American Society of Gene + Cell Therapy

February 17, 2025

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

RE: Comments for Docket No. FDA-2024-D-4311 "Frequently Asked Questions – Developing Potential Cellular and Gene Therapy Products; Draft Guidance for Industry"

Dear Sir/Madam:

The American Society of Gene & Cell Therapy (ASGCT) appreciates the opportunity to comment on FDA's Frequently Asked Questions (FAQ) draft guidance. ASGCT is a nonprofit professional membership organization comprised of more than 6,400 scientists, physicians, patient advocates, and other professionals working on cell and gene therapies (CGTs) 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. Given this mission, we provide the following comments to ensure that FDA's FAQ guidance can be of the broadest possible use for CGT developers and sponsors.

General Comments

ASGCT welcomes this FAQ initiative and appreciates the broader effort FDA has put into public engagement in recent years. The Society encourages FDA to continue sharing information through a variety of methods including town halls, public workshops, and guidance documents. It is ultimately patients who benefit from more efficient development of CGTs.

ASGCT believes that this FAQ draft guidance is a good resource for those new to the CGT regulatory space. The information contained within is generally clear and provides a solid roadmap for product development by simply referring to existing regulations and guidance documents. However, for companies and individuals with more regulatory experience, and who are facing challenges within the currently articulated frameworks, ASGCT believes this FAQ guidance has limited utility.

We are encouraged by the Federal Register's comment that the draft guidance "may be updated to include additional FAQs as appropriate." ASGCT urges FDA to embrace that opportunity to expand this resource to address more complex issues. We also encourage the Agency to set and publicize a regular update schedule.

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In summary, while ASGCT acknowledges this FAQ draft guidance is a useful foundational document, we ask FDA to strongly consider opportunities to expand the scope and address a wider set of topics.

Specific Comments

Page and Question Reference	*Text + Recommendation*	*Comment*
IV. PRODUCT DEVELOPMENT CONSIDERATIONS		
Pages 19-20 **"Q13. What is the difference between product characterization testing and release testing?"**	"Prior to initiating Phase 2 or 3 clinical investigations on the drug, release tests must be qualified, tests must have predefined AC, and tests must comply with current good manufacturing practice (CGMP). In contrast, characterization tests do not need to be qualified, have AC, or comply with the CGMP requirements for testing and release for distribution. Release tests must be validated prior to BLA submission." … "Some release tests are performed on a sample of the final product. ~~necessary to confirm safety of the product prior to release but are not performed on the final product; s~~ Such samples should be acquired at the necessary and appropriate manufacturing steps. For example, tests for mycoplasma and adventitious agents should be performed on cell culture harvest material prior to further processing. Tests for sterility, endotoxin, and identity should be performed on formulated product in the final labeled container to ensure that microbial contamination and product mix-ups (such as those that may occur during final DP manufacturing steps) do not occur."	ASGCT recommends that FDA add additional detail for sponsors explaining why characterization assays are necessary as part of an IND submission, given the Agency's response that characterization tests do not need to be qualified or included for product release. Our concern is that including elements that are *not* necessary for characterization assays, without providing additional guidance on their positive use, may be confusing. In addition, this contributes to ongoing confusion around the need to establish acceptance criteria for and include non-critical, unqualified characterization assays in important development studies such as comparability studies.

Pages 20-21 **"Q14. What information should be submitted regarding critical quality attributes?"**	"In traditional product development, CQAs of the product are evaluated during each phase of clinical development, and in some cases (less common for rare diseases) characterization data from ~~many~~ DP lots ~~can~~ may be correlated to clinical outcomes. For rare diseases, some aspects of the development programs, such as limited population size and fewer lots manufactured, may make it challenging to follow traditional product development strategies. For more details, refer to FDA's guidance entitled "Human Gene Therapy for Rare Diseases: Guidance for Industry," January 2020 (hereinafter referred to as "GT for Rare Diseases Guidance") [Ref. 23]."	We respectfully assert that correlation of characterization data and clinical outcomes is not standard even in common diseases, let alone rare diseases. We propose the indicated changes to this answer to acknowledge this nuance and reflect FDA's latest thinking cited in finalized guidance documents.
V. PRODUCT DEVELOPMENT CONSIDERATIONS		
Page 26 **"Q23. What approach should be taken if there is no available animal model of disease in which the investigational product can be evaluated?"**	"When animal models of the target disease are not available or if the investigational CGT product is incompatible with an animal model, the sponsor should provide supporting data from other sources. Some examples include in vitro studies, in silico studies, in vivo studies using an analogous animal product, and relevant nonclinical or clinical data from studies evaluating a related product or indication."	ASGCT notes that most CAR T-cell therapies do not have any established animal models. This answer suggests that sponsors provide data from other sources; we recommend the Agency provide additional clarification whether reviewers expect an orthogonal approach using a combination of varying sources like the examples provided.
Pages 27-28 "**Q26. What is the FDA's recommendation regarding tumorigenicity studies before the first use of**	"If the sponsor considers a tumorigenicity study unnecessary, they should provide a scientific justification with supporting data in their submission to OTP for review."	In this answer, there is no reference to FDA's expectation for de-risking potential tumorigenicity. We ask FDA to consider providing additional information about

CGT products in human subjects?"		expectations (ex: cytokine independent growth assays or ISA). We also request that FDA cross-reference to existing guidance or, if not applicable, include a note that this is standard agency practice.
VI. CONDUCTING HUMAN TRIALS		
Pages 33-35 **"Q34. What should sponsors consider when using a surrogate endpoint as a primary outcome measure for a later phase clinical trial intended to support approval of a CGT product?"**	"For accelerated approval, FDA accepts evidence of a demonstrated effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit or on an intermediate clinical endpoint (a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict a clinical benefit)."	In this answer, FDA mentions intermediate clinical endpoints in the opening paragraph but does not provide additional guidance later on. ASGCT recommends the Agency provide additional information specific to intermediate clinical endpoints.

The Society would welcome the opportunity to work with the Agency on this guidance. Thank you for the consideration of these comments. If you have any questions, please do not hesitate to contact Margarita Valdez Martínez, Chief Advocacy Officer, at mvaldez@asgct.org.

Sincerely,

David Barrett, JD
Chief Executive Officer
American Society of Gene & Cell Therapy