INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

5 March 2024

Dockets Management Staff
Food and Drug Administration
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA–2023–D–4299 for Potency Assurance for Cellular and Gene Therapy Products; Draft Guidance for Industry

To whom it may concern:

The International Society for Stem Cell Research (ISSCR) appreciates the opportunity to comment on the Food and Drug Administration's (FDA) draft guidance for Potency Assurance for Cellular and Gene Therapy (CGT) Products.

The ISSCR is an independent, global, nonprofit organization that promotes excellence in stem cell science and applications to human health. ISSCR represents 4,700 scientists, educators, ethicists, and business leaders across 80 countries. Our vision is a world where stem cell science is encouraged, ethics are prioritized, and discovery improves understanding and advances human health.

ISSCR commends FDA's desire to assure the potency of human CGT products at all stages of the product lifecycle. Additional guidance from the FDA will help our members, who are at the forefront of research and innovation, in their work. To complement FDA's initiatives and foster progress in this field, we offer the following comments and recommendations:

1. **Retrospective testing**. ISSCR requests that FDA provide additional guidance on retrospective testing of retained samples of Drug Product. Specifically, clarification on whether it is required, what the impact will be if it cannot be done, and what steps are necessary to establish the stability of the retains. It is common practice that one will likely have several potential potency assays in early-stage clinical development. If an assay continues to evolve and is not finalized and validated until pre-Phase 3, then ideally, there would be a retrospective analysis of retains from the doses administered in the Phase 1 and 2 clinical trials. Providing additional instructions will help stakeholders meet FDA expectations and maximize efficiency.

2. **In vivo performance of cell therapies.** ISSCR recommends that FDA provide its perspective on aspects of cell therapy potency that are related to the persistence, biodistribution, and integration of cells. For instance, a CAR-T cell therapy may exhibit potency in killing target cells during testing, but it may not be clinically effective if it does not survive, proliferate, and reach the target tissue/cell. Similarly, it is critical for cells like neurons to integrate and form functional connections with the appropriate cells in the recipient. We acknowledge the complexity of this topic, but we believe that having general information on the FDA's views would help align stakeholder efforts.

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Thank you for considering our views on the draft guidance for Manufacturing Changes and Comparability for Human and Cellular Gene Therapy Products. If the ISSCR can clarify any of these views or be of assistance, please contact Tyler Lamb, ISSCR's Director of Policy at tlamb@isscr.org or Denise de Villa, ISSCR's Manager of Policy at ddevilla@isscr.org.

Respectfully submitted,

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Chair, Manufacturing, Clinical Translation, and Regulatory Committee