American Society of Gene + Cell Therapy

December 23, 2021

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-0776: Studying Multiple Versions of a Cellular or Gene Therapy Product in an Early-Phase Clinical Trial

Dear Sir/Madam:

The American Society of Gene & Cell Therapy (ASGCT) appreciates the opportunity to comment on this guidance document. ASGCT is a nonprofit professional membership organization comprised of more than 4,800 scientists, physicians, and other professionals working in gene and cell therapy in settings such as universities, hospitals, and biotechnology companies. 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. 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.

The Society would like to thank the Agency for responding to the interest of sponsors by providing this valuable guidance for developing gene and cell therapy in cases in which sponsors plan to develop multiple products in parallel. The potential to allow for sharing of a control group is a provision that ASGCT supports.

ASGCT recognizes that the Agency has elected to focus this guidance on early-phase studies, because this type of approach may be more commonly taken. However, much of the guidance seems to be generally applicable, regardless of the phase of development. These trial designs may be applicable to later-stage studies in some cases; perhaps this guidance could be broadened in scope to apply to any situation where multiple versions of a cellular or gene therapy product may be brought into the same trial. For instance, some umbrella trial designs may include a separating step where participants are placed into different study arms based on one or more biomarkers. Given this happens in both early and late stage development, ASGCT recommends that such separation, as outlined in the Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics Guidance for Industry, should be similarly applied to this guidance. ASGCT encourages the Agency to consider whether the guidance necessarily is limited to topics relevant to early-phase clinical trials.

Lines	Comment/Issue	Proposed Change
III. SCOPE		
86-89	*"If sponsors are interested in conducting a study that is outside the scope of this guidance, we recommend the sponsor request a pre-IND meeting with the Office of Tissues and Advanced Therapies (OTAT), CBER, to discuss their proposed clinical trial design."* Comment: ASGCT recommends that the guidance be amended to allow discussion of development plans at either a pre-IND or INTERACT meeting. The Society requests an opportunity for sponsors to communicate with FDA before the pre-IND stage to determine if the products qualify as "multiple products," especially considering that the Agency usually grants only one pre-IND meeting, and thus the pre-IND meeting is ideally preserved for discussing the detailed plans, and not solely the conceptual approach.	
IV. SUBMISSION OF INFORMATION TO INDS		
A. Overview		
115-125	*"For a clinical study with two different versions of the investigational product (Product A and Product B), we recommend that the sponsor submit two separate INDs, IND A and IND B. One of the INDs, IND A, will be considered the "Primary" IND, and should include CMC and P/T information for Product A. IND B will be considered a "Secondary" IND, and will include CMC and P/T information for Product B. Complete clinical information for the umbrella trial, including the clinical protocol and supporting documents (e.g., investigator brochure, informed consent form, Form FDA 1572), should also be submitted to the Primary IND A. This framework can be further extended to additional versions of the product; if the clinical study includes three different products (Products A, B, and C), then the CMC and P/T information for Product C should be provided in Secondary IND C."* Comment: ASGCT is concerned that submitting two INDs for product A and B that have some duplicate information and some information that needs to be cross referenced between the two will create both unnecessary duplication and additional burden for the Agency. ASGCT suggests that the Agency require sponsors only to include information that is different in the Secondary IND, from the Primary IND. This would allow the Agency to cross-reference the Primary IND rather than having sponsors repeat it.	*"For a clinical study with two different versions of the investigational product (Product A and Product B), we recommend that the sponsor submit two separate INDs, IND A and IND B. One of the INDs, IND A, will be considered the "Primary" IND, and should include CMC and P/T information for Product A. IND B will be considered a "Secondary" IND, and will include the CMC and P/T information for Product B that is novel or differential compared to Product A. Complete clinical information for the umbrella trial, including the clinical protocol and supporting documents (e.g., investigator brochure, informed consent form, Form FDA 1572), should*

		also be submitted to the Primary IND A. This framework can be further extended to additional versions of the product; if the clinical study includes three different products (Products A, B, and C), then the CMC and P/T information for Product C should be provided in Secondary IND C."
B. Adding Arms to the Study		
159-165	*"If the arm to be added includes a new version of the investigational cellular or gene therapy product, (e.g., Product C), we recommend that the sponsor submit IND C with CMC and P/T information for Product C.* - *IND C will be considered a Secondary IND. We recommend that the cover letter for a Secondary IND clearly state that the IND is a Secondary IND and specify the Primary IND number. The Secondary IND should cross-reference the Primary IND for clinical information."* Comment: ASGCT appreciates the information about adding another arm to the study with a new version of the product. The Society would like FDA to provide additional information for sponsors to consider how the agency determines the point at which the overall trial is negatively impacted by adding arms to which patients were not randomized.	
E. Reporting		
237-240	*"Sponsors must submit Annual Reports to each IND (21 CFR 312.33). If desired, the sponsor can submit an integrated Annual Report that includes the clinical information and the CMC and P/T information for all products to the Primary IND, and submit that same Annual Report to each of the Secondary INDs"* Comment: ASGCT supports inclusion of the option to submit a copy of the same integrated Annual Report to all INDs. Sponsors would like clarity from FDA on if submitting a Drug Safety Update Report in place of the Annual Report is acceptable for all products related to the Primary IND.	

V. ALTERNATIVE APPROACHES		
271-272	"*There may be alternative approaches to structuring and organizing the INDs for the studies of multiple versions of an investigational product as described in this guidance.*" Comment: ASGCT thanks FDA for allowing alternative approaches to the outlined process.	

Thank you for consideration of these comments. Please do not hesitate to let ASGCT know if you have questions.

Sincerely,

Keith Wonnacott, PhD, Chair, ASGCT Regulatory Affairs Committee