The Society for Immunotherapy of Cancer (SITC) appreciates the opportunity to comment on the Food and Drug Administration’s (FDA) recent guidance: *Potency Assurance for Cellular and Gene Therapy Products; Draft Guidance for Industry.*

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 natural arising TIL and T cell engineered to express antigen receptors (CAR or TCR) therapies.

SITC commends the FDA for providing further clarity on potency assessment through this guidance. Our leaders look forward to working with the FDA to drive momentum for the field. As the FDA is aware, SITC leadership and members are very engaged within the field of cellular therapy development and manufacturing and our interest is reflected through multiple timely efforts. SITC has established a new Cellular therapy committee and has organized dedicated summits including SITC’s 2022 Cellular Therapy Regulatory Summit (full executive summary of this meeting can be found [HERE](https://www.sitc-oncology.org)), as well as the December 2023 SITC Release Criteria Summit (full meeting report to be released soon). These meetings included a dedicated session to discuss the challenges to assess potency for cellular therapies. throughout the discussions, SITC leaders worked to define core hurdles related to potency within cellular therapy drug development, summarized below

- Ideally, each cellular-based product would have an associated potency assay that ensures a minimum level of activity and allows for comparability;
- Cellular Therapy Products have inherent variability in the starting material thus increasing complexity and variability
- While many cellular therapy products have provided patient benefit in clinical trials, the field of oncology has been unable to accurately identify critical quality attributes that clarify mechanism(s) of action

The above hurdles have limited investigators’ ability to analyze/define potency across development. This has the potential to prevent many candidate drugs from reaching patients despite demonstrated efficacy in clinical trials. As such, SITC leaders have proposed a more flexible “phase-dependent” approach towards characterizing potency across development:

A. Early-stage development would allow for data collection to better define a product’s mechanism of action and potential measures of such activity;
B. Later stage development would work to refine identified measures of potency, ultimately aiming to characterize an assay array that would allow for measurements of product functionality and potentially safety;
C. Post-approval patient data should be analyzed and submitted through defined regulatory pathways that would allow for further refinement of product release specifications;

SITC believes that continued dialogue and development of the proposed regulatory approach above will greatly benefit cancer patients by allowing for continued clinical incorporation of safe and effective treatment options. While many of these considerations are briefly described throughout the draft guidance, we offer further thoughts
on how to continue progress on potency assessment of cellular therapies. SITC will continue to provide the FDA both resources and updates on our efforts in this arena.

In conjunction with the above considerations, SITC leaders reviewed the draft guidance and identified specific areas for additional feedback, detailed below:

- **Lines 105, 452**: Line 105 states that that "FDA may place a study on clinical hold on such grounds if the potency of the product to be administered in an investigation is not adequately assured, or the information in the IND is not adequate to assure the potency of the product to be administered in the study.” This line appears to suggest that all studies are to be included. In collaboration with FDA’s historical activities as well as SITC’s suggestion of a more flexible phase dependent approach, we highlight that such restrictions on early-stage studies may be inappropriate as potency measurements are still being refined. It would be beneficial if the draft guidance clarified that for Phase 1 studies, potency may not be the hold reason for an IND, or simply delete this sentence as the following paragraph describes Phase 2 and Phase 3 considerations. Such changes would also be appropriate in line 452.

- **Lines 114-117**: This sentence assumes that there is a direct correlation between the continuous value of the potency assay and the degree of clinical efficacy. We are not aware of such a continuous correlation and continue to consider potency assays only indicative of minimum level of activity. For example, a CART product with high IFNg release might have similar effect of a product with medium or low IFNg release. There is need for collection of retrospective data on potency assays and correlation with clinical outcomes to make recommendations on their predictive value.

- **Section IV-C**: It is possible for the mechanism of action of a given product to differ across clinical settings. For example, while CD19 CAR-T therapies work to deplete cancerous cells in settings of B-cell malignancies, in autoimmune diseases the mechanism of action is the deletion of self-reactive B cells. To date, there are no selection criteria for disease-specific potency assays. We encourage the consideration of including the word ‘proposed’ prior to each occurrence of the phrase “mechanism of action” to alleviate confusion regarding these examples.

- **Lines 278-280**: Please provide clarity for how sponsors should define evidence of a statistical relationship early with minimal clinical data.

- **Lines 335-337**: Please provide feedback on how this would affect/be applicable for tumor infiltrating lymphocyte (TIL) therapies.

- **Lines 348-355**: Please consider a scenario in which growth factor itself is a commercially available product and how this may apply to assessing potency per the described recommendations.

- **Line 363**: Assigning a time limit in culturing may be complicated for some products, including TIL. Initial outgrowth phases are often variable.

- **Lines 457-450**: Please provide clarity on available and/or potential pathways that allow for sponsors to refine appropriate acceptance criteria prior to later stages of clinical development. Many of the critical data to support statistical determination of acceptance criteria is not generated until the later stages of development, and therefore makes this process difficult.

- **Lines 532-533**: The word "should" is utilized when describing usage of potency assays, indicating that this is recommended and not required. It would be beneficial for sponsors if the FDA could clarify that potency assays are recommended but not required for all studies.
• **Lines 645-649**: Please provide clarity/definition for robust and robustness. It is important to define these terms as sponsors will subsequently have more clarity as to regulatory expectations and how best to meet them.

• **Lines 693-695**: Please provide an example for a mechanistic relationship between an attribute and a product’s biological activity. Please also consider inclusion of the word ‘statistically’ prior to the word “established”.

• **Line 743**: Please provide clarity if TIL therapies would fall under tissue-engineered manufacturing practices or only in the cases of where genetically-modified products are being used.

• **Section V-C-2**: This section describes recommendations for a product with an extremely short shelf life as well as for vector-transduced patient-specific cellular products. With an understanding that cellular products that undergo long-term culture tend to have less favorable cellular attributes that impact their persistence after infusion, rapid manufacturing and infusion is becoming more common as a strategy to improve fitness of the DP. A statement on minimally-recommended potency assays and quantitative acceptance criteria for patient-specific cellular product release for rapidly manufactured products is recommended.

SITC values our relationship with the FDA and appreciates the opportunity to provide comment on this important effort. Please consider the society and our volunteers as a resource as the field continues discussions and refinement on the topic. 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,

Mary Dean, JD, CAE  
Executive Director  
Society for Immunotherapy of Cancer (SITC)