American Society of Gene + Cell Therapy

November 5, 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-0875: S12 Nonclinical Biodistribution Considerations for Gene Therapy Products; International Council for Harmonisation; Draft Guidance for Industry

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 4800 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 appreciates guidance development on this topic. ASGCT appreciates the broad scope of this guidance to address GT products including purified nucleic acid (e.g., plasmids and RNA), microorganisms (e.g., viruses, bacteria, fungi) genetically modified to express transgenes (including products that edit the host genome), and *ex vivo* genetically modified human cells. The Society also appreciates that the draft document states that in some situations, nonclinical BD data generated with a GT product that consists of a previously characterized GT product that has the same vector structure and other characteristics that determine its tissue/cell tropism, but a different therapeutic transgene or an expression marker gene (e.g., adeno-associated virus vector of the same serotype and promoter with a fluorescent marker protein expression cassette) can potentially support waiving of an additional nonclinical BD study, with justification.

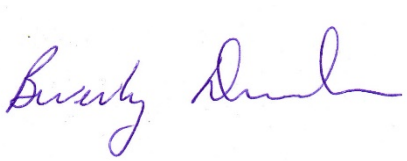
The Society offers the following specific comments and suggestions to provide additional clarity to developers of gene therapies:

Lines	Comment/Issue	Proposed Change
	1. INTRODUCTION	
	1.3 Scope	
33-34	"Evaluation of the nonclinical shedding profile of a GT product is outside the scope of this guideline." Comment: ASGCT recommends including within this guidance the evaluation of the nonclinical shedding profile of a GT product. Because shedding may be interpreted as a consequence of biodistribution, ASGCT views the topic to be relevant to the scope of this guidance document. Because nonclinical studies of shedding are not informative or predictive in studies using a non-replicative virus (such as AAV), such studies should not be required and should be left to a clinical evaluation.	"In studies using a non-replicative virus (e.g., AAV), nonclinical shedding studies are not required, and should be left to a clinical evaluation."
	4. DESIGN OF NONCLINICAL BD STUDIES	
	4.6 Sample Collection	
108-115	"Sample collection time points should reflect the anticipated time following GT product administration to reach peak, steady-state (i.e., plateau), and declining (if feasible) GT product levels in target and non-target tissues/biofluids. Additional time points can be included, as applicable, to more comprehensively capture the length of the steady-state period and to estimate persistence. Inclusion of time points to permit evaluation of GT product levels after repeat administration should be considered, when applicable. For replication competent vectors, sample collection time points should also cover the detection of the second peak level due to vector replication and the subsequent clearance phase." Comment: ASGCT suggests defining "persistence" in the glossary section as it relates to this guidance.	
NOTES		
251-253	"In general, it is recommended that a minimum of 5 rodents or 3 non-rodents per sex/group/time point be evaluated; however, inclusion of equivalent numbers for each sex may not be critical. Justification for these decisions should be provided." Comment: ASGCT recommends clarification regarding how unbalanced the numbers per sex could be, e.g., whether one animal in one gender would be sufficient to conclude the lack of distribution to gonads.	

254-259	*"If a novel delivery device system is planned for use in clinical trials, consider collecting BD data in conjunction with the pharmacology and/or toxicology studies conducted with the device system or its equivalent."* Comment: ASGCT recommends clarifying that regardless of whether the delivery system is a novel device, the same, or at least a similar material, medical device should be utilized throughout development to inform product labeling. Many GT products are not approved in combination with a specific medical device.	
GLOSSARY		
260-291	Comment: ASGCT recommends adding the following terms to the glossary: persistence, plateau, clearance, tissue tropism, and gene transfer efficiency.	

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

Sincerely,



Beverly Davidson, PhD
President, ASGCT