American Society of Gene + Cell Therapy

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

RE: Comments for Docket No. FDA-2022-D-0738, "Ethical Considerations for Clinical Investigations of Medical Products Involving Children; Draft Guidance for Industry, Sponsors, and IRBs"

Dear Sir/Madam:

The American Society of Gene & Cell Therapy (ASGCT) appreciates the opportunity to comment on the draft guidance document *Ethical Considerations for Clinical Investigations of Medical Products Involving Children; Draft Guidance for Industry, Sponsors, and IRBs*. ASGCT is a nonprofit professional membership organization comprised of more than 5,800 scientists, physicians, clinicians, and other professionals working in cell and gene therapy (CGT) 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.

ASGCT supports the protection of human subjects in FDA-regulated clinical investigations through adherence to current clinical trial regulations and robust Institutional Review Board (IRB) processes and commends practices that ensure vigorous safeguards for children involved in clinical research. The Society would like to thank the Agency for its efforts to produce this guidance to further clarify the Agency's thinking regarding ethical considerations for clinical investigations of medical products in children and agrees that housing this guidance on ethical frameworks within the existing IRB system, in accordance with 21 CFR 50.50-53 and CFR56, is a logical approach. Pediatric research principles, including the ethical questions addressed in this guidance, are of particular relevance for product sponsors, academic researchers, and interested patient groups currently engaged in bringing the next generation of current gene and cell therapy products to market given the pipeline's focus on pediatric

indications. Of the approximately 7,000 identified rare diseases, some 80% are estimated to have a known monogenic cause.[1] Among the rare disease population, around half impact children; the United States alone has approximately 15 million pediatric rare disease patients.[2] The CGT pipeline offers a unique opportunity to address pediatric diseases, many of which do not have available treatment options.

We appreciate that the Agency acknowledges the importance of pediatric clinical investigations for products indicated for this population and provides examples of how and when adult data may be considered. We agree with the Agency that "all available clinical data" should be used when assessing the risks of investigational drugs or devices which may have a prospect of direct benefit, including adult data when available, but that adult data may not be required for "pediatric conditions that present solely or primarily in childhood" where safety information can be obtained through non-clinical means.[3] The point is noted again in considering applications of Subpart D to pediatric clinical investigations: "[d]epending on the quality and applicability of these data, collection of relevant adult data prior to initiation of a trial in pediatric subjects may not always be necessary…[i]f relevant adult data are available, those data may inform the trial design for pediatric subjects. In some cases, adult studies may not be ethical or feasible."[4] The potentially very low incidence of rare genetic diseases in an adult population may make it unethical or highly challenging to collect safety data in this population prior to clinical development in the pediatric population, for many products under development. Hence, ASGCT appreciates that FDA has iterated a few examples of acceptable non-clinical data sources that might be used in those cases.

Additionally, we encourage the Agency to use external resources like ASGCT to help assess over time the innate differences between CGT and small molecule products when offering guidance on pediatric risk-benefit considerations. For genetic diseases with life-altering or life-limiting impacts and sometimes rapid onset and progression, it is important for IRBs to be mindful of potentially altered risk-benefit considerations for patients and/or parents[5] while never losing sight of their core responsibility to protect those involved in research.

Informed consent is also of special concern for the CGT field, drawing significant interest from patients, sponsors, clinicians, and other stakeholders in recent years.[6,7,8] CGT products may have a range of considerations not typical for small molecule drugs

[1] https://www.fda.gov/media/113807/download
[2] https://www.gao.gov/assets/gao-22-104235.pdf
[3] Guidance page 6, lines 209-213
[4] Guidance page 10, lines 344-346, 351
[5] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8172191/
[6] https://www.tandfonline.com/doi/full/10.1080/23294515.2020.1818876
[7] https://www.youtube.com/watch?v=y0nQA84M6q8&t=873s
[8] https://asgct.org/global/documents/advocacy/2021-fda-liaison-meeting/final-aav-integration-slides.aspx

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which must be adequately and compassionately explained to trial participants, which may include unique mechanisms of action, potentially durable treatment effect, uncertain oncogenic risk profile of some products, and the ethics of control arms in rapidly degenerative diseases. Children cannot provide consent for participation in a clinical trial themselves; hence, we agree that additional safeguards are vital. ASGCT also stresses the importance of informed consent in our Patient Education materials.[9]

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 Martinez, Director of Policy and Advocacy, at mvaldez@asgct.org.

Sincerely,

David Barrett, J.D.
Chief Executive Officer

[9] https://patienteducation.asgct.org/patient-journey/considering-a-clinical-trial