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

Reference: FDA Guidance for Industry Chemistry, Manufacturing, and Control Information for Human Gene Therapy Investigational New Drug Applications

Docket ID: FDA-2008-D-0205

Dear Sir/Madam:

PDA appreciates FDA's efforts to further clarify its thinking with respect to the content of the Chemistry, Manufacturing, and Control Information for Human Gene Therapy Investigational New Drug Applications. PDA further recommends this guidance include additional references to established regulatory guidance and pharmacopeial chapters that address topics specific to cell and gene therapy.

The scope of this document is unclear as it varies between describing the content and format of the material presented for INDs and a discussion of relevant GMP requirements. PDA proposes that the document be clarified against the intended scope. We recommend reorganizing the information or creating two separate documents to address the two topics. In its current form, the document is confusing and potentially in conflict with other guidances regarding GMPs for gene therapies and does not provide the appropriate focus on the respective topics.

Additionally, further guidance on what is classified as drug substance (DS) vs drug product (DP) with respect to these products would be welcome, for example adding clarity around the use of the terms "DS" and/or "DP" for ex vivo modification of cells. For these types of therapies, the distinction of what is a drug substance and what is a drug product is often unclear. Please see the attached detailed comments for additional rationale and recommendations.

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments were prepared by a committee of experts with experience in the practice of pharmacy as well as members representing our Biopharmaceutical Advisory Board and Board of Directors.

If there are any questions, please do not hesitate to contact me.

Sincerely,

Richard M. Johnson

Richard Johnson
President, PDA

Cc: Tina Morris, PhD, PDA
Josh Eaton, PDA

General Comments	Rationale	Critical Comment? Y/N
This document varies between the material presented for INDs and GMP requirements. Need to reorganize or remove the IND-relevant information from IND quality practices and create two separate guidance documents.	It is confusing and potentially in conflict with other guidances regarding GMPs for gene therapies and does not provide the appropriate focus on the respective topics.	Y

Specific Text Comments

Line No.	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
71-73	Thus, if a manufacturing change could affect product safety, identity, quality, purity, potency, or stability, you should submit the manufacturing change prior to implementation	More clarity on when manufacturing changes may be acceptable as being submitted in an annual report.	Aids in clarity and completeness	Y
182-183	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.	Further guidance on what is classified as DS vs DP would be welcome. Add clarity around the use of DS and/or DP for ex vivo modification of cells.	Not certain it is appropriate to call it DS if formulated, filled, and finished aseptically in a vial for administration ex vivo.	Y
261-264	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).	This requirement of product handling at the clinical site is new. Please provide clarity for the level of detail in Module 2 for product handling at the clinical site.	Since the detailed instructions are included in the Pharmacy Manual, it is reasonable to include only key operating conditions and parameters for the critical steps of the product handling.	Y

Line No.	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
261-264	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).	Need to delineate what activities are considered as CMC and therefore should follow GMPs versus activities which are regarded as Clinical	Aids in clarity and completeness	Y
277-280	V. MANUFACTURING PROCESS AND CONTROL INFORMATION (MODULE 3 OF THE CTD)	Add: For additional information on developmental principles for the manufacturing and control of biologically-derived drug substances, refer to "ICH Q11 Development and Manufacture of Drug Substances," dated November 2012 (Ref. 7).	ICHQ11 is already referenced for the Module 2 section for CQA's (lines 185-190) but it's absent from the Module 3 section. ICH Q11 applies to BLAs, but the scope states: "The guideline does not apply to contents of submissions during the clinical research stages of drug development. Nevertheless, the development principles presented in this guideline are important to consider during the investigational stages."	Y

Line No.	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
491 -546	Section c Control of materials	Suggest that this section cross references USP {1043} Ancillary materials for cell, gene and tissue engineering products.	Aids in clarity and completeness	N
493-499	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).	Delete Supplier for compendial and FDA-approved materials. More clarity on whether suppliers and CoAs are required for all raw materials including synthetic chemicals used in the manufacturing	Flexibility in supply chain. Ability to use compendial or FDA-approved materials from multiple qualified suppliers without amendments to filing.	Y

Line No.	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
493-499	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).	Requirements should align with USP <1043> (ancillary materials section)	Aids in clarity and completeness	Y
519 and 1052	i. Reagents	More clarification is needed regarding starting materials such as plasmids or helper virus. Can these be considered reagents (as defined in starting on line 519)? Or are these considered intermediates as defined starting on line 1052?	Aids in clarity and completeness	Y
578 – 580	In addition, porcine reagents should be tested for porcine circovirus (PCV) 1 and 2 and porcine parvovirus.	Suggest FDA address the need for including testing for zoonotic porcine hepatitis E virus so that this document is harmonized with EMA guidance on porcine trypsin testing.	Porcine hepatitis E virus types 3 & 4 are an increasing risk of zoonotic infection from porcine tissues. Stable unenveloped viruses.	Y

Line No.	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
609 - 614	We recommend that you ensure the AB serum used in your manufacturing does not have the potential to transmit infectious disease. For example, if your serum is derived from Source Plasma, you may reduce the risk of infectious disease by conducting additional testing for relevant transfusion-transmitted infections.	If there are viruses which would be exempted from the CFR-required tests, these should be noted. Otherwise, please add reference to the applicable CFR.	Aids in clarity and completeness	Y
830 -834	For insect cells, you may evaluate the presence of arboviruses in a susceptible cell line, such as baby hamster kidney (BHK21) cells. Insect cell lines with known viral contamination should be avoided.	Suggest that insect cells should be tested using method involving culture on sensitive cell lines with an electron microscopic evaluation endpoint as recommended in WHO TRS 978 Annex 3 and European Pharmacopoeia 5.2.3	Most insect viruses infecting insect cell lines produce silent infections not detected by CPE.	Y
918 and 1022	Sections xi and xii Master and Working viral banks	Update this section to include previous content from the 2008 version which mentioned the use of neutralizing antiserum if virus was cytolytic.	Aid in clarity and completeness.	Y
955-957	"Ensure absence of contamination, including sterility, mycoplasma, and in vivo and in vitro testing for adventitious viral agents."	Modify to: Ensure absence of contamination, including sterility, mycoplasma, and ***appropriate*** testing for adventitious viral agents	Reduce dependence on in vivo viral testing. Consider elimination of in vivo testing for adventitious viral agents for ethical reasons, or at least after demonstration of several batches	Y

Line No.	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
965-966	Ensure absence of replication competent virus in replication incompetent vectors	Reduce the replication competent virus to the level that pose the minimum risks to manufacturing operators or patients. Potentially reference the new RCR guidance and align principles for Replication Competent Virus testing.	Replication competent virus may be generated at a low frequency as a result of homologous recombination between viral vector sequences and viral sequences present in the cell	Y
970-972	Ensure sensitivity to anti-viral drugs, as applicable, for example, herpes simplex virus (HSV) sensitivity to ganciclovir	More clarity is needed on whether this recommendation applies to HSV when it is used as the helper virus	In the case of using HSV as helper virus for AAV production, this recommendation of anti-viral drugs may not apply as HSV is absent from the final AAV product	Y
974	Ensure transgene activity, if appropriate	Provide guidance on conditions where this activity testing would be expected and further description as to how this would be targeted to assess the relevant attribute of the viral vector versus the cellular product.	Currently, the modality of ex vivo gene therapy is challenged to separate the quality attributes of the viral vector from the final product with respect to potency.	Y

Line No.	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
1131 - 1136	In addition, we recommend that you provide any further information confirming the primary, secondary, or higher order structure; post-translational modifications; and/or distribution of cell types for the DS if it has not already been described in "Structure"	Suggest that guidance should indicate more details in the nature and degree of physiochemical and functional characterization would be expected for early phase I/II studies. It should also provide guidance on any specific elements of physical or functional characterization that could be unique to different types of GT products. Additionally, for GT products where DS is essentially the DP, further guidance on where this information would be located in the application should be provided.	Guidance needs to clarify what characterization testing is expected at different stages of clinical development.	Y
1177-1180	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.	For AAV drug, there are packaged residue host cell DNA and unpackaged residue host cell DNA. For unpackaged DNA, the limit of 10 ng/dose and the DNA size below approximately 200 base pairs may be achievable. However, for packaged DNA, it may not be possible to remove or reduce this DNA from the product to a level sufficient to assure safety. Therefore, we recommend that sponsors address the safety concern and justify the limit for residual DNA in the IND. This may include discussion of factors such as the cell lines and helper sequences used to make viral vectors that package non-vector DNA	For packaged DNA, it may not be possible to remove or reduce this DNA from the product to a level sufficient to assure safety.	Y

Line No.	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
1195-1198	Some vectors, including AAV, can package a large amount of non-vector DNA (e.g., plasmid DNA, helper virus sequences, cellular DNA), and it may not be possible to remove or reduce this DNA from the product to a level sufficient to assure safety.	Consider combining paragraphs.	Repetitive text from three paragraphs prior (line numbers 1161-1164).	N
1441 - 1448	To ensure safety of gene therapy products, you should also qualify the assays used to determine dose (e.g., vector genome titer by qPCR, transducing units, plaque forming units) prior to initiating dose escalation studies. 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, reproducibility, sensitivity, and specificity of the method.	Would be helpful if the term 'qualify' for test methods could be defined, since the details of what should be performed in the qualification protocol look very much like a validation study. For example: "Method qualification is a study conducted under protocol that establishes the performance capabilities of the method with designated test samples for the ICHQ2(R1) parameters applicable to the methods' intended use(s)."	This is an area of confusion for many – the distinction in study design between method qualification and method validation. The proposed definition is in alignment with generally accepted principles and practices for biotech products.	Y

Line No.	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
1506-1521	You should provide information on the reference standards or reference materials used for testing the DS in your original IND submission. We recommend that you provide the source and lot number; expiration date; certificates of analyses, when available; and/or internally or externally generated evidence of identity and purity for each reference standard. … In some cases, the reference material for an assay will be a well-characterized lot of the gene therapy product, itself. In this case, we recommend that you reserve and maintain a sufficient amount of material (e.g., part of a production lot) to serve as a reference material.	Add: Refer to S.3.1. for details regarding physiochemical and functional characterization of GT reference product lots. Add: The storage stability of GT product reference standards should be monitored with an appropriate stability protocol to assess its potential physical and functional degradation during clinical development.	Typically for biotech products there is a close correlation between the characterization studies defined in S.3.1. and the characterization conducted for reference standard lots. The impact on establishing product reference standard lots is a further reason why the S.3.1. section should have more details on phase-appropriate testing for physical and functional characteristics. Stability of product reference standards during development is critical to the accuracy of the product test data generated.	Y
2059-2063	You should provide information on the reference standards or reference materials used in testing the DP if not previously provided in "Reference Standards or Materials" (section 3.2.S.5 of the CTD).	If a DP reference standard is utilized separate from the DS, all previous discussion on reference standards would apply.	For GT products that use DP instead of DS for the product reference standard, this section should provide the same guidance as for DS reference standards.	Y