American Society of Gene + Cell Therapy



July 26, 2024

Dockets Management
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville MD 20852

**RE: Comments for Docket No. FDA-2024-D-1244 "Considerations for the Use of Human- and Animal-Derived Materials in the Manufacture of Cellular and Gene Therapy and Tissue-Engineered Medical Products; Draft Guidance for Industry"**

Dear Sir/Madam:

The American Society of Gene & Cell Therapy (ASGCT) appreciates the opportunity to comment on *Considerations for the Use of Human- and Animal-Derived Materials in the Manufacture of Cellular and Gene Therapy and Tissue-Engineered Medical Products; Draft Guidance for Industry*. ASGCT is a nonprofit professional membership organization comprised of more than 6,200 scientists, physicians, clinicians, and other professionals working in cell and gene therapy (CGT) in settings such as universities, hospitals, and biotechnology companies.

The mission of ASGCT is to advance knowledge, awareness, and education leading to the discovery and clinical application of genetic and cellular therapies to alleviate human disease. Many of our members have spent their careers in this field performing the underlying research that has led to today's robust pipeline of transformative therapies.

**General Comments**

ASGCT appreciates FDA's coordinated release of this draft guidance with the *Safety Testing of Human Allogeneic Cells Expanded for Use in Cell-Based Medical Products.* Together these documents provide a comprehensive guide to address the use of animal sources. This harmonization ensures consistency across related documents, which is a priority for sponsors.



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The Society respectfully requests added clarity on several overarching themes:

- Stage Appropriateness - It is not clear for what stage of development this guidance is primarily intended. It would be helpful to have additional phase-appropriate benchmarks or expectations for sponsors.

- Manufacturers and Sponsors - The introduction of the draft guidance (lines 20-21), notes that it is meant to guide "manufacturers of CGT and TEMP products." However, the final sentence of Section II (lines 88-89) suggests that some, or all, of the guidance is also relevant to "manufacturers of human- and animal-derived materials used in the manufacture of CGT products or TEMPS." This ambiguity may lead to confusion on which sections are applicable to which audience.
    - As a specific example: The beginning of Section III is directed toward the product sponsor (Line 95 - "In your IND, you must provide a list of all materials used…"). However later in Section III (lines 223-225) there is guidance on testing for communicable diseases, a responsibility that lies with the material manufacturer. It is unclear at what point within the section FDA's focus shifted from sponsor to material manufacturer.
    - ASGCT recognizes that sponsors are ultimately responsible for ensuring raw materials and manufacturing processes are compliant with regulations. We respectfully suggest an added paragraph reiterating FDA's expectations for joint responsibility.

- Terminology - The Society requests clarification of the terms used throughout the guidance. For example, in the introduction to Section III, sponsors are asked to provide information such as the "manufacturer, catalog number, source… **grade**, and stage at which the material is used in the manufacturing process…" (lines 97-99, emphasis added). However, "grade" is not a standardized term, and may lead to confusion from sponsors about what type of information they may need to provide. For example, "GMP-grade" may be used interchangeably to mean GMP-sourced, research-grade, or clinical-grade. Other terms that would benefit from greater clarity include "raw material" and "reagent;" while typically "reagent" is used in the context of analytical testing and "raw materials" for manufacturing, these are not universal terms.

Finally, we note that outside of academic and small-scale manufacturing settings, the field is increasingly moving away from human- and animal-derived materials and toward chemically derived options. We request FDA provide updated, or new, guidance on sponsors' use of these alternate pathways.

In addition to these general comments, the Society respectfully submits the following line edits and additional comments for consideration:

| III. General Principles: Human- and Animal-Derived Materials | | |
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| Lines/Text Reference | Comment | Text Recommendation |
| *Lines 95-99*<br><br>"In your IND, you must provide a list of all materials used in manufacturing and a description of the quality or grade of these materials (21 CFR 312.23(a)(7)(iv)(b)). We recommend that you provide such list in tabular format, including, but not limited to, manufacturer, catalog number, source (e.g., human, animal, bacterial, insect), grade, and stage at which the material is used in the manufacturing process (e.g., culture media, excipient)." | ASGCT suggests it is not necessary to provide specific catalog numbers for all materials. In particular, because these numbers may change with the material manufacturer. Depending on the material purchased, sponsors may not have access to all of the documentation requested in this section. | "We recommend that you provide such list in tabular format, including, but not limited to, manufacturer, ~~catalog number,~~ source (e.g., human, animal, bacterial, insect), grade, and stage at which the material is used in the manufacturing process (e.g., culture media, excipient)." |
| *Lines 127-149*<br><br>"A. Adventitious Agents<br><br>Human- and animal-derived materials increase the risk of introducing adventitious 129 agents, including viruses, parasites, bacteria, mycoplasma and agent(s) responsible for 130 transmissible spongiform encephalopathies (TSEs)…" | This section does not specify what types of materials FDA considers to be high-risk enough to warrant adventitious agent testing.<br><br>ASGCT requests additional clarification on the types of materials FDA is recommending for adventitious agent testing. | N/A |
| *Lines 153-154*<br><br>"As described in FDA's "Guidance for Industry: Q9(R1) Quality Risk Management," dated June 2006 (Ref. 4), risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards."<br><br>*Reference 4* | ASGCT appreciates that this section is aligned with ICH guidance, and the move toward a quantitative risk assessment approach. | We request correction of what we believe to be a typo in this section. Line 154 references the 2006 version of the Q9(R1) guidance, while the cited Reference 4 refers to the recent 2023 version.<br><br>"dated ~~June 2006~~ May |

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| Guidance for Industry: Q9(R1) Quality Risk Management, May 2023, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q9r1-quality-risk-569 management | | 2023 (Ref. 4)" |
| *Lines 181-191*<br><br>"CGMP regulations require identity testing of materials, and specific tests should be used if they are available (21 CFR 211.84(d)(1)). Although the production of an investigational drug for use in a phase 1 study is exempt from compliance with the regulations in 21 CFR part 211 (21 CFR 210.2(c)), manufacturers must follow statutory CGMP required under section 501(a)(2)(B) of the FD&C Act7, and you should consider implementing identity testing, even during phase 1 clinical investigations, in order to minimize any unintended compromise to product safety or quality. For example, if there is a similar material being used in the same facility, such as similar types of sera or media supplements, it is important to verify material identity. For phase 1 investigations, you should establish written procedures describing the handling, review, acceptance, and control of materials used in the manufacture (Ref. 5)." | ASGCT respectfully asserts that this paragraph is not in line with generally accepted practice for Phase 1 products. For example, FDA's guidance (*CGMP for Phase 1 Investigational Drugs*) does not require sponsors to identity test the full range of materials used at that stage. We agree that for certain materials (i.e. plasmids as a starting material) identification testing may be warranted as due diligence in Phase 1. However, we do not support the broad scope indicated in this paragraph, as across-the-board Phase 1 identification testing would be a significant burden on sponsors.<br><br>ASGCT requests additional information as to when Phase 1 identification testing is recommended for sponsors. For example, starting materials and raw materials may have different considerations.<br><br>It would also be beneficial to understand when identification testing is not needed. | N/A |
| *Lines 202-210*<br><br>"Materials of human or animal | FDA's general practice thus far has been to discourage pooling. While ASGCT | N/A |

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| origin may show donor-dependent variation in purity, strength, and quality profiles. When a material is a biologically complex mixture that may vary among lots, it is important to establish acceptance criteria for the attributes that will affect the performance of the material in your product manufacturing process. For example, materials derived from blood are frequently pooled during material manufacturing. Pooling is generally thought to improve lot-to-lot consistency of the material, but it may still be necessary for either you or the supplier to test certain attributes of the material to ensure that new lots will perform adequately in your product manufacturing process. The level of pooling may vary considerably by supplier, or even among lots from the same supplier." | appreciates the level of flexibility shown in this paragraph, it is unclear whether the Agency is trying to actively encourage the practice for the sake of consistency, or indicating openness to pooling if a sponsor wishes to pursue it.<br><br>The Society requests clarification on instances in which pooling would or would not be appropriate. Given each manufacturer handles pooling differently, additional context on the Agency's intention for this section would be helpful. | |
| **IV. Materials Derived from Human Blood and Blood Components** | | |
| Lines/Text Reference | Comment | Text Recommendation |
| *Lines 256-262*<br><br>"The collection, processing, compatibility testing, storage and distribution of human blood and blood components must be performed in accordance with applicable requirements for current good manufacturing practices (21 CFR part 606) and must be collected in accordance with applicable requirements for donor eligibility and donation testing requirements in 21 CFR part 630, subpart B, 21 CFR part 640, and | For products that are licensed and have their own BLA and/or Master File, it should be sufficient to cross reference that BLA and/or Master File rather than providing details on collection, processing, and storage.<br><br>ASGCT requests an additional statement that clarifies when companies can cross-reference data in existing BLAs or Master Files to fulfill this requirement. | We propose that FDA could include language in line with its FAQ on combination products:[1]<br><br>"For collection, processing, compatibility testing, storage and distribution information for products that are licensed or have a master file, a sponsor may cross reference the information. For |

[1] US Food and Drug Administration. (2022). *Frequently Asked Questions About Combination Products.* https://www.fda.gov/combination-products/about-combination-products/frequently-asked-questions-about-combination-products

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| 21 CFR 610.40. We recommend that you source your blood and blood components from blood establishments that are FDA-registered." | We also note that ASGCT remains concerned with the final rule Biologics License Applications and Master Files (89 FR 9743) ('BLA DMF final rule'). The BLA DMF final rule codifies a policy that BLAs cannot incorporate information about drug substance, drug intermediate or drug product through referencing a drug master file.<br><br>DMFs are the main way that proprietary information can be shared with the agency without having to disclose it to drug sponsors. By eliminating the ability for BLAs to reference DMFs that contain information about components, there is little incentive to develop or move towards standardized components, which can be deployed across applicants, as there would be no proprietary protections on that investment. | reliance on the data, the applicant should provide a right of reference letter from the license or master file holder. The applicant may cross-reference a master file that resides in any medical product center (i.e., CBER, CDER, CDRH)." |
| *Lines 378-385*<br><br>"Manufacturers of culture media used in manufacture of CGT or TEMP products who wish to provide confidential information about their media to FDA should submit a Type II drug master file (DMF) to the Center for Biologics Evaluation and Research (CBER). If a MF is available for a material, a letter of authorization that authorizes the cross-reference of information in the MF and that is signed by the person who submitted the cross-referenced | This section indicates that sponsors do not need to list components if they reference a master file. However, this does not align with ASGCT members' experience of reviewer expectations.<br><br>ASGCT respectfully requests FDA expand this section to provide clarity on what is minimally required in the sponsor dossier. | N/A |

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| information should be included in an IND submission (21 CFR 312.23(b)).” | | |
| **V. Human-derived Feeder and Bystander Cells and Cell-derived Particles** | | |
| Lines/Text Reference | Comment | Text Recommendation |
| *Line 393-395*<br><br>“Some examples include immortalized feeder cells, allogeneic cells irradiated at high dose to yield cell particles, and cells that have been genetically modified to express certain stimulatory proteins.” | The term “cell particles” in this section could refer to a number of different outcomes. For example, irradiated cells may still be living but not proliferating, or they may be broken into parts and fully dead.<br><br>ASGCT requests additional definition on the term “cell particles.” | N/A |
| **VI. Materials Derived from Animals** | | |
| *Lines 450-453*<br><br>“For all bovine-derived materials, including those with indirect contact, you should provide documentation reflecting freedom from adventitious agents and bovine spongiform encephalopathy (BSE) (e.g., documentation that the herds are born, raised, and slaughtered in a country with negligible BSE risk).” | It is not always clear to sponsors when they need to have certificates reflecting negligible BSE risk. This is especially true for sponsors looking retrospectively for raw material suitability. In addition, the negligible regions are not universally defined.<br><br>The Society suggests FDA provide a recommendation, or source reference, that sponsors can utilize as it relates to regions the Agency believes have negligible BSE risk. | N/A |
| **IX. Communication with the FDA Regarding the Use of Human- and Animal-derived Materials** | | |
| *Lines 548-549*<br><br>“Changes to materials for products under an IND or a biologics license | ASGCT agrees that sponsors should report major changes through the IND amendment or BLA supplement process, | N/A |

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| application (BLA) should be reported in an IND amendment or BLA supplement, respectively." | as appropriate. However, the broad scope of this statement is ambiguous.<br><br>We request FDA clarify the intent for reporting product or material changes, and how like-for-like substitutions apply to this statement. | |

Thank you for your consideration of these comments. ASGCT looks forward to continued collaboration with the Agency on issues critical to the development of, and manufacturing of, CGTs. If you have any questions, please do not hesitate to contact Margarita Valdez Martínez, Chief Advocacy Officer, at mvaldez@asgct.org.

Sincerely,

David M. Barrett, J.D.
Chief Executive Officer