treated in clinical studies only.	

		The Agency should clarify further what criteria are used to determine whether, in addition to LTFU of subjects treated in clinical trials, LTFU of patients treated post-approval is required. The Agency mentions the small number of patients studied in clinical trials. It would be helpful to quantify what "limited" means (line 1057). If other criteria are used by the Agency, they should be explained. Also, it is assumed the same risk-based approach can be used post-approval to determine the duration of LTFU and to revise design of LTFU study as new information becomes available. It would be helpful to provide examples to illustrate this concept. This comment also applies to Section VI on page 26.	
Page 7	Question 4:	Text not necessary in cross reference to increase readability.	Consider deleting "for recommendations on how to perform clinical LTFU observations.)
Page 9	Section IV.B. Lines 348-350	Please clarify how the Agency defines the term "persistence"; particularly in the following sentence: "Data collected in clinical study in your GT product indicates product persistence, even though data from your preclinical studies suggested that the product did not persist.	
Page 9	Section IV.B. Line 361	The Agency recommends that preclinical biodistribution studies (either as a separate study or as a component of a toxicology study) using methods shown to be sensitive and quantitative to detect product sequences be conducted. Please clarify when these studies should be	

		conducted and submitted to the Agency relative to the submission of a BLA or IND.	
Page 12	Section IV.C Line 477 Line 501	The Agency may wish to modify this sentence to take into account when the vector is not persistent but the transgene is persistent (as for CAR T cell therapy for example). Providing an example of what would constitute an appropriate "vector integration assay" would be helpful.	
Page 14	Table 1	Recommended durations of follow-up within Table 1 are not fully consistent. We recommend the Agency adds a duration (such as it is indicated for the AAV vectors) in the third column for all products where there is currently a "yes". Similarly, for where "Product specific" is indicated, it would be helpful to add a range of duration in parentheses.	Consider adding "(10-15 years)" in 3rd column rows 7, 8, 9, and 12. A footnote could be added to differentiate requirements for follow-up for pediatric patients and for adults (see Comment below on Page 16).
Page 14	Table 1 Lines 620-623	Recommended durations of follow-up in Table 1 and in lines 620-623 are not fully consistent. The Agency should consider making these durations exactly the same to avoid confusion; or delete lines 617 to 623 and refer to Table 1.	
Page 15	Section V.	In this section, the Agency may wish to clarify when efficacy LTFU would be recommended and give proactive examples.	

Page 15	Section V. Lines 565-566	LTFU protocols may not always be separate from the main study. We believe the language in the guidance should provide flexibility on this point.	Typically, LTFU observations are conducted under a protocol (LTFU protocol) that **may or may** not be separate from the main study protocol and may begin immediately after the main study protocol ends.
Page 16	Lines 620-623	For products using integrating vectors, the Agency should consider 15 years of follow-up for pediatric patients and 10 years for adults. This comment highlights one of the main reasons to encourage dialogue prior to finalization of LTFU protocols. Changes made in lines 620 to 623 should be consistent with Table 1.	A bullet, or sub-bullet could be added after line 620 and 622 to indicate this different duration of follow-up for pediatric patients and adult patients. This could be added as a footnote in Table 1 as well for each type of products where applicable. Suggested changes by line: 620: "**Ten to** fifteen years for integrating vectors…" 622: "**Ten to** fifteen years for genome editing products." 623: "**Two to** five years for AAV vectors."
Page 17	Section V. D. Line 657	The template for health care providers mentioned could be provided by the Agency as an Appendix.	
Page 17	Section V. C. Lines 634-636	The Agency recommends modification of duration of the LTFU observation period based on ongoing assessment of product persistence, transgene expression, and clinical findings. Please clarify whether this recommendation could apply to individual clinical trial participants. Would the use of tests similar to those used to determine persistence of	

		integrated vectors in preclinical models e.g. PCR, be acceptable to establish loss of persistence in an individual clinical trial participant? Additionally, please clarify whether demonstration of loss of persistence by an approved test would permit discontinuation of LTFU in that research subject.	
Page 18	Section V. D. Lines 695-699; 723-728	Can FDA comment on the ability to utilize digital technology to contact subjects where no additional specific screening is required?	V. D. Elements of Long-Term Follow-Up Observations Lines 695-699 and 723-728
Page 18	Section V. D. Lines 700-703	The Agency recommends appropriate follow up for subjects in whom vector persistence had been shown. Please clarify whether loss of persistence would permit discontinuation of monitoring of persistence at subsequent visits/contacts.	
Page 18	Section V. F. Lines 877-879	The Agency recommends specific vector integration site analysis when cells are known to have high replicative capacity and survival. Please clarify whether GT products made from terminally differentiated circulating lymphocytes are considered cells with high replicative capacity and survival.	
Page 22	Section V. F. 1 Line 874	The Agency should provide quantitative definitions of polyclonal, oligoclonal and monoclonal. Oligoclonal is particularly vague.	
Page 26	Section VI.	In this section, it might be useful for the Agency to clarify whether the recommendation to include efficacy in LTFU post-approval would be influenced by whether the approval was based on Subpart E (accelerated	

		approval; 21CFR601) or not. This may be of interest for products with Regenerative Medicine Advanced Therapy (RMAT) or Breakthrough Therapy designations.	
ADDITIONAL COMMENTS			
Page 15	Section V.	A LTFU study can begin immediately after the first patient in the main study protocol has their last visit and enrolls in the LTFU study.	We either recommend to 1) modify the language as follows: "Typically, LTFU observations are conducted under a protocol (LTFU protocol) that is separate from the main study protocol, and may begin immediately after the **first subject completes their last visit in the main study and enrolls in the LTFU study** ~~main study protocol ends~~." Or to delete the end of the sentence "and may begin… main study protocol ends" to leave flexibility for sponsors as to when the LTFU study starts (if applicable).
Page 16	Section V.C. Line 603	"the nature of the exposure" is not very clear. The Agency should consider clarifying what this means (route of administration? duration of exposure? dose?)	Providing examples of the nature of the exposure in this context may be helpful.
Page 17	Section V.D. Line 647	When referring to "sampling plan (for patients test samples, such as blood)" to be included in LTFU study, it would be helpful for the Agency to clarify whether such study would still be considered "observational".	Consider removing the word "observational" from the guidance to refer to LTFU, or consider defining "observational" in Definitions (page 28) or providing a reference for the definition.

Page 27	Section VI. Line 1077-1083	The Agency could include the possibility to use an existing Registry to conduct long-term follow-up of patients post-licensure. This would be in line with the 21st Century Cures act for advanced therapies for RMAT designated products. It might be helpful for the Agency to clarify when LTFU should be in a clinical versus a Registry. What would be the reason for requiring one versus the other?	Suggested edits in bold: For instance, we may recommend that you establish a registry, **or use an existing patient registry**, to systematically capture and track data from treated patients**,** with solicited sample collection **(if applicable)**, and follow-up of adverse events to resolution or stabilization to collect additional pertinent data. It may be necessary to establish a registry system, or use an existing patient registry, to specifically capture adverse event data from treated patients who receive a GT product. This registry system can be a part of the PVP plan and reviewed at the time of licensure.
Page 27	Section VI. Line 1080	"It may be necessary to establish a registry system to specifically capture adverse event data from treated patients who receive a GT product. This registry system can be a part of the PVP plan and reviewed at the time of licensure." We wish to emphasize the need to use uniform definitions for events, event severity and event duration across marketing authorization holders since it is likely that this LTFU data will be compared. Since FDA is regulating across Sponsors it is envisioned that they would play a role in codifying these standards.	
Page 27	Section VI. Line 1087	"Your study protocol should include specific adverse events of interest that you intend to evaluate, and the duration of observation for all patients enrolled in your post-marketing study."	

		To promote quality and consistent/systematic analyses of LT safety and among different GT products, a harmonized method of collection and assessment of data should be established for GTs, wherever possible, eg, criteria used for severity of adverse events (e.g., Lee, Penn, etc., for CRS); dictionary used to code AEs, drugs, etc.	

Subject: Comment on FDA Draft Guidance for Industry Titled "Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up; Draft Guidance for Industry"

Docket #: FDA-1999-D-0081

ARM is an international multi-stakeholder advocacy organization based in Washington, D.C. that promotes legislative, regulatory, and reimbursement initiatives necessary to facilitate access to life-giving advances in regenerative medicine worldwide. ARM comprises more than 300 leading life sciences companies, research institutions, investors, and patient groups that represent the regenerative medicine and advanced therapies community. ARM takes the lead on the sector's most pressing and significant issues, fostering research, development, investment, and commercialization of transformational treatments and cures for patients worldwide.

It is out of that dedication today that we submit our comments:

After review of the guidance in total, ARM and its members have generated a combination of general and specific comments on this document, and in general commend the FDA for addressing key topics of concern to the retroviral delivered gene therapy industry. In particular, we have found the inclusion of the section "Summary of revisions from the 2006 RCR Guidance" to be extremely helpful and request similar sections in future guidance which acts to either revise existing guidance or supplant existing guidance.

In addition, this new guidance from the Agency regarding RCR amplification is very helpful, particularly in regard to each lot of ex-vivo transduced cells and culture supernatant be RCR tested regardless of the length of time that the cells are cultured after transduction. For consistently RCR-negative products, where this RCR testing can be reduced or eliminated from each batch release upon submission and FDA concurrence was also very helpful. Identifying all the contents for such a submission also struck the appropriate level of detail for such advice, since the package needs to contain all elements to address the Agency's concerns (a discussion of safety features in the vector design which reduces the likelihood of generating RCR, a description of vector testing in accordance with current guidance, and manufacturing experience).

This new guidance from the Agency regarding vector supernatant assays including the culture of supernatant on a permissive cell line for a minimum of five passages to amplify any potential RCR is very helpful and the guidance is appreciated. Similarly, Agency feedback on cell testing (it should be accomplished by co-culture with a permissive cell line for a minimum of five passages to also amplify any potential RCR) was additionally helpful. Our reviewers also applaud the new guidance from the Agency regarding supernatant testing and found Appendix 1-1 to be informative, particularly in regard to the sufficient amount of supernatant be tested to ensure a 95% probability of detection of RCR if present at a concentration of 1 RCR/dose equivalent. This is a safety concern and is therefore of major importance, so the guidance is appreciated.

On the subject of testing, we would appreciate additional clarity on testing requirements between different use cases, for example between a viral vector product and a gene-modified cell therapy product. In addition, for sponsors interested in reducing or eliminating extensive testing over time, clarity on the level of data required for such a process to occur would be appreciated. Given the level of complexity surrounding supernatant testing use-cases, we would also recommend that FDA include example calculations for determine testing and dosing volumes.

Last, the ARM reviewers happily welcome the removal of the need to collect and archive patient samples if RCR testing after 1 year were negative. FDA's revision of recommendations for post-delivery follow up for RCR product is both timely and helpful.

Our additional comments on specific sections of the text can be found below, under Appendix 1 – Detailed comments on FDA Guidance.

Overall, we commend the FDA on generating this guidance, and appreciate the level of detail provided. Our members look forward to utilizing your revised guidance in the generation of novel therapeutics.

Respectfully Submitted,

Robert J. Falb

Director, U.S Policy & Advocacy

Alliance for Regenerative Medicine, 1900 L Street NW, Suite 735, Washington D.C. 20036

Appendix 1 – Detailed comments on FDA Guidance:

Line Number	Comment and Rationale	Proposed Change (if applicable)
162 - 166	Lines 339 - 341 of this draft guidance also recommends that methods such as PCR may be used in lieu of culture based methods; particularly, when time constraints are present or when you have accumulated sufficient data. Suggest adding the line regarding using PCR instead in the case of time restraints.	
246 - 247	This sentence recommends testing ex vivo transduced cell culture supernatant for RCR, but the remaining discussion only includes transduced cells. Was it the intention of the authors to exclude ex vivo transduced cell culture supernatant testing from the recommendation? Since any infectious RCR would enter and integrate into the cell genome, it could be assumed that testing the cells only would be sufficient to determine if and when RCR was present. Also, current manufacturing processes involve a continual cycling of media for cell growth which would not allow for any accumulation of replicating virus in the system.	Recommend asking the agency to separate testing requirements for the vector supernatant and the ex-vivo modified cells, so there will be no confusion. Recommend removing ex vivo transduced culture supernatant testing requirement.

267	Suggest addition of word 'Even if ex vivo …"	
291 - 296	If the intention is to require ex vivo supernatant testing, what is the recommendation for volume? The patient dose calculation is not applicable here.	
294 - 296	In instances where vector is manufactured in advance or in early studies where the vector dose may be variable, testing the vector stock to achieve the 1 dose equivalent may be a problem. Can it be suggested that where one dose equivalent is unknown, the previous rules would apply where the vector is tested based on lot size?	We recommend that sponsors be allowed to propose and justify an appropriate volume for testing to reach 95% probability of detection of RCR per dose equivalent.
354 - 356	Does the agency feel that it is worth the safety risk to pseudo-type an HIV mutant with VSV-G for representation of lentiviral vectors? Would other controls be suitable since this and other forms of positive control are not readily available for general use similar to the RCR positive control banked at the ATCC?	Additional guidance related to lentiviral vectors would be helpful and where positive controls are not readily available.
414 - 423	The Agency recommends the development of a risk assessment to propose appropriate periodic patient monitoring for RCR, which is helpful feedback to sponsors. However, the Agency also notes that provisions should be made "in the BLA" to collect relevant clinical samples, including biopsies when relevant, for RCR testing upon development of an adverse event suggestive of a	Additional details would be helpful for conducting appropriate risk assessment leading to periodic patient monitoring for RCR.

	retrovirus-associated disease, including death or the development of neoplasms. In this provision, FDA's intent is unclear. Is the Agency suggesting a post-market commitment, based upon the risk assessment? If so, then this needs to be more clearly articulated. Alternatively, if this is not the FDA's meaning for these provisions, more details are needed as the BLA would not contain sample collection and testing provisions, instead only the clinical trial and patient informed consents from the trials would contain this information.	
426 - 446	The guidance regarding patient follow-up is helpful, which details they should be followed for up to fifteen years following product licensure to monitor for delayed adverse events. However, this guidance is helpful in that it outlines the possibility if all post-treatment assays are negative during the first year of monitoring, collection of yearly follow-up samples may be discontinued. The Agency continues to recommend that annual clinical history be obtained to determine clinical outcomes suggestive of retroviral disease (e.g., cancer, neurologic disorders, hematologic disorders). If an adverse event suggestive of retroviral disease occurs, samples should be collected and tested for RCR. To test for RCR, FDA recommends that sponsors use either serologic detection of RCR-specific antibodies or a polymerase	No change requested.

	chain reaction assay for RCR-specific DNA sequences.	
563 - 573	We believe there may be a technical error in this calculation: when you are infecting 1e8 cells at a MOI = 0.5 then you are adding 5E7 TU to the cells. If the vector titer is 5e7 TU/mL and you need to add 5e7 TU to the cells, then you should add 1 mL of the vector to achieve a MOI of 0.5 therefore the dose is 1 mL, not the 5ml given in the original calculation.	

Subject: Comment on FDA Draft Guidance for Industry Titled "Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs); Draft Guidance for Industry"

Docket #: FDA-2008-D-0205

ARM is an international multi-stakeholder advocacy organization based in Washington, D.C. that promotes legislative, regulatory, and reimbursement initiatives necessary to facilitate access to life-giving advances in regenerative medicine worldwide. ARM comprises more than 300 leading life sciences companies, research institutions, investors, and patient groups that represent the regenerative medicine and advanced therapies community. ARM takes the lead on the sector's most pressing and significant issues, fostering research, development, investment, and commercialization of transformational treatments and cures for patients worldwide.

It is out of that dedication today that we submit our comments:

After review of the document in total, we have compiled a combination of general and specific comments on the draft guidance. From a general perspective, we see many positive features of this guidance but also believe there to be much room for additional clarification from the FDA. Due to the varied nature of these general comments, and requests for clarity, we have supplied feedback in a bulleted list for easy reference.

- We in general applaud the FDA on this guidance. We appreciate the new label guidance language including testing recommendations within Autologous vs Allogeneic therapeutics. In addition, we would like to highlight our appreciation for the follow sections:
  - Within Section V, we appreciate FDA's effort to strike the right balance regarding level of detail on this subject matter;
  - A.4.A Specification (3.2.S.4.1) lines 1243 – 1255 and 1258 – 1261;
  - B.5.a. Specifications (3.2.P.5.1) lines 1839 – 1871;
  - C.2. Adventitious Agents Safety Evaluation (3.2.A.2) lines 2142 – 2144.
  - Content covered in 1506-1521; this strikes the right balance between informative vs prescriptive level of detail for the scope of this guidance

- Content covered in lines 2134-2150 is very helpful and provides an excellent level of detail on the subject
- In some cases, guidance seems directed towards BLA applicants, not necessarily for those sponsors in early clinical development

- The current guidance does not provide additional information on particle assessment; we ask the FDA to provide this information.

- The current draft does not provide guidance for information to be included in IND as mentioned in section 3.2.R; we ask the FDA to provide this information.

- We ask that the FDA to clarify the timing of application of the guidance recommendations: The draft guidance indicates that the guidance recommendations apply to CMC information for human gene therapy INDs. However, some of the guidance recommendations are applicable to the original IND submission, while others may be applicable to different phases of development after the initial IND submission, and some are applicable as information to be submitted at the time of BLA submission which may have been collected during the IND stage.
  - We recommend that the Agency clearly articulate, identify, and separate the recommendations in the guidance into 3 general categories that apply at 1) the time of original IND submission, 2) those that are applicable during the IND stage but after the original submission (and clarify when they are applicable), and 3) information that is expected at the time of BLA submission.
  - We request additional clarification on expectations around documentation to be included within an IND for ancillary materials (plastics certifications, CoA etc.)

- We ask the FDA to please clarify the scope of the guidance, which has been stated to cover "gene therapy applications". However, this general approach may not be appropriate in several instances. Some of the guidance recommendations may be more suitable for ex vivo gene therapy products as opposed to in vivo gene therapy products. For example, some of the recommendations regarding shipping and handling are specific for ex-vivo gene therapy products and either may not apply or may not be necessary for an in-vivo gene therapy at the IND stage. We recommend that the Agency distinguish the recommendations for ex vivo gene therapy products from in vivo gene therapy products throughout the guidance.
  - We recommend that the FDA might also consider a separate guidance that addresses CMC considerations for AAV type vectors.

- Given the complexity surrounding CMC for Gene Modified Cell Therapy vs CMC for direct viral vector Gene Therapy, we recommend FDA to generate a separate guidance for gene therapy products consisting of cells genetically modified ex vivo.

- It would be helpful if the guidance could make allowances and recommendations to leverage existing knowledge and data, for example when one platform for gene therapy such as same vector and manufacturing process is used with a different gene construct for a separate IND. The guidance should share FDA's thoughts on this and recommendations on how, when, and what types of data sponsors can leverage and reference from another previously submitted IND.

- Please add a glossary of terms and use consistent terminology throughout the guidance**.** Certain terms will benefit from clear definition and consistent use, for example vector vs viral vector; ex vivo vs in vivo GT, etc.

- We note that for "Quality Overall Summary (Module 2)" the level of detail and information recommended in this section is not consistent with industry practice for early stages of development and does not provide a tremendous benefit to the Agency. In current practice, many sponsors do not begin including Module 2 sections until Phase 3/Pivotal Trial, so clarification is needed regarding the stages of development for which this type of information would be expected.

- Analytical Comparability – Though this concept is embedded throughout the guidance (lines 1105 - 1120); it carries such importance that a stand-alone section on this topic is warranted. Additionally, reference could be made to ICH Q5E for this topic. In the stand-alone section, it would be helpful to provide suggestions for methodology that would be acceptable, when clinical data would be required, and how to think of comparability when improvements are made to the product for safety and/or efficacy.

- Additional clarification on what FDA sees as distinction between DS and DP in materials in continuous use during manufacture of a Gene Therapy. Could the Agency clarify whether it would be possible for a process to have two distinct drug substances and hence to file two drug substance CTD sections in a BLA? For example, for autologous genetically modified cells, would the active substance (transduced cells), as well as the virus used for genetic modification be both considered drug substance for a BLA? It would be helpful for the FDA to review the EU Directive 2009/120/EC to compare to definitions of what is an active substance and what are the starting materials for genetically modified

cells. Global regulatory convergence would be helpful. In addition, it would be helpful for the FDA to clarify what distinguishes raw, starting, and ancillary materials in a continuous manufacturing process.

- Request FDA to provide section specific cross-reference to existing master files where appropriate.

- We recommend providing some further clarification regarding what is meant by a 'relevant' biological activity. For example, functional expression of the transgene in the target cell vs cell killing activity of the transduced cell product.

In addition to the general comments above, we have included specific line item comments in the sections below, title "Appendix 1 – Detailed comments on FDA Guidance".

Overall, we would like to again commend the FDA for generating such a comprehensive guidance document on the complex field of CMC for Human Gene Therapy IND's. We see the release of such detailed and forward-looking guidance as a mark of the Agency's commitment to collaboration and growth with the industry. Our members look forward to utilizing your revised guidance in generation of novel therapeutic products.

Respectfully Submitted,

Robert J. Falb

Director, U.S Policy & Advocacy

Alliance for Regenerative Medicine

Appendix 1 – Detailed comments on FDA Guidance:

Line Number	Comment and Rationale	Proposed Change/Recommendation
16-45	Include a statement cross referencing Current good tissue practice and CFR 1271 to clarify applicability	
38	The link to information on the submission of an eCTD directs to an FDA page "Page not found"	
50 - 52	Human gene therapy products are defined as all products that mediate their effects by transcription or translation of transferred genetic material or by specifically altering host (human) genetic sequences.	ARM suggests including the following definition for Gene Therapies to clarify the scope of this section: "Gene therapy is defined as a medical intervention intended to prevent, treat, cure, or diagnose a disease or medical condition by regulating, repairing, replacing, adding, modifying, or deleting a genetic sequence or sequences, in somatic cells."
54 - 57	Gene therapy products meet the definition of "biological product" in section 351(i) of the Public Health Service (PHS) Act (42 U.S.C. 262(i)) when such products are applicable to the prevention, treatment, or cure of a disease or condition of human beings.	Clarification that gene therapies can be biologicals even if synthetically manufactured
71 - 73	Provide clarification and examples of the different types of changes (e.g. major vs. minor) that need to be described in an IND amendment. Indicate if changes can be immediately	

	implemented upon submission of the IND amendment, or, if there is a period of time for FDA review and approval.	
72-73 II footnote	Link to reference 2 does not work. The draft guidance states "if manufacturing change could affect product safety, identity, quality, purity, potency or stability, you should submit the manufacturing change prior to implementation".	Please clarify whether the sponsor implement the change following notification or must gain approval from the agency prior to implementation. Please clarify if a manufacturing change is known not to have an impact on the attributes listed, do the sponsors have to notify the agency of the change?
106 - 118	Lead time ~~(e.g., 30 days)~~ for FDA review before release of a new lot of clinical trial material.	Removal of "(e.g., 30 days)"
122 - 123	Provide clarification on what "all" labels mean. Is this drug product primary and secondary labels?	
123-124	Please clarify whether a mock-up label will be sufficient.	
134 - 139	Providing information that categorical exclusions regarding the Environmental Assessment are ordinarily available is helpful, however providing an example where one is needed could be of additional assistance.	
137	Clarify what is meant by "ordinary circumstances".	

143 - 170	This section seems to refer to INDs, but also notes Drug Master Files, which are frequently referenced in the context of other submissions.	We request that FDA clarify whether this section applies to other submissions beyond just INDs (e.g., BLAs, NDAs, etc.).
175 - 206	The information requested in Module 2 is extensive and may not be available for most products in early IND stages. For example, a description of critical quality attributes or a description of the mechanism of action may not be available until later in the IND stages.	
185 - 187	It is premature to specify verified Critical Quality Attributes as they are linked to clinical outcomes and there is no clinical data for most products when an original IND is filed. We suggest providing this clarification, and/ or conforming the language used to ICH Q8 and Q11, both of which refer to "potential CQAs," reflecting the preliminary, evolving nature of CQAs at that stage.	"Potential preliminary critical quality attributes (CQAs) that are relevant to the safety and biological activity of the product as they are understood at the time of submission."
187-206	Although the section is labeled as "General Information," these specific lines describe establishing CQAs in the context of pharmaceutical development and manufacture.	We believe this information should instead be captured in section 3.2.P.2, "Pharmaceutical Development."

193	Clarification of 'in - process materials'	Change to specify: reagents, biological starting materials, animal derived materials. All materials other than Drug Substance, Drug Product, and excipients.
214 - 215	For the purpose of this guidance, a Drug Substance is defined as an active ingredient that is intended to furnish biological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease.	Definition of permutations of Drug Substance should also include a scenario of nucleic acid and nuclease (individually are not Drug Substance but together confer activity)
220 - 228	More guidance is necessary as to where to place information in the CTD structure for a continuous process if there is no distinct Drug Substance and Drug Product.	One approach would be to follow the same recommendation as the Europeans definitions in Directive 2009/120/EC.
238 - 239	This section references the use of a "tentative expiry date, if applicable," but does not define or explain the term, or describe when it might be applicable or appropriate.	We suggest incorporating a clearer explanation of these concepts into the final version of the guidance.
243 - 252	The Agency provides helpful guidance here, stating separate CTD sections should be provided for device versus gene therapy product sections.	
254 - 274	FDA requests Drug handling and preparation for administration instructions at the clinical site should be provided in section 5.3 [of the IND], the "Clinical Study Reports" section, yet provides no examples of a Pharmacy Manual nor guidance (included when the IND is	We request that FDA consider explicitly recommending in the final guidance that sponsors cross-reference the Pharmacy Manual in this section, particularly with respect to certain drug handling and preparation activities that occur at the clinical site (e.g., transport to bedside).

	submitted) regarding the level of detail needed. We request this feedback in the final version of the guidance to assist is compliance to this new requirement. A high level description of the Pharmacy Manual and the supportive in use data would seem to meet the Agency's review needs.	
256 - 258	This section introduces significant detail for the Quality Overall Summary, which may be challenging to produce for IND. FDA should clarify expectations for including this information in other sections of the IND based on type of product such as cell, gene, or gene modified cell therapies.	Suggest changing to "...description of how the product will be shipped to the clinical site, as well as general instructions for receiving and handling at the clinical site…"
256 - 265	Draft guidance recommendation: "Your summary in Module 2 should also include information for product handling at the clinical site prior to administration (such as thawing, washing, or the addition of diluent or adjuvant, loading into a delivery device, and transport to the bedside) and summary information on product stability prior to and during administration (e.g., in - device hold times and temperatures)." Comment: The detailed recommendations and	We recommend that the guidance specify that the recommendations in this section do not apply to AAV vector based in vivo gene therapy. Proposed change: "**When applicable to your specific product, on a case by case basis**, your summary in Module 2 should also include information for product handling at the clinical site prior to administration (such as thawing, washing, or the addition of diluent or adjuvant, loading into a delivery device, and transport to the bedside) and summary information on product stability prior to and during

	emphasis on shipping and handling considerations appears to be based on inherently more unstable ex vivo gene therapy and cell therapy. But the detailed recommendations such as including information for product handling at the clinical site prior to administration (such as thawing, washing, or the addition of diluent or adjuvant, loading into a delivery device, and transport to the bedside) and summary information on product stability prior to and during administration (e.g., in - device hold times and temperatures) would not be applicable to in vivo gene therapy, e.g. with AAV type vector delivery. The stability profile of AAV - based gene therapy is more in line with biologics than cell therapies or ex vivo gene therapy and should be treated as such.	administration (e.g., in - device hold times and temperatures)."
260 - 261	This section also references a significant level of detail for Quality Over Summary; please refer to comment on lines 256-258. If this is level of details is specific or critical for certain technologies - i.e. ex-vivo modified cell therapies and not gene therapies – we request that this be highlighted.	
267 - 274	Draft guidance recommendation: "Details regarding product stability	We recommend that the guidance specify that the detailed recommendations in

	after preparation for delivery and delivery device compatibility data should be included in Module 3 (sections 3.2.P.8 and 3.2.P.2.6, respectively) of the CTD (Ref. 2). Instructions for drug handing and preparation for administration at the clinical site (e.g., Pharmacy Manual or Instructions for Use) should be provided in the "Clinical Study Reports" section of your IND (section 5.3 of the FDA "M4E(R2): The CTD – Efficacy; Guidance for Industry," dated July 2017 (Ref. 9)). Detailed information about the delivery device may be included in "Regional Information" (section 3.2.R of the CTD) (Ref. 2)." We recommend that the information regarding product stability after preparation for delivery and delivery device compatibility data, as well as detailed information about the delivery device should be considered on a case by case at the IND submission stage.	this paragraph regarding delivery device would not be applicable to all gene therapy INDs to the same level of detail and should be considered on a case by case basis. Proposed change: "**Considerations and data for product stability after preparation for delivery and delivery device compatibility would vary on a case by case basis and would depend on the type of gene therapy product, e.g. ex vivo or in vivo gene therapy and type of delivery device**. Details regarding product stability after preparation for delivery and delivery device compatibility data should be included in Module 3 (sections 3.2.P.8 and 3.2.P.2.6, respectively) of the CTD (Ref. 2)**, as applicable.** Instructions for drug handing and preparation for administration at the clinical site (e.g., Pharmacy Manual or Instructions for Use) should be provided in the "Clinical Study Reports" section of your IND (section 5.3 of the FDA "M4E(R2): The CTD – Efficacy; Guidance for Industry," dated July 2017 (Ref. 9)). Detailed information about the delivery device may be included in "Regional Information" (section 3.2.R of the CTD) (Ref. 2) **as appropriate**."

Section V 277-2150	The amount and detail of information required in this section seems more in keeping with a BLA, not an IND, and so should be refined	
282	Drug substance section should describe how to cross reference Drug Substance that are common across multiple product/INDs.	
282	This section should provide information on Master Files as an alternate means for tools and reagents	
333 - 334	How does this differ from the information to be provided in General Properties (3.2.S.1.3)? Consider limiting the information provided in this section to a description to cell lineage and type.	
342 - 344	How does the description of "composition" in General Properties (3.2.S.1.3) differ from the information to be provided in Structure (3.2.S.1.2)?	
371 - 378	Process controls for shipping conditions are not predictable, stable, and consistency meeting a specific performance criterion is difficult. This would be part of ship tests and shipping validation for late stage products. Suggest striking shipping conditions from this section.	
376 - 377	Guidance states: "Changes and updates to this information should be submitted as an amendment to the IND prior to implementation…"	Can FDA clarify if implementation means prior to manufacturing the next batch using the revised process, or whether it means prior to

	Clarify what "implementation" means and whether approval is required before implementation. FDA should clarify that the Agency will get back to the Sponsors to let them know whether the proposed change is acceptable; or whether the 30-day rule should be applied. For major changes we anticipate the FDA would inform the Sponsor that the amendment is acceptable.	treating the first patient with the drug product manufactured with the revised manufacturing process. ARM requests that implementation refer to treating the first patient with the revised manufacturing process.
380 - 397	The Agency requests sponsors disclose how each manufacturing run (i.e., batch, lot, other) should be submitted with an explanation of the batch (or lot) numbering system. Batch numbering is a very complex process for sponsors, with various companies involved in the manufacture and testing of material often using disparate schemes. Oftentimes, batch numbering changes as additional processing or testing steps are performed for the same batch, or to facilitate various releases performed at different sites or by differing vendors. This information could be a complex flow diagram which changes frequently, so the relevance of this request to the IND seems limited.	

382 - 384	The request to include lot number description and explanation of numbering system is highly detailed and demanding. Is this requirement specific to the potential to pool sub lots? Is there an aspect of this requirement that is more pertinent for gene modified cell therapies? Please clarify the scope of this section.	
396	Guidance indicates that a yield is required in an IND. Can FDA clarify or remove this requirement? A defined yield requirement may not be feasible for IND, as if the yield changes an amendment will be required.	Remove statement requiring inclusion of yield
401 - 406	Draft guidance recommendation: "The description of your manufacturing process should include a flow diagram(s) and a detailed narrative. Your description should clearly identify any process controls and in - process testing (e.g., titer, bioburden, viability, impurities) as well as acceptable operating parameters (e.g., process times, temperature ranges, cell passage number, pH, CO2, dissolved O2, glucose level)." Comment: It would be helpful if the FDA could clarify what is meant by process controls by providing examples, and how they differ, if so, from in -	FDA should note, in developing clarifying language for inclusion in final guidance, that determination of operating parameters is a step-wise process done during development; as a result, narrow normal operating ranges typically are used in early development.

	process testing and operating parameters.	
411 - 414	This potentially puts a burden on the IND holder to update the IND based on changes in the procedures held by the contract manufacturer. Typically, these types of procedures are reviewed by the Quality Unit and determined to be acceptable and are subject to regular audit. The guidance should specify that the Sponsor should insure that appropriate procedures are in place, rather than require a description of the CMO procedures. In fact, this is specified in the guidance language on the Quality Unit below.	
423	"Extensive culture time" is not clear.	Remove statement or clarify at which point the requested information is needed for cell cultures
424	Define extended time	
435	Should this description of the cell substrate be provided in Control of Materials (3.2.S.2.3)?	
440 - 441	Draft guidance recommendation: "You should outline any in - process testing to ensure vector quality as appropriate (e.g., titer, impurities)."	We recommend that detailed in-process testing to ensure vector quality not be expected during initial IND submission stage for vector used for in vivo gene therapy because the in - process testing may not be as critical for in vivo gene therapy as for ex vivo gene therapy because of the

		short duration from production to final use for ex vivo application. Also, the examples given may not be appropriate for the initial IND submission stage.
443-451	Paragraph references Drug Substance when it may not apply	Move to another sub-section (e.g. ii. Manufacturing process) out of the vector sub-section, or make this statement its own subsection
445 - 446	For viral vectors that are used in the ex vivo modification of cells would both the vector and the genetically modified cells be considered Drug Substance?	N/A
453 - 469	It would be helpful to clarify the level of detail required in describing sample "chain of custody" (in IND vs available for inspection). Similar comment for line 639.	
471 - 477	Regarding the Agency's request for calibration of the irradiator source, further clarifications are needed. Is the Agency asking the type, frequency, and methodology for product irradiation, or for calibration records for each batch? The latter is more relevant to batch release decisions and should therefore be a GMP compliance request during inspections. However, information on the type, frequency, and methodology for product irradiation in general, is a potential safety concern and therefore	

	inclusion into the IND is warranted.	
486 - 487		Please move to section 3.2.S.6. Container Closure System as it is more pertinent
491 - 546	Suggest that this section point sponsors to other sources of information including: USP {1043} Ancillary materials for cell, gene and tissue engineering products, ISO standards, and other relevant reference standards.	
496	Typically, information on supplier is provided only for starting materials (i.e., Banking Systems).	Please clarify, in the final guidance, whether FDA intends for supplier information to be provided for other materials/ component suppliers.
493 - 499	Draft guidance recommendation: "You must provide a list of all materials used in manufacturing (21 CFR 312.23(a)(7)(iv)(b)) and a description of the quality and control of these materials. This information may be provided in tabular format and include the identity of the material, the supplier, the quality (e.g., clinical - grade, FDA - approved), the source of material (e.g., animal, human, insect), and the stage at which each material is used in the manufacturing process (e.g., culture media, vector purification)."	Please clarify for compendial materials, referencing the compendia is adequate and further details (e.g. CoA) are not required

	Comment: We recommend that the FDA clarify what is meant by "FDA - approved" quality for the materials used in manufacturing for gene therapy products.	
501 - 504	Draft guidance recommendation: "This includes information on components, such as cells, cell and viral banking systems, and reagents, as described in more detail below; it also includes raw materials and equipment, such as culture bags, culture flasks, chromatography matrices, and tubing, that come into contact with the product." Comment: We recommend that the guidance differentiate between critical raw materials from other raw materials. Some of the raw materials listed, e.g. culture bags, culture flasks, chromatography matrices, and tubing, product would likely not fall into the critical raw material category. The level of detail recommended may not be appropriate for the initial IND submission but may be collected appropriately during the IND stage and the information can provided to FDA at the time of BLA submission.	For the IND stage, we recommend that FDA limit the list to only the critical raw materials (media, resins, etc.). Please clarify whether this includes all product contacting materials used in the manufacturing process, and will this detail be required for all Clinical Phases (First Time in Humans to Pivotal study)

502 - 504	This is a significant level of detail that will require potentially redundant / frequent updates to the IND in the future.	
506 - 510	This level of detail will restrict sourcing in the future and require unnecessary updates to the IND.	Possibly reduce the requirement to critical raw materials (see 501-504 comment)? We also suggest that this language be revised to reflect that CoA's are to be provided in S.2.3 (consistent with the recommendation in the draft guidance at lines 735-736)
510 - 517	FDA recommends use of clinical grade materials "when available."	We suggest that FDA include, in the final guidance, examples of any specific materials, or categories of materials, recommended to be of clinical grade.
521 - 525	Draft guidance recommendation: "For purpose of this guidance, reagents (or ancillary materials) are those materials used for manufacturing (e.g., cell growth, differentiation, selection, purification, or other critical manufacturing steps) that are not intended to be part of the final product." Comment: It will be helpful to include a definition of "Reagents" with examples. We recommend that the section on "reagents" include raw materials. Alternatively, if reagents are considered distinct from "raw materials," we recommend that the FDA	

	consider including a separate subsection on "raw materials" within the section on control of materials. Also, if considered distinct for this Guidance, it would be helpful to clarify what the difference between ancillary materials and raw materials.	
526	Examples include fetal bovine serum, digestive enzymes (e.g., trypsin, collagenase, DNase/RNase, restriction endonucleases), growth factors, cytokines, monoclonal antibodies, antibody coated beads, antibiotics, media, media components, and detergents.	
548 - 566	Can the Agency clarify the bovine requirements or further delineate between primary and secondary sources? For primary bovine source material used in manufacturing IND should the filing contain the source/information on the herd location for birth to slaughter; and other information relevant to (TSE)? For secondary material from bovine sources, does the material need only be identified, and source and qualification of material should be documented?	
578 - 580	Suggest also including testing for zoonotic porcine hepatitis E virus so that this document is harmonized with EMA	Porcine hepatitis E virus types 3 & 4 are an increasing risk of zoonotic infection from porcine

	guidance on porcine trypsin testing.	tissues and should be teste for as a stable unenveloped viruses.
590 - 595	Please clarify how much information should be provided in the IND about monoclonal antibodies generated from mouse hybridomas used to purify reagents used during manufacture of gene therapy products	
599	The use of FDA-approved human AB serum should be processed from blood or plasma collected at FDA licensed facilities.	Please clarify if sponsors from the EU and ROW must also purchase from US-based suppliers?
599 - 601	The requirement of "FDA - approved" human albumin put unnecessary burden on overseas manufacturers.	Change to: "If human albumin is used, you should use FDA - approved products or provide evidence and QA justification for use of non-FDA approved of the plasma sources."
603 - 605	Extend the sources to include non - US countries.	"If human AB serum is used (e.g., for ex vivo genetically modified cells), you should ensure the serum is processed from blood or plasma collected at FDA licensed facilities or Plasma Master File should be provided"
609 - 614	Suggest detailing which viruses should be screened for.	
623 - 658	Consider adding 'processing' to cover tissue that may have been processed prior to use in manufacture.	For autologous or allogeneic cells or tissue, you should provide a detailed description of the cell source, the collection procedure, and any related handling, culturing, processing,

		storage, and testing that is performed prior to use in manufacture.
623-660	Please clarify if this level of detail is required for an IND across all Phases and consider removing the requirement to list consumables such as tubing. Suggest the guidance specifically states that "the IND should specify cell yield quality checks to be performed at the collection site and manufacturing site." However, the materials used for collection e.g. tubing / containers should not be part of the CMC section of the IND, but should form part of the local site documentation Details on the collection of cells at the clinical sites should not form part of the CMC IND, but instead form part of the local site documentation. Line 626 rewrite to read 'detailed description of the cell source(s), the collection procedure(s)……' The collection protocol for cells should not form part of the CMC IND, but instead form part of the local site documentation	Information required in this section is very detailed (e.g. listing all materials used for collection of cells) and will add a lot of detailed information into the IND if the study uses more than one collection site. Welcome the guidance to standardize material used for collections and full standardization of volumes or numbers of cells to be collected, enrichment steps, labelling and tracking of collected samples, hold times and transportation conditions to the manufacturing facility. However, feel that setting standard criteria on the quality of the starting material, from point of collection, itself is more important than detailed standardization of the collection method. The quality of the cell yield should be confirmed at the collection site before shipment, and the quality of the starting material prior to start of manufacture at the manufacturing site e.g. Acceptable criteria for each cellular therapy product should be developed by the Collection Facility in conjunction with the clinical team, and this process defined in SOPs or specific testing criteria can be specified

	Addition of Freeze / thaw of collected samples to the bullet point list starting on row 631 Addition of quality criteria e.g. viability	in a Study Reference Manual (SRM) or other local documentation, for example microbiological analysis, cell count, phenotyping, viability, sterility etc. The manufacturing site should conduct GMP testing when the biological starting materials are received and accepted in to the GMP manufacturing facility. It is the Manufacturer's responsibility to verify the incoming starting material samples in terms of integrity and accompanying documentation according to internal SOPs. Cell source: The IND can state a preferred cell source, as well as an alternate source, to ensure that patients are not deprived from GT with CD34+ cells for whom the preferred cell source is not a suitable option (e.g. children too small for mobilization, contra-indications for specific procedure, not sufficient cell yield from BM harvest, not sufficient cells from cord blood, …) unless the risk/benefit for the specific cell source is not acceptable. This may be adapted as clinical development progresses and any differences in safety/efficacy between cell sources are evaluated. Setting of devices is fairly standardized, however sites may use different devices based

		upon their experience. Manufacturers could recommend standard start settings; however, this may depend on the device. The quality of the cell yield may depend on the experience and talent of the local staff and their capability of appropriately adapting the settings during the procedure if needed. Hence, some flexibility should be allowed. This could be managed by the accreditation of the site (e.g. FACT, JACIE etc.). Such accreditation ensures the high quality of the overall process (personnel, equipment, infrastructure of the facility, packaging/labelling, storage, shipment etc.) Also, since accreditation implies regular checks on accuracy of cell counting it provides reassurance that an appropriate cell number is collected and transported. The guidance would benefit by the addition of Freezing/thawing information, if applicable, should be performed according to well defined and standardized procedures, with documented cell survival rate and appropriate cell function after freeze/thaw. The guidance would benefit from the addition of criteria to assess quality of starting materials (e.g. viability, colony

		forming capacity, sterility, …), where appropriate in the IND.
639	It would be helpful to clarify the level of detail required in describing sample "chain of custody" (in IND vs available for inspection).	
651-658	For multi-center studies it is proposed to list all collection sites in the IND.	Please clarify which section of the IND these sites should be listed in for example Section 3.2.S.2.1 Manufacturers Is it therefore a requirement for all collection sites to have an FDA establishment identifier?
656	Perhaps a further note regarding the FDA establishment identifier for those establishments outside of the USA – if required.	
666 - 669	Tissue culture always presents the risk of further propagating endogenous pathogenic agents. Provide examples of acceptable approaches to determining if manufacturing procedures allow for the further propagation of pathogenic agents.	
718 - 722	Please provide examples of acceptable abbreviated cell bank qualification.	
724	Starting materials section	Description of other starting materials in non - banked or synthetic Drug Substance production processes should be added (or cross reference to ICHQ7)
830 - 834	Suggest that insect cells should be tested using method involving culture on sensitive	Most insect viruses infecting insect cell lines produce silent infections not detected by CPE.

	cell lines with an electron microscopic evaluation endpoint as recommended in WHO TRS 978 Annex 3 and European Pharmacopoeia 5.2.3	
832 - 833	Draft guidance recommendation: "Insect cell lines with known viral contamination should be avoided." Comment: We recommend the final guidance align with and cite here the ICH Guideline Q5AR1 on Viral Safety Evaluation of Biotech Products. In that guidance, section III on Cell line characterization in subsection C on Acceptability of cell lines discusses the concept that some cell lines will contain endogenous viral sequences. Further, it recommends that sponsors perform a risk analysis that includes the viral clearance evaluation data. We also recommend that the guidance text acknowledge that it may not be always possible to avoid complete insect cell lines with known viral contamination and so would like guidance from FDA on if an appropriate strategy establishing sufficient clearance through virus validation clearance studies and testing may be an acceptable alternative (per the EMA 1996 Note for guidance viral validation studies')	Addition: Insect cell lines with known viral contamination should be avoided **when possible**. Add reference to ICH Q5AR1 guideline (section III on Cell line characterization in subsection C on Acceptability of cell lines) and add to references.

848 - 850	Provide clarity on the frequency of testing required. Should this testing be done a single time?	
852 - 859	Draft guidance recommendation: "Assess the ability of new cell lines to form tumors. We recommend that you perform tumorigenicity tests for cell lines that have not been previously characterized for their potential to form tumors." Comment: It will be helpful to clarify the recommendation to assess the ability of new cell lines to form tumors and to perform tumorigenicity tests for cell lines that have not been previously characterized for their potential to form tumors. We recommend FDA to consider that it may not be possible in all situations. Also, it will be helpful to provide more detail regarding the criteria and expectations, e.g. for methodology, frequency, and timepoints, for these tests. We recommend that this data and information not be expected with the original IND submission. Also, we recommend that a one - time test for tumorigenicity for new cell lines be acceptable.	We recommend that the final guidance specify the mechanisms and methodology that would be acceptable to FDA to test for tumorigenicity. Also, it will be helpful for the final guidance to clarify the frequency and timepoints for when this data should be collected and submitted to FDA.
911	Draft guidance recommendation: "Transgene expression and/or activity."	

	Comment: It would be helpful to clarify the recommendation for MCB testing to include transgene expression and/or activity. It appears that this section describes testing of a bacterial MCB used to manufacture a plasmid and does not apply to a transgene product. Therefore, it is unclear how a transgene activity assay applies. Further clarification would be very helpful.	
918 and 1022	Previous version from 2008 mentioned the use of neutralizing antiserum if virus was cytolytic.	
974	We suggest this sentence is qualified to indicate what type of test is expected.	
994	"For integrating viral vectors…" This is confusing in relation to the Master Virus Bank. For example, rAAV integrate (randomly). It is not possible to test a baculoviral vector bank used to manufacture rAAV. [Assume that requests sequencing & characterization of master cell bank after infection with WCB. If this is a retrovirus that integrates at multiple locations is LAM-PCR or similar PCR-based approach required?]	To re-phrase for clarity. - if Master Cell Bank/Working Cell Bank or Master Seed Virus /Working Seed Virus (or both) are being referred to in relation to sequencing the integrated DNA.

1043 - 1044	Distinction should be made between sponsor and manufacturer throughout the document as they are not always one and the same	Manufacturing intermediates should be defined by the sponsor but should maintain separate compliance standards.
1046 - 1047	It may not be reasonable to set a duration for all hold steps with limited manufacturing experience. For example, for process intermediates that are stored frozen, the hold time to be controlled is determined based on stability data acquired with manufacturing experience.	"The duration of production steps and hold times should be recorded to…"
1052 - 1054	It is not clear why DNA plasmids would be considered process intermediates and not critical starting materials which would be described in Control of Materials (3.2.S.2.3). Please clarify the rationale around this.	
1054-1056	FDA refers to "DNA plasmid intermediates…derived from qualified banks…" and references V.A.2.c. of the guidance; however, that section does not describe or address DNA plasmid intermediates or associated banks. Should the plasmid used for transfection be considered as intermediate? What control does the agency expect for this intermediate?	We request that FDA clarify this in the final version of the guidance, including, for example, whether FDA is of the view that the plasmid used for transfection should be considered an intermediate, and what controls are expected with respect to this intermediate.
1067 - 1096	FDA requests a description of the manner in which the	

	Quality Unit's testing and oversight are separated from the manufacturing unit. Can the Agency provide more guidance or examples to elucidate this request (i.e., would an org chart suffice)?	
1082 - 1084	It is unclear what level of detail is intended by this language. We would assume that very high-level statements would suffice; additional clarity requested.	
1082 - 1084	Please clarify that if this is a broad requirement, why is this not included in 3.2.A.1? Please indicate where in 21 CFR 312 does this requirement originate?	This requirement should be clarified in the guidance document, or at the minimum, clarified to describe the Quality Control Unit in 32A1. In line 2128 that placement is recommended in 32A1.
1110 - 1113	Please provide definition of significant change or reference to appropriate guidance	
1111 - 1113	Provide clarity on what is considered a significant manufacturing change. How should a sponsor consider proving comparability in these circumstances?	
1123 - 1124	For cases where this is difficult to achieve, please provide guidance on acceptable alternative approaches.	
1130 - 1135	Further guidance here would be helpful; in particular, examples of the type(s) of analytical method(s) the Agency would expect to have represented in this section. This level of detail is often not available early in	

	development; therefore, an approach that considers the different stages of development is recommended.	
1131 - 1136	Suggest that guidance should indicate if this level of detail would be expected for early phase studies.	
1177	In early phase, there is often limitation in the suitability of "off the shelf" testing for DNA impurities and product - specific assays take a great deal of effort to qualify. Please clarify the Agency's view on these assays.	
1177 - 1180	Draft guidance recommendation: "Since some cell substrates also harbor tumorigenic genetic sequences or retroviral sequences that may be capable of transmitting infection, we recommend that you take steps to minimize the biological activity of any residual DNA associated with your vector. This can be accomplished by reducing the size of the DNA to below the size of a functional gene and by decreasing the amount of residual DNA. We recommend that you limit the amount of residual DNA for continuous non - tumorigenic cells to less than 10 ng/dose and the DNA size to below approximately 200 base pairs." Comment: The scientific community and scientific	We recommend that the final guidance acknowledge that it may not be possible for all types of vectors, e.g. AAV, and add "when possible" to provide flexibility on a case - by - case bases.

	literature on this topic agrees that such size reduction— i.e. limiting the amount of residual DNA for continuous non - tumorigenic cells to less than 10 ng/dose and the DNA size to below approximately 200 base pairs— is not possible for AAV vectors based on the current state - of - the - art - technology, except in limited cases where the overall does may be very low.	
1208 - 1210	Draft guidance recommendation: "Typical product - related impurities for viral vectors may include defective interfering particles, non - infectious particles, empty capsid particles, or replicating recombinant virus contaminants. These impurities should be measured and may be reported as a ratio, for example, full vs empty particles or virus particles vs infectious units." Comment: We recommend that FDA consider noting that it may be possible to measure the presence of defective interfering particles via standard assays such as TCID50, depending on the nature of the serotype and transgene. Also, we recommend that FDA consider noting that TCID50 type assays can also serve as infectivity/potency tests.	

1225 - 1283	We applaud FDA for including this level of detail/clarity, inclusive of the cited examples, as it pertains to safety related items. This is helpful to industry. As development progresses, often analytical methods are optimized, or new analytical methods are introduced. It would be helpful if FDA could also provide a summary of expectations regarding specifications when bridging between analytical methods.	
1277 - 1279	The wording should be softened to be consistent with what is known about product development at the time of IND, or to specify if this is specific for products consisting of genetically modified cells, vs AAV products for example.	
1333 - 1346	The Agency provides the current maximum acceptable levels of replication - competent adenovirus (RCA) particles in the final product, which is helpful to Industry.	
1441 - 1448	Would be helpful if the term 'qualify' could be defined since the details of what should be performed in the qualification protocol look very much like a validation study.	This is an area of confusion for many – the distinction between qualify and validate – and could be clarified in this guidance
1444 - 1448	Draft guidance recommendation: "In your original IND submission, you should provide a detailed description of the qualification	Proposed change: "In your original IND submission, you should provide a description of the appropriate qualification (e.g., sterility, samples;

	protocol (e.g., samples; standards; positive/negative controls; reference lots; and controls evaluated, such as operators, reagents, equipment, dates) and data supporting the accuracy, reproducibility, sensitivity, and specificity of the method." Comment: Although the recommended approach may be applicable for some qualification protocols at certain appropriate stages, we recommend FDA to consider that it may not be possible to provide such detailed description at the time of original IND submission in all cases. Additional flexibility would be very helpful.	standards) and data summary regarding intended use.
1479 - 1489	Draft guidance recommendation: "You should include a table with test results for all of the batches (or lots) of Drug Substance that you have manufactured. For early stage INDs, this may include only toxicology lots or developmental batches and a single manufacturing run for clinical grade material. Please note that batches manufactured in different ways should be clearly identified in the submission. We recommend that you annually update this section of your IND as new batches are produced. You should indicate any batches that fail to meet	

	release specifications and any action taken to investigate the failure (as outlined in "Process Validation and/or Evaluation (3.2.S.2.5)" (section V.A.2.e. of this guidance). We recommend that you retain samples of all production lots for use in future assay development, validation, or comparability studies." Comment: We recommend FDA to consider providing flexibility for the recommendation to provide such detailed data— i.e. test results for all of the batches (or lots) of Drug Substance manufactured— with the initial IND submission. There may be limited or no process validation during early stage IND. It will be helpful to provide more flexibility with this recommendation. We particularly would like to see explicit allowance to provide clinical batch results at a later date (but before human studies are initiated), if a platform manufacturing approach is followed	

1480 - 1481	For ex vivo genetically, modified autologous cell products, clinical grade material manufactured from starting material obtained from patients will not be produced until the IND is accepted. Could the data submitted in the IND for "clinical grade material" be from an engineering batch using starting material from healthy donors?	
1550 - 1552	Does this information / justification need to be included in 3.2.S.7.1 or in another section? Please specify. If it needs to be included in S.7.1, it could be redundant with information in the analytical methods and justification of specifications sections.	
1662 - 1664	This information could be redundant with some information in Drug Substance. Suggest adding language to allow a reference to similar information in corresponding Drug Substance section.	You should describe the parameters relevant to the performance of the DP in your IND (or reference relevant DS if appropriate).
1690 - 1692	Suggest clarification if there is a specific type of gene or cell therapy to which this applies.	

1710 - 1715	The use of rapid sterility or strategies to select representative or surrogate measures to ensure sterility assurance should be described and recommendations provided. This will be a significant challenge for all cell-based gene therapy manufacturers - especially those who have limitations of amount of Drug Product material or time to perform Drug Product release sterility testing.	
1717 - 1727	Regarding the FDA's comments on in - use and in - device stability data, it is recommended that this concept be elaborated upon and the importance highlighted as it relates to safety.	
1719 - 1720	Should the information pertaining to the diluent be presented in a separate Drug Product section?	
1756 - 1762	“Final product controls” and “release testing” are part of section 3.2.P.5, Control of Drug Product.	Suggest removing reference to “final product controls” and “release testing” from the noted lines.
1758 - 1760	This statement is vague and should be clarified. Specifically, what level of detail is needed? For "product contact materials and equipment used", the material of construction for tubing and the manufacturers or model numbers for equipment may be excessive for IND inclusion	

	but Management of Changes for filters is relevant.	
1765 - 1769	There is not more information in V.B.2.e (line 1710)	Remove this reference or provide language as appropriate.
1777 - 1780	Please review; justification for acceptance criteria and details on quality of intermediates may be an unnecessary level of detail for IND	
1788 - 1790	This information has typically not been included in the IND. Suggest wording is softened so Sponsor's know that this should be a point of emphasis in manufacturing but is not required to be included in the IND.	
1796 - 1802	The inclusion of this information and level of detail, particularly the examples, is helpful and appreciated. As development progresses, often analytical methods are optimized, or new analytical methods are introduced. FDA should also provide a summary of expectations when bridging between analytical methods.	
1798 - 1799	Please provide clarification on whether this is needed for compendial excipients. Typically, this information is not included for compendial excipients.	
1806	Please provide clarification on whether analytical procedures need to be described if they are compendial. Typically, descriptions of compendial methods are not included.	

1818	Please provide clarification on whether justification is needed if compendial monographs are used. Typically, this information is not included for compendial monographs.	
1822 - 1824	Please provide additional guidance on the information to be included in the submission for approved products used as excipients.	
1837	Please include recommendations regarding visual inspection of cellular drug products and recommendations for batches where the output may be a single drug product unit (i.e. autologous therapies).	
1839 - 1873	Provide clarification on the process used to contact FDA for short shelf life products.	
1869 - 1871	Please clarify the wording "have this assay in place". Does the assay need to be qualified or validated by the time pivotal studies start? If a phase 1 study could be considered pivotal, what level of qualification or validation is needed?	
1885 - 1959	The Agency's guidance for late - detected sterility failures during the in - process sterility testing process is very helpful and appreciated.	
1894 - 1897	Provide similar recommendations for mycoplasma and/or adventitious agent testing for products with short shelf life.	

1949 - 1955	Clarify requirements for cryopreserved products where product release may occur after obtaining results from the full 14 - day sterility test. Should sterility test be performed on the product both prior to and post - cryopreservation?	If you freeze Drug Product before use, we recommend that you perform sterility testing on the product prior to cryopreservation to increase ability to recover microbial species and so that results will be available before the product is administered to a patient.
1963 - 1964	We recommend that identity assays uniquely identify a product and distinguish it from other products in the same facility.	Consideration of how to identify products with multiple drug substances and how to individually characterize purity of each
1963 - 1965	This could lead to double testing and duplication of effort since this testing already occurs at the start of Drug Product manufacturing. The Quality systems in place should ensure that mix - ups don't occur once Drug Product manufacturing starts. Suggest removal of this wording.	
1963 - 1965	How can this be done on an autologous Drug Product with one or few Drug Product bags or vials? What about the sterility risk that performing such test on the Drug Product vial/bag imposes?	
1964 - 1966		Please clarify whether FDA expects identity of final labeled product to be completed for investigational product.
1977 - 1998	The Agency's guidance on upper acceptance limits for endotoxins in these products is very helpful and appreciated.	
1981 - 1988	This drug product section references 3.2.S.3.2 but has	Purity testing includes assays for pyrogenicity or endotoxin

	language that is less flexible than S.3.2 (lines 1203 - 1221). We recommend that FDA use language that encourages more flexible, phase appropriate, raw material and drug product testing requirements throughout the guidance, including aligning this section more closely with 3.2.S.3.2 with regards to specific cell populations.	and residual manufacturing impurities, as outlined under "Impurities (3.2.S.3.2)" (lines 1203 - 1221) of drug substance, which **may** include but are not limited to proteins; DNA; cell debris; reagents/components used during manufacture, such as cytokines, growth factors, antibodies, and serum; and in the case of ex vivo genetically modified cells, any unintended cellular populations. The assays required to demonstrate product purity should be phase appropriate and may evolve during clinical development as you develop a greater understanding of the impurities present in your product.
1993	LAL often performed quickly and inexpensively, allowing a timely release of ex vivo modified cells that may constitute the DP. This also removes the requirement for use of animals.	The guidance could be clearer that tests such as LAL are sufficient and that the rabbit pyrogen test is not required (if LAL tests controlled sufficiently).
2003 - 2004	If potency is used to verify the appropriate dose level as specified in lines 1257 - 58, this statement appears to be in conflict with the referenced statement "Your IND should also include specifications for measuring an appropriate dose level (i.e., strength or potency) at Phase 1."	
2068	Typo	"...materials of construction FOR each…"

2085 - 2099	Can early development batches could potentially be leveraged to provide tentative information (retest date)? This approach has been so successful in recent years that even select EU countries allow a more flexible approach which mimics the retest date test philosophy. Absent a clear need due to unique challenges with this therapeutic class, this is problematic.	
2120 - 2132	Earlier in S.2.3, the Agency requesting that industry continue the current practice of including COAs for raw material put in A.1, but tabular summary information on raw materials in S.2.3, with hyperlinks to the COAs in S.2.3. To prevent confusion and aid in consistency, the same request should be included in this section. Similarly, description of the Quality Unit and the quality control (QC) and quality assurance (QA) responsibilities were mentioned as required in the Process Validation and/or Evaluation (3.2.S.2.5) section above, but also requested here. Harmonization of information into one section would be highly desirable, as information spread across multiple sections can lead to redundant information, or worse information which is updated in one section but	

	incomplete or incorrect in another section.	
2122 - 2124	FDA should provide a diagram, illustrating the manufacturing flow of the manufacturing areas, information on all developmental or approved products manipulated in this area.	For contract manufacturing in multi - product CMO, cross reference to Type V MF for DP facility information
2128 - 2129	See comments above on QA Unit.	
2128 - 2129	This seems to contradict advice given for 32S25 PV&E.	
2131	COAs do not go in the Facilities section.	Move COAs sentence to 3.2.A.2 or 3.2R section.
2131 - 2132	Including COAs for ALL raw materials and reagents seems unnecessary. Suggest changing to ask for only critical reagents or raw materials.	
3.2.A	This section lacks sufficient details on the information to be submitted. Please consider adding details analogous to those provided in the 1999 Guidance for Industry Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product.	