The Society for Immunotherapy of Cancer (SITC) appreciates the opportunity to comment on the Food and Drug Administration’s (FDA) recent draft guidance: *Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products*.

SITC is the world’s leading member-driven organization specifically dedicated to improving cancer patient outcomes by advancing the science, development and application of cancer immunology and immunotherapy. For decades, SITC members have been at the forefront of cancer immunotherapy research working to develop and advance novel therapeutics into the clinic for the treatment of various cancers, including modalities such as CAR T-cell therapies and other novel cellular therapies.

SITC leadership and members are very engaged within the field of cellular therapy development and manufacturing. This is reflected in the number of efforts recently completed and ongoing throughout SITC including our Cellular Therapy Regulatory Summit (full executive summary of this meeting can be found at [this link](#)), the creation of the longstanding SITC Cellular Therapy Committee, and large increase in cellular therapy-focused abstracts presented within the SITC Annual Meeting.

SITC commends FDA for providing further clarity through this guidance, and look forward to continuing to work with FDA to move the field forward. Based on the previously described efforts, and solicitation of comments from our membership, please find specific feedback regarding the draft guidance below:

1. **Footnote 1:** The footnote states, ‘For the purposes of this guidance "cellular therapy products" include certain tissue-engineered medical products..." We suggest adding the word 'also' prior to the word ‘include’ to clarify that it is in addition to standard cellular products

2. **Lines 74-75:** This sentence suggests the potential for manufacturing changes to cause a clinical hold. How should manufacturers reconcile or approach this, particularly for changes under IND given that there is no specified review window by the FDA? If manufacturing changes need to be reviewed, we suggest providing a timeline in which the review will take place.

3. **Lines 193-198:** Additional clarity regarding a reasonable percentage of clinical data produced pre-change versus post-change is needed due to the potential variability in comparable parameters post change. Additional clarity could include the threshold for data need post-change, a numerical or percentage standard, comparability assays that show equivalence, as well as what additional clinical data is needed.

4. **Line 632:** During a comparability assessment, some release acceptance criteria might be unrelated to a manufacturing change, for example presence of adventitious virus in starting material or product. In this example the failure of the release criteria is due to inherent donor variability and not reflective of batch failure or manufacturing issues. In these cases, providing clarity as to whether it would be acceptable to use data from batches that failed certain release acceptance criteria, if it can be justified that those criteria are unimpacted by a manufacturing change, would be warranted.

5. **Lines 684-687:** This sentence states that assays used for extended characterization don’t need to be qualified but should be scientifically sound. How can one know an assay is scientifically sound if the assay and equipment is not qualified? This may also be confusing given other FDA definitions of qualification and validation. We recommend that FDA consider adding appropriate references from CFR or other guidance documents. It may provide clarity if the wording stated that the assay doesn’t need to be fully validated according to the Analytical Procedures and Methods Validation guidance.
(6) As a general comment, SITC highly encourages the creation of a FAQ for this guidance that addresses potential questions, some of which become apparent through open comment. Past FDA guidance FAQ’s have been valuable resources for the field that are highly utilized.

SITC values our relationship with the FDA and appreciates the opportunity for providing comments on this draft guidance. If there are any questions or concerns regarding the comments or the guidance at large, please contact Mary Dean, SITC’s Executive Director, at mdean@sitcancer.org.

We look forward to future iterations of this effort and appreciate any feedback.

Best,

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