American Society of Gene + Cell Therapy

June 14, 2022

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

RE: Comments for Docket No. FDA-2021-D-0404, "Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products; Draft Guidance for Industry."

Dear Sir or Madam:

The American Society of Gene & Cell Therapy (ASGCT) appreciates the opportunity to comment on the draft guidance document, *Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products*. ASGCT is a nonprofit professional membership organization comprised of more than 5,500 scientists, physicians, clinicians, and other professionals working in gene and cell therapy 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. By bringing together members from diverse backgrounds, ASGCT strives to be a catalyst for transformative medicine using genetic and cellular therapies to control and cure human disease. We appreciate FDA's ongoing willingness to hear from stakeholders about ways to improve and adapt policies to consider the unique attributes of these therapies.

I. General Comments

ASGCT appreciates that FDA is working to provide additional guidance to CAR T therapy sponsors to further promote development of new therapies for patients. We believe this guidance broadly strikes an appropriate balance between setting baseline expectations for sponsors and providing needed flexibility to evaluate data for individual development programs based upon the benefit-risk of the unmet medical need and the condition being treated. Additionally, ASGCT appreciates the document's broad applicability to other genetically modified lymphocyte products.

That said, ASGCT has several specific suggestions for adjustments or edits that we believe would represent improvements in the final guidance.

II. Specific Comments

The majority of ASGCT comments relate to *Section IV. CMC Recommendations* of the draft guidance. In general, as ASGCT shared at our 2021 FDA Liaison Meeting,[1] advances in manufacturing and analytical techniques have improved control and characterization of products in the cell and gene therapy field at large, but the link between product characteristics and clinical performance is still evolving. Small clinical trial populations that are characteristic of cell and gene therapy product development make statistical analysis of CMC data challenging. Rapid innovation in the field warrants a CMC framework that remains flexible, risk-based, and correlated with the extent of clinical experience. ASGCT appreciates the inclusion of specific CAR T CMC considerations in this draft guidance and offers suggestions on specific subsections below.

1. Cellular Starting Material

ASGCT acknowledges FDA's concern that CAR T cells produced using starting material from patients who have received CAR T cells previously may have unexpected effects on CAR T manufacturing as well as the quality attributes and potency of the final product. However, ASGCT does not regard testing for residual CAR T as feasible, due to a lack of tools (e.g., reagents) and because the typical patient will not have this kind information available to them. Additionally, such testing is not necessary from a safety standpoint and does not yield a clinical benefit to most patients.

Upon enrollment of a subject otherwise meeting all enrollment criteria, it will not be possible to evaluate the level of CAR T cell expression (line 154-155), the vector copy number (VCN) (line 157) nor the potential differences in the CAR T cells (line 160-161) of previously administered CAR T cells that were produced by another manufacturer and administered at another clinical site. This would require the knowledge of the identity of the CAR construct as well as the nucleotide sequence, which are proprietary in most cases and, therefore, not accessible.

As FDA notes in this section, CAR T cell manufacturing includes evaluation of the product at multiple steps (e.g., expansion or transduction rates) as well as the quality attributes and potency of the final product. If previous CAR cells have an impact on the efficacy of the product, this will be caught as part of the existing manufacturing controls.

Additionally, pre-conditioning, such as chemotherapy or is generally used prior to CAR T cell infusion, to enable CAR T cell engraftment and persistence. This pre-conditioning is likely to remove previously administered CAR T cells, considerably reducing the risk

[1] *Recommendations on CMC Expectations for Gene and Cell Therapy Products*. https://asgct.org/global/documents/advocacy/2021-fda-liaison-meeting/final-cmc-issues-for-liaison-meeting.aspx

of any adverse effects due to previous CAR T cell infusion. The subjects should therefore meet all clinical enrollment criteria, including the ability to tolerate non-myeloablation preparative regimen, such as chemotherapy or total body radiation.

Therefore, ASGCT encourages FDA to remove requirements for evaluating previously administered CAR T cell levels in the cellular starting material (line 146-162) from the guidance because the information cannot be feasibly obtained, nor is it clinically relevant. If previous CAR cells have an impact on the safety or efficacy of the product, this will be caught as part of the existing manufacturing controls.

ASGCT recommends that sponsors or manufacturers of commercially approved, genetically modified IEC products instead be required to either offer VCN testing upon clinician request, or release specific primer/probe nucleotide sequences that enable detection of their products.

2. *Vector Manufacturing and Testing*

ASGCT notes that FDA requires vectors to be "well-characterized" in the context of an IND submission. The guidance states:

> *"The GT CMC Guidance (Ref. 3) provides recommendations for manufacturing and testing of the vector. The vector should be well-characterized prior to initiation of clinical studies"* (lines 236-237).

ASGCT notes that this language does not align with FDA's other early-phase guidance documents and recommends the language be amended to clarify the Agency's expectations for vector testing and manufacturing prior to initiation of clinical studies. Clearly specifying that vector expectations are aligned with other Phase I guidelines will help streamline IND submissions and reduce burdens on both the Agency and sponsors. Thus, ASGCT suggests replacing lines 236-237 with:

> *"The vector intended for use in initiation of clinical studies should be manufactured under conditions that are appropriate for the phase of development,[2] and the relevant quality attributes of the vector should be well-characterized."*

3. *Managing Manufacturing Changes and Assessing Comparability During the CAR T Cell Product Life Cycle: Change Management*

ASGCT anticipates that sponsors will potentially make multiple changes to the manufacturing procedure during early clinical development (i.e., Phases 1 and 2) to

[2] *Guidance for Industry: CGMP for Phase I Investigational Drugs*. https://www.fda.gov/media/70975/download.

establish a scalable and robust manufacturing process. ASGCT notes that the guidance requires an IND to be updated to reflect CMC changes in the manufacturing process, regardless of the product development stage (lines 665-666). Such a change would be described as new chemistry information requiring an information amendment under 21 CFR 312.31(a). The guidance also explains that each change will be assessed on a case-by-case basis by the Agency, and recommends that sponsors communicate with OTAT (e.g., through an IND amendment requesting advice or a formal meeting request) while considering such changes (lines 620-622).

While the guidance focuses on the changes that would result in a new product or have major implications to product quality, safety, efficacy, or stability, ASGCT recommends the FDA provide examples that specify what changes the agency generally anticipates being minor (vs major), as well as what type of information sponsors should submit in IND updates to verify these minor changes. Suggested examples of minor changes could be:

- Changes in cell hold times;
- Extensions of product shelf-life or an in-house reference material according to a protocol submitted to the IND;
- Minor modifications to an analytical procedure with no change in the analytical technique/methodology;
- Certain acceptance criteria or method performance; or
- Introduction of new computer system or automation of a process step without a change in the manufacturing process.

Providing examples such as these will help IND sponsors assess the regulatory expectations about what data are expected to support minor changes and would also help alleviate the uncertainty and reduce the burden on the Agency to provide feedback to each individual sponsor. Assisting sponsors in differentiating between major and minor changes via guidance would allow FDA to direct its resources toward reviewing major changes that have the potential to affect product quality and patient safety. Given limited Agency resources and the large number of pending INDs, this ability to prioritize would benefit both FDA and sponsors.

ASGCT acknowledges that the guidance states FDA will assess each change on a case-by-case basis and supports the Agency in this effort. However, specific examples of what constitutes a minor versus a major change would be extremely helpful to ensure sponsors are able to satisfy Agency expectations with respect to additional information. Providing examples in guidance is also consistent with prior guidance practices. For example, in a recent guidance related to post-approval CMC changes, FDA provides as

an appendix, a list of examples of changes that it would consider minor, and therefore reportable in the annual BLA report.[3]

ASGCT notes the draft guidance recommends that sponsors communicate with OTAT (e.g., through an IND amendment requesting advice or a formal meeting request) while considering manufacturing changes (lines 620-622). As you know, the IND regulatory framework generally contemplates that sponsors will notify FDA of changes (via a protocol amendment, an informational amendment, or an annual report), but it does not require FDA to approve those changes before the sponsor implements them. See 21 CFR 312.30 (protocol amendments), 21 CFR 312.31 (informational amendments), and 21 CFR 312.33 (annual report). The regulations do allow, of course, for sponsors to request Agency feedback on amendments, particularly informational amendments. Given that FDA recommends that sponsors communicate with OTAT when considering manufacturing changes, ASGCT seeks clarity on what FDA anticipates its response time for review/feedback on those amendments would be and whether the change may be implemented before such feedback is received. ASGCT suggests that a 30-day review timeframe may be appropriate, as this is the standard review timeframe for initial IND applications.

Finally, ASGCT highlights the potential for many changes to be made to the manufacturing process before initiating a pivotal study. The guidance is unclear on whether the Agency expects submission of each manufacturing change for implementation or whether multiple expected changes may be combined into one submission for discussion and review. Thus, ASGCT also requests guidance on when manufacturing changes should be combined into one submission.

4. *Managing Manufacturing Changes and Assessing Comparability During the CAR T Cell Product Life Cycle: Comparability Study Design*

As ASGCT has previously recommended to FDA (see Footnote 1), keeping CMC guidance consistent increases clarity on FDA expectations and avoids risks of divergences between therapeutic areas. Additionally, some of the detailed criteria required as part of establishing comparability may not be appropriate, particularly for early-stage studies.

For example, ASGCT seeks greater clarity on Agency expectations regarding specifications and statistical analysis. The draft guidance states that:

[3] Guidance for Industry, CMC Postapproval Manufacturing Changes for Specified Biological Products To Be Documented in Annual Reports (December 2021). There is also a CDER Guidance, Changes to an Approved NDA or ANDA (April 2004) that similarly includes examples of major, minor and moderate post approval changes.

> *"Comparability studies should be analyzed using appropriate statistical methods and predefined acceptance criteria based on lots shown to be safe and effective" (Lines 714-716).*

As we noted above, multiple changes to the manufacturing process may be required during product development, often with limited batch datasets at each stage. ASGCT members who are sponsors believe the goal of studies to compare products before and after a process change is to prospectively ensure comparable safety and efficacy of an investigational product within bounds supported by risk assessments, rather than ensure identical performance on all measured characteristics. This philosophy is reflected in the draft guidance as well (lines 671-676). Requiring statistical analyses in setting comparability acceptance criteria is often not realistic given the lack of sufficient batch numbers that can be generated during clinical development and an insufficient understanding of the clinical impact of biological variation.

Therefore, ASGCT recommends that FDA allow a more flexible and pragmatic approach to manufacturing process changes and comparability assessment. Statistical analysis expectations should consider that low replicate batches are an inherent feature of CGT investigational products. We propose greater weighting of science and risk-based arguments and decision making that includes qualitative data.

ASGCT also suggests adding language on using the statistical methodologies referenced in the guidance, along with how these methodologies specifically relate to quality product development, as well as other methods of analyses, beyond statistical methods. ASGCT notes a lack of clarity in the guidance on making qualitative comparisons as part of comparability analyses. The limited data sets and vague range of CQAs provided in the guidance will not adequately aid sponsors in anticipating FDA's expectations.

Last, the guidance states that if there is insufficient demonstration of analytical comparability, then a new study may be requested and that this may delay product licensure (lines 678-80). ASGCT is concerned that this standard for comparability is too rigid for early-stage studies and that greater flexibility should be afforded.

ASGCT appreciates the ongoing partnership and opportunity to engage in a scientific dialogue with FDA. We also appreciate the continued engagement with the community to share and discuss FDA's thinking, such as the 2021 CTGT Advisory Committee Meeting and this draft guidance document. In addition to the recommendations above, we suggest that FDA consider the following CMC policy approaches:

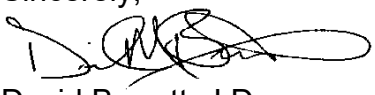
- Keep CMC guidance consolidated to increase clarity in the Agency's views and avoid risks of divergence between therapeutic areas.

- Greater coordination between OTAT and other offices with less experience in CGT to assist with product review consistency.
- Continue to engage with the scientific community at conferences and meetings, including sharing case studies – where possible, these should include blinded datasets representing broad areas/large samples to provide context and assist cross-field collaboration.
- Continue to engage across HHS agencies and stakeholders, such as with the Bespoke Gene Therapy Consortium (BGTC).

III. Conclusion

Thank you for your consideration of these comments. If you have any questions about the Society's comment, please do not hesitate to contact Margarita Valdez Martínez, Director of Advocacy and Policy, at mvaldez@asgct.org.

Sincerely,



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