November 14, 2018

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

Re: Docket No. FDA-2008-D-0205: Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments on FDA's Draft Guidance for Industry "Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)" (Draft Guidance or Guidance).

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers, and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products.

General Comments

We commend the FDA for an excellent job in drafting the Draft Guidance; overall, it is well written and comprehensive. It effectively provides guidance on a range of CMC topics relevant to gene therapy products. However, BIO notes that the Draft Guidance is quite prescriptive and does not necessarily match modern manufacturing. BIO would like to see a better balance between the information that FDA needs to see in order to allow an IND to move forward and over-reporting of information that may be unnecessary. On the whole it seems that much of the information required in the Draft Guidance is more appropriate for a BLA filing, an approved product, or post approval changes to a product rather than an IND.

More specifically, several sections in the Guidance (lines 65-66, 117-118, 376-377) directly or indirectly seem to suggest that CMC information provided in the IND represents a "commitment" and "is subject to FDA review prior to releasing a new lot of clinical trial material". The terms "commitment" and "lot release" are generally used in the context of licensed products and in this regard could be interpreted that CMC changes made during clinical development are subject to review and prior approval before implementation. Such a requirement could potentially restrict and delay development including continuous improvement of products under clinical development, which critically depends on regulatory flexibility while process and product knowledge are accumulated. BIO would appreciate if FDA could clarify the meaning of the terms "commitment" and "lot release" in this context or consider removing this language from the Guidance to avoid possible misinterpretation.

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BIO finds that the scope of the document is not clear. The Guidance states in line 25 that the scope of the Guidance covers gene therapy applications generally. However, some recommendations, such as those regarding shipping and handling, are specific to ex vivo gene therapy and are not appropriate for in vivo gene therapy products. In addition, we would appreciate clarification regarding the quality expectations on gene modifying agents, such as viral vectors. When used in the ex vivo manufacture of gene therapy products, the vector should be considered a critical starting material, which should be well characterized and appropriately controlled but not necessarily to the same extent as a drug substance. We ask FDA to provide specific recommendations for the product type and differentiate recommendations for ex vivo gene therapy products from in vivo gene therapy products.

We find that the Draft Guidance recommendations are unclear for which stage of development they would apply to. For some recommendations, the Draft Guidance specifies the expectation for the timing (e.g., information expected with the original IND submission), however; for most of the recommendations, the timing of application of the recommendations needs to be clarified. Additionally, the Draft Guidance includes recommendations for different stages including initial IND submission, during IND stage of clinical development phases, and CMC information to be submitted at the time of BLA submission. We ask FDA to clarify and specify when the individual recommendations in the Guidance would apply at the time of original IND submission.

The Guidance seems to suggest that analytical assays should be qualified/validated to be fit for their intended use. In this regard, the Guidance recommends assay qualification during early phases of product development, with an increasing expectation that assays be fully validated for late stage development and licensure. It would be greatly appreciated if FDA could provide more clarity, and perhaps examples, to differentiate between the terms "assay qualification" and "assay validation" in the context of specific ICH Q2 validation parameters (e.g., accuracy, linearity, precision), and explain how this applies to early versus late stages of product development.

It is BIO's understanding that FDA, per Draft Guidance considers, a gene vector employed as an ex vivo gene therapy product a "Drug Substance" (e.g., lines 181-183, 230-231, etc.). BIO believes this would provide for a novel interpretation of the term "Drug Substance" (per 21 CFR 207.1, 207.3, 314.3, etc.) subjecting gene vectors used as intermediates for subsequent manufacture (i.e., ex vivo gene vectors) and gene vectors intended as Active Pharmaceutical Ingredients (i.e., in vivo gene vectors) to equal quality standards (see 21 CFR 312.23(a)(7)). In this regard, while the Guidance provides the definition of the term Drug Substance (i.e., 21 CFR 314.3(b)), it is silent on the rationale for interpretation of an ex vivo gene vector as a Drug Substance. BIO believes it is important to define and differentiate quality control and release expectations for gene vectors with different end-uses. To that end, it would be equally beneficial and greatly appreciated defining and differentiating testing expectations for the other materials referenced in this (or other similar) guidances as follows: raw materials, starting materials, and Drug Substance Intermediate.

BIO believes a section in the Guidance discussing how Sponsors can leverage and reference existing knowledge and data, for example, when same technology or manufacturing process features such as same vector are used for a subsequent gene therapy product, would be beneficial.

Finally, BIO believes that the Guidance would benefit from a glossary for consistent interpretation of terminology used in the Guidance.

Conclusion:

BIO appreciates this opportunity to comment on the Draft Guidance for Industry "Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)." Specific, detailed comments are included in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Victoria A. Dohnal, RAC
Senior Manager, Science & Regulatory Affairs
Biotechnology Innovation Organization (BIO)

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
II. BACKGROUND		
Lines 52-54:	The Draft Guidance states, "Some examples of gene therapy products include nucleic acids, genetically modified microorganisms (e.g., viruses, bacteria, fungi), engineered site-specific nucleases used for human genome editing, and ex vivo genetically modified human cells."	BIO suggests editing the text to read: Some examples of gene therapy products include nucleic acids, genetically modified microorganisms (e.g., viruses, bacteria, fungi), engineered site-specific nucleases used for in vivo human genome editing, and ex vivo genetically modified human cells.
III. ADMINISTRATIVE INFORMATION (MODULE 1 OF THE CTD)		
A. *Administrative Documents*		
Lines 117-118:	The Draft Guidance states, "that you allow sufficient lead time (e.g., 30 days) for FDA review before release of a new lot of clinical trial material…." BIO finds this statement lacking clarity. While we appreciate that sufficient review time is necessary to allow adequate assessment of the information and data submitted, unless a substantial change has been made, the 30-day review lead time prior to releasing a clinical lot could be highly challenging for an IND granted a priority designation which is pursuing development under highly compressed time-lines.	BIO suggests the 30-day time-period be reconsidered and this sentence is revised as follows: ….that ~~you allow sufficient lead time (e.g., 30 days) for FDA review before release of~~ a new lot of clinical trial material is released concurrently with submitting relevant lot information to the FDA for review, unless a substantial CMC change (e.g., scale up) is being implemented.
B. *Labels*		
C. *Environmental Analysis*		
D. *Previously Submitted Information*		

SECTION	ISSUE	PROPOSED CHANGE
Lines 150-153:		We believe that FDA intended to cite the 21 CFR 314.420 Drug Masters Files (DMF) regulations and not 21 CFR 312.23(b)) in this section.
IV. SUMMARY OF QUALITY INFORMATION (MODULE 2 OF THE CTD)		
Lines 173-274:	The Draft Guidance discusses Module 2 of the CTD. BIO believes that Module 2 is not needed. All CMC information should be provided in Module 3.	BIO suggests that the information in section IV, including product handing at the clinical site, should be moved to the appropriate portion of the Module 3 Guidance if not there already. If the Agency insists on a Module 2 summary section, we ask the Agency to indicate whether the IND should follow the format of the guideline or CTD format, and if Module 2 can be presented as a single document.
A. *General Information*		
Lines 181-183:	The following statement: "You should indicate if the DS is formulated into a DP for administration or if the DS is used for ex vivo genetic modification of cells" seems to imply that gene vector is considered a DS even when used for ex vivo genetic modification of cells.	We would appreciate if FDA could clarify the expectations for content and format of the CTD submission for different types of products (e.g., product containing AAV vector vs. ex vivo genetically modified cells). One interpretation of this statement is that FDA expects two distinct DS sections CTD 3.2.S.1 – S.7 whereby (1) one contains the gene vector information and (2) other, information pertinent to ex vivo genetically modified cells. This would appear to be supported by the language provided in lines 230-231 "When the manufacturing process includes more than one DS, we recommend that you provide separate DS sections for each active ingredient of the final product."

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		Furthermore, it would be greatly appreciated if FDA would clarify the rationale behind considering a gene vector "Drug Substance" rather than a "starting material" as per EMA Guideline (Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells issued in July, 2018). As a follow up comment, it would be highly beneficial if FDA could also clarify the CGMP expectations for viral or bacterial vector production from early to late stage product development including reagents used in their preparation.
Lines 185-187:	Because this Guidance pertains to gene therapy products in development, we recommend adding more explicit language reflecting the state of CQA understanding in early-phase programs. ICH Q8 and Q11 both use the term "potential CQAs" to reflect the evolving nature of product understanding, and similar language should be considered here.	BIO suggests editing the text to read: Your summary should also include a description of potential 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. As your product progresses through development, the list of potential CQAs may be revised as your knowledge of the product increases. For additional information…
Lines 193-196:	Per ICH Q11, drug substance CQAs that specifically relate to quality of the final drug product may be presented in eCTD section 3.2.P.2. Otherwise, ICH Q11 suggests that the rationales for drug substance CQA designations should be presented in the DS section 3.2.S.2.6, with supporting data in other DS sections such as 3.2.S.3.1 and 3.2.S.7.	BIO suggests giving Sponsors the option to put this information where the CQAs are most relevant – either DS or DP. As such, we suggest editing the text to read: Information to support a CQA and results from specific studies or published literature may be included in Module 3 of the CTD in section 3.2.S.2.6 or section 3.2.P.2, depending on whether the attribute pertains to drug substance or drug product.

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		Information may also be linked to the relevant nonclinical or clinical sections of the application in the CTD.
Lines 198-206:	This product development recommendation does not involve Module 2 and should be in the Background section.	BIO suggests moving this paragraph to section II of the Draft Guidance.
B. *Drug Substance and Drug Product*		
C. *Combination Products*		
D. *Product Handling at the Clinical Site*		
Lines 256-265:	The Draft Guidance discusses information for product handling at the clinical site. The product shipping and handling recommendations would not apply to all types of gene therapy products, but only to some, such as ex vivo gene therapy products, where such considerations apply. The detailed recommendations 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 AAV vector based in vivo gene therapy products, which have a more robust stability profile that is in line with other biological products such as monoclonal antibodies with respect to shipping and handling considerations. The differences in recommendations based on product type should be specified and acknowledged.	BIO suggests specifying that the recommendations in this section do not apply to AAV vector basted *in vivo* gene therapy. As such, we suggest editing the text to read: For ex vivo gene therapy products, 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).”

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Lines 269-272:	Instructions for product handling at the clinical site should be included in Module 3. The Pharmacy Manual or similar instruction document should be part of the trial master file but need not be submitted to the IND.	BIO suggests deleting the following text: 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)).
V. MANUFACTURING PROCESS AND CONTROL INFOMRATION (MODULE 3 OF THE CTD)		
A. *Drug Substance (3.2.S)*		
Line 355:	BIO believes that sites which only store the DS should not be included in the IND.	BIO suggests editing the text to read: contract manufacturer(s), involved in the manufacture, and testing, ~~and storage~~
Line 375:	There are some minor changes that may not need to be submitted prior to implementation.	Sponsors should be allowed to assess the impact of the changes and decide if they need prior approval or can be assessed as annual reportable.
Lines 376-378:	As outlined in the comment provided to lines 65-66, the following statement: "Changes and updates to this information should be submitted as an amendment to the IND prior to implementation (21 CFR 312.23(a)(7)(iii)), as indicated in section II. Background of this guidance", could be interpreted to mean that CMC changes made during clinical development are subject to review and prior approval before implementation.	BIO suggests revising the text as follows: Changes and updates to this information should be submitted as an amendment to the IND prior to implementation (21 CFR 312.23(a)(7)(iii)), as indicated in section II. Background of this guidance.

SECTION	ISSUE	PROPOSED CHANGE
Lines 396-397:	Yield is process-related and not a CQA. It should be tracked in the Quality System but not included in the IND.	BIO suggests deleting the following text: When known, please include the yield expected per batch.
Lines 401-406:	The Draft Guidance states, "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)."	BIO asks FDA to clarify whether process controls include in-process testing and operating parameters. If not, then the Guidance should clarify how they differ and provide examples of process controls like the parenthetical examples provided for in-process testing and operating parameters.
Lines 430 and 466:		BIO suggests the Draft Guidance provide expectations for process and controls for cell modification using non-viral vectors.
Line 432-434:	The Draft Guidance states, "For the manufacture of gene therapy vectors (e.g., viral vectors, bacterial plasmids, mRNA), you should provide a description of all production and purification procedures."	BIO asks FDA to provide more clarity on whether this refers to an mRNA expressing the modifying enzymes.
Lines 491-1031:	This section contains a definition of reagents (or ancillary materials) but not critical components, and mentions starting materials only regarding banking systems.	BIO suggests that this section could be divided into subsections: material classification (starting materials, critical components, ancillary materials), human and animal derived material, banking systems.
Lines 501-504:	The Draft Guidance states, "This includes information on components, such as cells, cell and viral banking systems, and reagents, as described in more detail	The Draft Guidance appears to be including all raw materials, which can be an overbearing amount of information at the IND stage. FDA should only expect

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	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."	information on critical raw materials at the IND stage (e.g., media, resins), and not non-critical raw materials, such as culture bags, culture flasks, chromatography matrices, and tubing, product. Such detailed information is more appropriate for submission with the BLA.
Lines 506-510:	The request for documentation is too general and does not reflect relative risks or complexity between materials used in manufacturing. Without further clarification, the Sponsor may interpret this to mean they should submit test results and COAs for USP-grade salts and buffers, which was probably not the Agency's intent here.	BIO suggests striking these two sentences and instead, maintain the requests for documentation for the critical materials described in the subsections that follow (e.g., reagents, cells, banks.).
Lines 521-525:	The Draft Guidance states, "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."	BIO asks FDA to clarify whether "reagents" includes raw materials; and if not, a separate sub-section on "raw materials" should be within the section on control of materials.
Lines 548-621:	It appears that subsections ii-v are more appropriate as subheadings underneath "i. Reagents."	BIO suggests reformatting the subheadings accordingly.
Lines 655-658:	Collection site EINs and accreditations should not be in Module 3 unless they perform significant product-specific operations.	BIO suggests deleting the following sentence: In your IND, you should include a list of collection sites, their FDA Establishment Identifier, and any accreditations for compliance with established standards (e.g., Foundation for the Accreditation of Cellular Therapy (FACT)), if applicable.

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Lines 676-688 and 688-693:	Similar type of information is presented in two "sections".	We suggest editing the text to read: For allogeneic cells or tissues, you must perform donor screening and testing, as required in 21 CFR Part 1271, Subpart C, except for those cells and tissues that meet the exceptions in 21 CFR 1271.90(a). Donors of all types of cells and tissues must be screened for risk factors and clinical evidence of relevant communicable disease agents and diseases, including: human immunodeficiency virus (~~HIV~~ HIV-1; HIV-2); hepatitis B virus (HBV); hepatitis C virus (HCV); human TSE, including Creutzfeldt-Jakob disease; and Treponema pallidum (syphilis) (21 CFR 1271.75) and if the material is leukocyte-rich cells or tissue, In addition, donors of viable leukocyte-rich cells or tissues should be screened for human T-lymphotropic virus (~~HTLV~~ HTLV-1, HTLV-2) and cytomegalovirus (21 CFR 1271.85). ~~You must also test a specimen of donor cells or tissue for evidence of infection due to relevant communicable disease agents, including: HIV-1; HIV-2; HBV; HCV; syphilis; and if the material is leukocyte-rich cells or tissue, HTLV-1, HTLV-2, and cytomegalovirus (21 CFR 1271.85).~~
Lines 741-1031:	BIO suggests moving subsections viii-xii underneath "vii. Banking Systems," since all of these subsequent passages relate to cell or viral banks.	BIO suggests reformatting the subheadings accordingly.

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Lines 803-806, 868-870, 950-951:	Starting with section V.A.2.c.viii and continuing through the end of V.A.2.c, the Sponsor is advised to refer to section V.A.4.b of the guidance regarding the analytical methods used for bank qualification, corresponding to eCTD section 3.2.S.4.2. Section V.A.4.b (3.2.S.4.2) does not provide these details, nor should it. Methods used for bank testing are adequately delineated in ICH Q5A and Q5D. eCTD section 3.2.S.4.2 should be limited to descriptions of analytical methods used for drug substance lot testing.	BIO suggest removing all references to Section 3.2.S.4.2 relating to methods for bank qualification.
Lines 832-833:	The Draft Guidance states, "Insect cell lines with known viral contamination should be avoided."	The Guidance should align with and reference the ICH Final Guideline Q5A(R1) on Viral Safety Evaluation of Biotech Products. The section on acceptability of cell lines in the ICH Q5A(R1) Final Guidance discusses the concept that some cell lines will contain endogenous viral sequences and recommends a risk analysis that includes the viral clearance evaluation data. Accordingly, FDA should acknowledge that it is not possible always to avoid insect cell lines with known viral contamination, and should recommend a risk-based approach to evaluate viral clearance.
Lines 835-841:	The recommendation in the Draft Guidance is unclear because it does not specify whether this recommendation needs to be followed routinely or at certain timepoints (e.g., after changeover or when the cells are banked). Also, as mentioned in our general comments, it is not specified whether this	BIO asks FDA to specify when this this recommendation applies (e.g., after changeover or when the cells are banked), and also when this recommendation applies with respect to the stage of development (i.e., with original IND submission or during IND stage after submission of original IND).

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	recommendation should be followed before original IND submission, with information included with original IND submission, or if this is a recommendation that applies during IND stage after original IND is submitted but the information is provided to FDA with the BLA submission.	
Lines 845-848:	The recommendation for a one-time test of end of production cells (EOP) or mock production cells of similar passage history, to be tested for their suitability to produce the vector is appropriate for establishing stability of the cell bank. However, such data is not suitable for the initial IND submission stage, but perhaps the data can be collected during the IND stage, and submitted to FDA at the time of BLA submission.	BIO suggests including the following text: Data on cell bank stability, such as the one-time test of EOP or mock production cells of similar passage history, is not expected with the original IND submission, but should be collected during the IND stage and can be submitted with the BLA. Additionally, the Final Guidance should reference ICH Guideline Q5D, section 2.3.3 on Cell Substrate Stability.
Lines 852-859:	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 is unclear and as a global expectation for all gene therapy is impractical. The criteria and expectations need to be fleshed out.	BIO believes that the Final Guidance should specify the mechanisms and methodology that would be acceptable to FDA to test for tumorigenicity. Also, the Final Guidance should clarify the frequency and timepoints for when this data should be collected and submitted to FDA.
Line 911:	For the purposes of bacterial MCB qualification, testing for transgene expression and/or activity of the plasmid seems excessive. Plasmid identity and sequence ought to be sufficient to infer proper performance of a bacterial MCB used in plasmid production.	BIO recommends striking line 911.

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Lines 1016-1020:	The Draft Guidance states, "You should perform sequence analysis of the gene insert, flanking regions, and any regions of the vector that are modified or could be susceptible to recombination. The entire vector sequence will be necessary to confirm identity for licensure."	It may not be possible to sequence all the regions beyond GOI because of the limitations of the sequencing technique (e.g., it is not possible when using Sanger sequencing to sequence all the regions). As such, the terminology should be clarified. Additionally, BIO believes that this recommendation should apply to viral vector banks only.
Lines 1033-1041:	BIO notes that this section is usually not populated until process characterization work is completed. Critical control steps are typically not established in early stage manufacturing. Treating any in-process steps in which in-process tests with acceptance criteria are performed as critical control steps may not be appropriate in early phase clinical manufacturing	BIO recommends that the Agency remove the following statement from here and similar statement from line1771-1778 (3.2.P.3.3): You should describe the control of critical steps and intermediates in the manufacturing process. Critical control steps include those outlined in the "Description of Manufacturing Process and Process Controls" (section 3.2.S.2.2 of the CTD and section V.A.2.b. of this guidance). We recommend that you also consider any steps in which in-process tests with acceptance criteria are performed as critical control steps. Additionally, we suggest moving this requirement to 3.2.S.2.2 to avoid confusion that critical controls have already been defined.
Lines 1043-1044:	The following statement is unclear: "Manufacturing intermediates should be defined by the manufacturer."	We believe that FDA intended to state that if certain critical intermediates were manufactured by manufacturer other than the IND Sponsor, then appropriate description of the manufacturing process and handling should be included. As such, BIO asks that FDA revises this sentence for improved clarity.

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Lines 1052-1065:	The Guidance advises Sponsors to present plasmid materials information in eCTD section 3.2.S.2.4, which seems to be unique among critical raw materials which are otherwise presented in section 3.2.S.2.3.	BIO asks the Agency to consider relocating plasmid material information to section 3.2.S.2.3, for consistency.
Lines 1177-1180:	The Draft Guidance states, "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."	The recommended size reduction may only be possible for AAV vectors if the dose is very low. However, in general, the recommended reduction is not possible for AAV vectors.
Lines 1082-1084:	The request for details of the Sponsor's Quality Unit seems out of place in eCTD section 3.2.S.2.5 and in the IND in general. Review of quality systems and practices is usually a matter for inspection, although we acknowledge that FDA reviewers may want a line of sight to certain aspects of this when reviewing INDs from smaller firms or academic Sponsors.	BIO asks FDA to consider striking this text. If the Agency has concerns about quality oversight by smaller firms or academic Sponsors, we recommend that they request this information during IND review.
Line 1058:	BIO believes that the Guidance should acknowledge the unavailability of reference standard for some gene therapy products, such as autologous products.	BIO suggests adding the following text: In the absence of analytical reference standards, appropriate performance indicators for analytical methods should be developed.

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Lines 1195-1201:	A risk-based approach should govern the selection of systems for AAV production, taking into account the levels of encapsidated DNA, their sizes, the nature of their sequences (i.e., tumorigenic risk), dose levels, and benefit-risk to the patient. Accordingly, the Guidance should advise Sponsors to be prepared to provide data and proper controls to ensure product safety commensurate with the cell lines and helper viruses being used.	BIO suggest adding the following text to the end of line 1201: Sponsors should provide necessary quality data, risk assessments, and/or details of their process and product control strategy to address and mitigate potential risks posed by the manufacturing systems used.
Line 1279:	BIO believes that the Guidance should explicitly state that DS release specifications are not needed for a continuous process with no isolated DS.	BIO suggests adding the following text: For a continuous process with no isolated DS, a release specification for the DS may not be needed.
Lines 1287-1289:	The request for a description of "all the analytical procedures used during manufacturing to assess your manufacturing process and product quality" far exceeds what is typically provided for biological products in eCTD section 3.2.S.4.2. As currently worded, all in-process measurements and characterization assays would need to be described, even if those assays have no bearing on product safety or batch disposition.	BIO suggest editing the text to read: You should provide a description of all the analytical procedures used for drug substance lot release and stability testing ~~during manufacturing to assess your manufacturing process and product quality~~.
Lines 1444-1448:	The Draft Guidance states, "In your original IND submission, you should provide a detailed description of the qualification protocol (e.g., samples; standards; positive/negative controls; reference lots; and controls evaluated, such as operators, reagents, equipment, dates) and data supporting the accuracy,	The recommended detailed description is only possible for very few qualification protocols and at different appropriate stages. This recommendation is not appropriate for original IND submission and as such, BIO suggests it be deleted from the Guidance.

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	reproducibility, sensitivity, and specificity of the method."	
Lines 1456-1458:	BIO believes that phase appropriate language is needed in the Guidance. Validated assays should not be expected at Phase 1 trial stage but may be appropriate at Phase 3 in some circumstances, but may not be possible for all programs and for all sites at Phase 3. These considerations should be noted.	BIO suggests editing the text to read: In addition, you should validate tests used to determine dose prior to initiating clinical studies to demonstrate efficacy when possible, or to support licensure at the time of BLA submission.
Lines 1478-1481:	Typically, batch data presented in this eCTD section are limited to Quality-released clinical DS lots. Toxicology and developmental lot data are often presented elsewhere, such as in 3.2.S.2.6.	BIO asks FDA to confirm the scope of lots presented in 3.2.S.4.4.
Lines 1484-1485:	Failed batches are not typically included in eCTD section 3.2.S.4.4, nor are summaries of quality investigations conducted on lots which are out-of-specification. It may be the Agency's intent to ensure that data from released out-of-specification (OOS) lots of gene-modified autologous cell products are presented in this section. If this is the case, this scenario should be explicitly highlighted.	If the Draft Guidance is referring to OOS lots of autologous products, BIO asks the Agency to consider the following revision: For gene-modified autologous cellular product lots which failed to meet release specifications but were released for clinical use, you should clearly indicate which batches these are and provide details regarding actions taken to investigate the failures.
Lines 1580-1582:	BIO suggests specifying that stability method qualifications should be presented in eCTD section 3.2.S.4.3. As currently worded, the text implies that method qualification results should be presented in 3.2.S.7.3.	We suggest editing the text to read: Information on the qualification of analytical procedures used to generate stability data should be included in section 3.2.S.4.3 ~~your original IND submission~~.

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B. *Drug Product (3.2.P)*		
Lines 1703-1708:	It is unclear what solutions the Agency is trying to propose in this section. "A final container that can be sampled for release testing" is too vague.	BIO asks FDA to provide clarification.
Lines 1794-1835:	If all excipients used in the drug product are compendial, eCTD section 3.2.P.4 is often very brief and simply cites the pharmacopeial standard(s) each component must meet.	BIO suggest adding text stating that all pharmacopeial-grade excipients should be identified and are exempt from further listing in 3.2.P.4.
Line 1845:	The Draft Guidance states "Product lots that fail to meet specifications should not be used in your clinical investigation without FDA approval." BIO suggests the Agency consider circumstances where out-of-spec product can be administered with notification instead of approval, along the line of language used in the EMA GCP ATMP draft guidance. This is critical to ensure timely access to potentially life-saving investigational products in populations with an unmet medical need.	We suggest the Agency to consider circumstances where out-of-spec product can be administered with notification instead of approval. We suggest modifying the text as follows: "Exceptionally, in case where the product lot failed to meet specifications but the administration of the product is necessary to avoid an immediate significant hazard of the subject, taking into account the alternative options for the subject and the consequences of not receiving the product, the use of the product in clinical investigation may be acceptable without prior approval. A patient can be treated with non-conforming product without prior notification or approval from FDA. In such cases notification by the Sponsor to FDA may be made after administration. The notification which would include, the Sponsor's risk assessment and a justification supporting administration of the product, should be submitted to the FDA within 14 days of the release."

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Line 1885:	BIO appreciates the guidance on sterility testing strategy from the perspective of timing. However, additional guidance is needed for strategies for limited samples.	From the perspective of limited sample availability, such as for autologous products, additional guidance is needed.
Line 2016:	BIO believes that the Guidance should acknowledge the unavailability of reference standard for some gene therapy products, such as autologous products.	BIO suggests adding the following text: In the absence of analytical reference standards, appropriate performance indicators for analytical methods should be developed.
C. *Appendices (3.2.A)*		
Lines 2123-2124:	For manufacturing performed at CMOs, it may not be possible for the Sponsor to obtain information about "all developmental or approved products" which are manipulated in the same area as the IND product manufacturing.	If this is a requirement for the CMOs' drug master files, then cross-referencing may be a potential solution. Otherwise, it may be difficult for Sponsors to satisfy this request.
VI. REFERENCES		