July 29, 2024

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

Re: Docket No. FDA-2024-D-1244 for *Considerations for the Use of Human-and Animal-Derived Materials and Components in the Manufacture of Cell and Gene Therapy and Tissue-Engineered Medical Products*

Dear Sir/Madam:

The Alliance for Regenerative Medicine (ARM) is pleased to submit comments to the US Food and Drug Administration (FDA) in response to recently released draft guidance titled *Considerations for the Use of Human- and Animal-Derived Materials and Components in the Manufacture of Cell and Gene Therapy and Tissue-Engineered Medical Products.*

ARM is the leading international advocacy organization championing the benefits of engineered cell therapies and genetic medicines for patients, healthcare systems, and society. As a community, ARM builds the future of medicine by convening the sector, facilitating influential exchanges on policies and practices, and advancing the narrative with data and analysis.

We actively engage key stakeholders to enable the development of advanced therapies and to modernize healthcare systems so that patients benefit from durable, potentially curative treatments. As the global voice of the sector, we represent more than 400 members across 25 countries, including emerging and established biotechnology companies, academic and medical research institutions, and patient organizations.

General Comments

ARM members support much of the content of this draft guidance with some general feedback on two issues:

Information Sharing: Sponsor vs. Supplier of Materials

FDA seeks additional information on the materials used in the manufacturing of CGT and TE medical products – sponsors feel they may not always be able to provide such information and recommend the Agency seek some relevant material specificities from suppliers. Additionally, based on the stage of development and criticality of the material(s), sponsors may not be informed about all aspects of the chemistry and manufacturing controls (CMC) which suppliers of the material have in place; some of this information may also be considered proprietary by the supplier. It would be appreciated if the Agency would consider reducing some of the reporting burden on sponsors by relying on master files provided by suppliers and/or prior knowledge of information about materials from vendors that may be accessible to the Agency.

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Risk Assessments

There is lack of clarity in the draft guidance on how risk assessments are used, both in defining the adequacy of materials in treatment and in research-use only cases, with focus on quality and safety. A specific example could be in handling an autologous product: sponsors seek additional detail on what criteria should be in place for manufacturing material from patients with a viral infection, when there is no opportunity for patient recovery unless a CGT treatment is given.

ARM appreciates the opportunity to engage with the Agency on the topic of the human-and animal-derived materials and components in the manufacture of cell and gene therapy (CGT) and tissue-engineered (TE) medical products. Please see additional detailed line-by-line comments below.

Sincerely,

Michael Lehmicke
Senior Vice President, Science and Industry Affairs

Specific Comments

II. BACKGROUND		
Lines/Section/Text Reference	*Draft Guidance Text*	*Comment/Recommendation*
Lines 54-59	N/A	Please consider adding a reference to the FDA guidance "Safety Testing of Human Allogeneic Cells Expanded for Use in Cell-based Medical Products"[1] to this paragraph, as safety testing on MCB and WCB are discussed extensively there.
Lines 78-81	"Human- and animal-derived materials can also contribute to product variability by affecting the reproducibility of your manufacturing process or the quality of your final product. For example, differences among serum lots used for cell culture may lead to differences in cell growth rate or differentiation potential."	Variability is not defined and therefore it is hard to conclude what is adequate "similarity" and when serum lots are "different". We request the Agency provide language around risk assessments and their use to define what is adequate, i.e. define what is considered adequate or acceptable variability. Also, it would be helpful to have specific guidance how to address variability in reagents in terms of its effect on DP

[1] Safety Testing of Human Allogeneic Cells Expanded for Use in Cell-Based Medical Products; Draft Guidance for Industry

		quality (e.g. number of runs, need for functional testing, etc).
Lines 81-82	"…underscore the need for early studies…"	We ask the FDA to expand on phase-appropriateness of defining critical attributes and acceptance criteria in this paragraph.

III. GENERAL PRINCIPLES: HUMAN- AND ANIMAL-DERIVED MATERIALS		
Lines/Section/Text Reference	*Draft Guidance Text*	*Comment/Recommendation*
Section III: GENERAL PRINCIPLES: HUMAN- AND ANIMAL-DERIVED MATERIALS	N/A	We request the Agency define acceptance criteria for recommendations around human- and animal-derived materials.
Line 97	"...source, grade, and stage..."	Please clarify the meaning of "grade" or revise to "quality" or similar, more specific terminology. Also, in this guidance, excipient is categorized as a stage – "formulation" may serve as a better term.
Lines 96-98	"We recommend that you provide such list in tabular format, including, but not limited to, manufacturer, catalog number, source…"	We request the removal of "catalog number" from the requirements of materials used in manufacturing. The description of the materials, manufacturer, etc. are sufficient information. Catalog numbers change constantly and it may not always be beneficial to file this type of information.
Lines 129-131	"Human- and animal-derived materials increase the risk of introducing adventitious agents, including viruses, parasites, bacteria, mycoplasma and agent(s) responsible for transmissible spongiform encephalopathies (TSEs)."	We ask that the Agency clarify that comments on quarantining materials refer to incoming materials to the facility, not pending mycoplasma testing for harvest or intermediates manufactured at the facility.
Lines 131-135	"If the manufacturing process of the material includes steps that you rely upon to remove or inactivate potential infectious contaminants from these materials, the regulatory submission should describe how the manufacturing method for the material has been	We request more detail in this section in cases where removal or inactivation of the potential infectious contaminant cannot be demonstrated. It would be helpful if the guidance had clearer language on use of this material and the regulatory risks (e.g. clinical hold if potential infectious contamination cannot be demonstrated).

	demonstrated to remove adventitious agents."	
Lines 158-160	"Process qualification or viral clearance validation studies can help to assess risk, and the manufacturing process can be designed to mitigate risks, where appropriate."	It is unclear which process is being referred to in this section. Cells as products (x-vivo Gene Therapy) or Tissue Engineered Medicinal products do not have processes to remove adventitious agents. We ask the Agency to clarify whether the process being referred to is the "material" process.
Line 185 - 186	"...should consider implementing identity testing, even during phase 1 clinical investigations..."	Implementation of phase 1 identity testing from materials can be cost prohibitive; it may also disincentivize developers of complex therapies from pursuing rare disease treatments due to the potential increased cost of goods sold (COGS) when performing phase 1 studies. We ask the Agency to consider removing, limiting this to "critical reagents". Recommended text could read: "…should consider implementing identity testing on excipients", or "…should use a risk-based approach to implementing identity testing".
Line 195	"…and establishes the reliability of the supplier's analyses…"	We ask the FDA to clarify expectations for the reliability of supplier's analyses, i.e. whether this line refers to identity only for early stage.
Lines 213-217	"To help ensure material consistency, we therefore recommend that you evaluate whether it is necessary to test material performance when accepting a new lot (e.g., including an assay to evaluate whether the new lot of material performs adequately and as intended, including a comparison to previously used lot(s), if applicable)."	While earlier in this section the requirement for identity testing was clarified to apply to a phase 1 study, functional testing for the material to assess variability is not specified in the same way. For early clinical development of cells as products and Tissue Engineered Medicinal Products, the sources of variability from the starting material may make it difficult for a sponsor to develop an appropriate functional test for a complex material until there is more experience with the process itself. It would be helpful to state in this paragraph that such testing is not required early in development.

IV. MATERIALS DERIVED FROM HUMAN BLOOD AND BLOOD COMPONENTS		
Lines/Section/Text Reference	*Draft Guidance Text*	*Comment/Recommendation*
Lines 340 - 344	"You should document the entire human AB serum manufacturing process, starting with any processing steps performed on the donated source material, defibrination steps (if applicable), and the conditions of heat inactivation (time and temperature) and irradiation (type of irradiation and irradiation dose in kGy), if applicable."	For manufacturers of cells as product and TEMP, Human AB serum, if used, is typically purchased. The qualification of the supplier and the information provided by the supplier on a batch-by-batch basis likely does not cover this level of detail. Usually, the qualification of the supplier will reveal the presence of a Plasma Master File, which is cross-referenced in the application. It would be helpful if this guidance stated whether a cross-reference to the Plasma Master File is acceptable if the serum or plasma product is purchased.
Section IV.C.4, Human-Derived Proteins in Culture Media	N/A	This section is specific to culture media. We ask the Agency to consider broadening the scope since marketing language is typically inconsistent and there is a lack of standardization, e.g. "xeno-free, serum-free, animal free, etc". Sponsors should be mindful of this and assess the component origin and its impact on safety. We recommend changing this section title to "Human-Derived Proteins in Materials used in Manufacturing".

V. HUMAN-DERIVED FEEDER AND BYSTANDER CELLS AND CELL-DERIVED PARTICLES		
Lines/Section/Text Reference	*Draft Guidance Text*	*Comment/Recommendation*
Lines 395-397	"Ascertaining complete absence of residual cells from the final product may be technically challenging, and the feeder or bystander cells and cell-derived particles may thus be present in DS and DP as impurities."	One challenge from the residual feeder/human cell substrates is the breakdown of their cellular structure causing increased levels of residual cellular impurities, such as residual cellular DNA and proteins, in the drug product. As noted by the Agency, the complete removal of these feeder/bystander cells is technically challenging, and therefore it is inevitable that the total residual DNA/protein impurity levels are expected to increase in products which utilize human-derived

		feeder/byproduct cells, considering also there are also DNA/protein impurities expected to be present from the cell product starting material. Given that identifying and limiting residual DNA/protein impurities caused specifically by the breakdown of feeder/bystander cells would be technically challenging, it is recommended that controlling residual feeder cell/bystander impurity on the cellular level is sufficient, and further control of residual DNA/proteins that may be contributed by these feeder/bystander is not warranted. In addition to the adventitious agent safety related recommendations, we request FDA add recommendations on residual cell, protein and DNA impurity controls while considering the above-mentioned technical challenges and rationale. We suggest revising the lines as follows: "Ascertaining complete absence of residual cells from the final product may be technically challenging, and the feeder or bystander cells and cell-derived particles may thus be present in DS and DP as impurities, which may be controlled at a cellular level."