INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

29 July 2024

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

Re: Docket No. FDA-2024-D-1243, Safety Testing of Human Allogeneic Cells Expanded for Use in Cell-Based Medical Products; Draft Guidance for Industry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for Stem Cell Research (ISSCR) appreciates the opportunity to comment on the Food and Drug Administration's (FDA) draft guidance for Safety Testing of Human Allogeneic Cells Expanded for Use in Cell-Based Medical Products.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 appreciates FDA's desire to share their recommendations for determining the appropriate cell safety testing to support an Investigational New Durg application (IND). Additional guidance from the FDA will support our members, who are leading research and innovation, in their efforts. To complement FDA's initiatives and foster progress in this field, we offer the following comments and recommendations:

I. General Comment

Genomic Testing. ISSCR requests that FDA provide information about testing for proliferative intermediate cell populations. For instance, if the manufacturing process for an iPSC-derived product includes production of an intermediate cell bank (ICB) of cells with significant proliferative capacity, what are the testing requirements for the ICB?

Thank you for considering our views on the draft guidance for Safety Testing of Human Allogeneic Cells Expanded for Use in Cell-Based Medical Products.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,

Melissa Carpenter, Ph.D.
Chair, Manufacturing, Clinical Translation, and Regulatory Committee

INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

II. Specific Comments

Section (Line)	Issue	Proposed Change
V. Testing Recommended for Highly Expanded Cells		
A. Master Cell Bank		
304 – 313	The draft guidance states: "Cell lines that are cultured extensively often accumulate mutations during cell expansion. Mutations in protooncogenes, such as p53, are of particular concern. Therefore, we recommend that continuous cell lines that contribute cells to the final product be evaluated by performing whole genome sequencing. The whole genome sequencing method used should have a read depth of at least 50X, and at a minimum, the results should be compared to a database of cancer associated mutations. Justification should be provided for the sequencing method, read depth, and for conclusions related to the safety of the product." Reads at 50x depth are well beyond current standards in the field and will most certainly return an overwhelming number of findings with unknown clinical significance.	ISSCR requests that FDA provide clarity regarding the requirement for 50x sequencing depth. What is the target sensitivity to rare events that is being sought through this requirement? Additionally, can guidance be given on how to assess these findings? From a resource perspective, could 30x coverage be sufficient?
324 – 327	The draft guidance states: "Alternatively, if cytogenetic testing is performed, G-banding analysis or other sensitive methods should be used to confirm the cells have a normal karyotype. The karyotypes of at least 20 cells should be analyzed." Count, analyze, and karyogram have specific meanings in cytogenetic terminology. When the term 'analyze' is used in the context of a cytogenetic test refers to a	ISSCR recommends adding the following language to the guidance: "The karyotypes of at least 20 cells should be counted, analyzed, or karyogrammed."

	different level of review than counting or karyogram. For reference, in a prenatal clinical diagnostic case the requirements would be to count 20, analyze 4 of these 20 cells and karyogram a minimum of 4 of the 20 cells. Please use this precise language to avoid confusion.	
327 – 331	The draft guidance states: "An acceptance criterion for cytogenetic test results with justification for discrepancies should be established. Cytogenetic testing is not recommended for continuous cell lines or highly expanded genetically modified cells that have been subjected to whole genome sequencing as recommended above." Not recommending cytogenetic testing after sequencing has been completed can be challenging for many investigators. Sequencing data would need to be reviewed/analyzed/interpreted for a normal/abnormal distinction for the product to continue to be released or program to be continued. In contrast, cytogenetic testing frequently provides a clearer 'go/no go' distinction that may still be very useful in the context of deciding what cell line or lot to utilize.	ISSCR recommends that both sequencing and cytogenetic testing be considered as necessary testing, as they each may serve different purposes.
B. Working Cell Bank		
370 - 374	Table 1 (line 410) indicates that PSC MCB and WCB should be tested as outlined in Section V, but the Section V.B. indicates that WCBs may not require genetic assessment.	ISSCR requests that FDA confirm whether WGS and cytogenetic analysis are not required for WCBs.