American Society of Gene + Cell Therapy

March 26, 2024

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

RE: Comments for Docket No. FDA-2023-D-4299 Potency Assurance for Cellular and Gene Therapy Products; Draft Guidance for Industry.

Dear Sir/Madam:

The American Society of Gene & Cell Therapy (ASGCT) appreciates the opportunity to comment on the *Potency Assurance for Cellular and Gene Therapy Products; Draft Guidance for Industry.* ASGCT is a nonprofit professional membership organization that is comprised of more than 6,200 scientists, physicians, patient advocates, and other professionals working in gene and cell therapy (CGT) in settings such as universities, hospitals, and biotechnology companies.

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. 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.

General Comments

The CGT field has grown rapidly in recent years,[1] and we have the potential to deliver safe, effective, and transformative therapies to patients who often have no other options. Without a doubt, advances in manufacturing processes have improved production, control, and characterization of CGT products. However, the link between product characteristics and clinical performance often remains product-specific, particularly early in development. Potency assays play a key role in informing this link, and ideally reflect the product's mechanism of action. However, there are technical and scientific challenges associated with potency test design, execution, and analysis. In addition, regulatory inconsistencies in the Agency's approach to potency testing have caused development delays, including clinical holds which can result in loss of funds for the biotech company to continue operating as a viable entity.

[1] American Society of Gene and Cell Therapy, Citeline. (2023). *Gene, Cell, & RNA Therapy Landscape: Q4 2023 Quarterly Data Report.* https://asgct.org/global/documents/asgct-citeline-q4-2023-report.aspx

These effects could result in stopping further development of products to address unmet medical needs of patients suffering from serious and life-threatening diseases.

The Society appreciates FDA's efforts in developing a cohesive strategy to address the complexities associated with evaluating and assuring potency. The draft guidance, however, does not provide needed clarity and direction to sponsors in the CGT field. While we offer specific comments on sections of the draft guidance below, there are three overarching themes that need to be addressed in the final guidance.

1. Phase Appropriateness – Although the Agency acknowledges the degree of potency assurance should be phase appropriate (lines 92-94), ASGCT recommends that the guidance acknowledge this throughout the document and clarify that potency assays, critical in late-stage development/pivotal trials, may not be possible early in clinical development due to assay complexity/variability, small sample sizes (difficult to reach statistical significance), and/or lack of mechanistic understanding. Examples of places within the draft where phase appropriate language is essential are Section IV.C (Gaining Product and Process Understanding), IV.D (Risk Assessment), and IV. F (Control Strategy).

2. Number/Type of Assays – ASGCT recommends a risk-based approach which includes the development of one robust *in vitro* potency assay addressing the main mechanism of action of the final drug product for product release. The Society suggests that additional measures of potency throughout development and manufacturing should be implemented as characterization assays providing qualitative information, rather than requiring release testing with "acceptance criteria." It is also recommended to provide expectations for the type or types of potency tests for classes of therapeutic products such as CAR-Ts (individual product CMC data including potency tests are proprietary, but when large numbers of products in a class exist, generalized information about acceptable potency assays could be shared by the Agency). Additionally, there are potential unintended consequences for patients as additional testing ultimately leads to less product for patient dosing.

3. Integration with Existing Standards – ASGCT recommends that the potency assurance strategy not add additional complexity and requirements to already existing quality risk management system ICH Q9 (R1),[2] manufacturing change plans, and product control strategies. The additional documentation and analysis specific to potency assurance creates a significant burden on sponsors, which is largely redundant to existing quality expectations.

ASGCT has provided FDA with scientific information related to potency in multiple forums, including our 2021 FDA Liaison Meeting presentation.[3] We are happy to provide this and other

[2] International Council of Harmonisation. (2023). *Quality Risk Management Q9(R1)* [Harmonised guideline]. https://database.ich.org/sites/default/files/ICH_Q9%28R1%29_Guideline_Step4_2022_1219.pdf

[3] American Society of Gene and Cell Therapy. (2021). *ASGCT-FDA Liaison Meeting: Recommendations on CMC Expectations for Gene and Cell Therapy Products.* https://asgct.org/global/documents/advocacy/2021-fda-liaison-meeting/final-cmc-issues-for-liaison-meeting.aspx

information to the FDA again to inform revisions as appropriate. We appreciate the Agency considering these themes as overarching principles as the guidance is finalized.

Specific Comments

I. INTRODUCTION

Setting attribute acceptance criteria for CGT products in early development is often not feasible due to sample and batch limitations. Release assays critical in late-stage development/pivotal trials, such as potency assays, may not be possible early in clinical development due to assay complexity/variability, small sample sizes (difficult to reach statistical significance), and/or lack of mechanistic understanding. Hence sponsors aim to improve consistency of product quality over the course of clinical development as additional manufacturing and batch experience is accumulated.

The Society appreciates the Agency's intent to adopt a flexible, risk-based approach. Small clinical trial populations, which are characteristic of CGT product development, make statistical analysis of CMC data from CGT batches challenging. If implemented properly, the potency assurance strategy could be a positive step towards addressing these challenges. However, we also see the potential for the potency assurance strategy to add significant burden to product development with little added benefit. We suggest the information necessary to implement the multi-faceted strategy approach in the draft seems better suited for late-stage products, and this should be stated in the text as appropriate.

ASGCT appreciates the Agency's acknowledgement that mechanisms of action (MOA) may not be fully understood (lines 278-280). This is particularly true of early-stage development. However, the Agency's proposal to use evidence of a statistical relationship between a product attribute and nonclinical/clinical outcomes for determining a potency-related critical quality attribute (CQA) is not feasible in early development due to limited samples and manufacturing experience. Potency is defined as "*the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data…*" (lines 15-16).[4] ASGCT requests clarity on how the Agency envisions the strategy being applied to early-stage products where statistical analyses of laboratory and clinical data are limited.

II. BACKGROUND

The Society appreciates FDA's acknowledgement of the rapid pace of clinical development for CGT products, and the unique challenges associated with this. Added clarification on how to "*progressively implement a strategy for potency assurance during product development*" (lines 45-48) is requested for every stage of the product lifecycle. Phase specific examples will help minimize challenges and bottlenecks throughout the process.

The draft guidance states, "*potency assays and their corresponding acceptance criteria should be designed to make meaningful contributions to potency assurance by reducing risks to*

[4] U.S. Congress. (2024). *Code of Federal Regulations.* 21 C.F.R. § 600.3(s). https://www.ecfr.gov/current/title-21/chapter-I/subchapter-F/part-600

product potency" (lines 51-54). The Agency notes that complementary approaches will be used to assure potency while stating that potency assays are only one part of the overall strategy. The Society believes that the development of one robust *in vitro* potency assay, addressing the main MOA(s) of the final drug product, should be sufficient for lot release. Additionally, we suggest allowing continuous validation of potency assays during review and post-licensure to refine acceptance criteria for products where high replicate batch data is challenging (e.g., autologous products). To this point, ASGCT recommends one potency assay per product as a part of the potency assurance strategy.

The intent behind the reference to the quality risk management (QRM) system[5] is sound. Given the extensive information already available in the existing QRM guidance, an added layer of risk management may not be necessary. For example, CQAs can be assessed in both systems. The potency assurance draft guidance as written does not outline how these risk assessment metrics will work at various stages of development and/or in tandem. The Society requests clarity on how the Agency foresees these systemic approaches being utilized.

III. REGULATORY FRAMEWORK

B. Investigational CGT Products

The FDA has not historically considered potency a safety issue which would warrant a clinical hold. However, language in this section and in section IV.G indicate that there are instances in which insufficient potency assurance could result in a clinical hold, even at an early phase. The draft guidance did not provide clarity on when the Agency believes that potency, or lack of a potency assay, creates a safety risk. ASGCT requests that FDA provide clarity, including a rationale for why this language was added and/or examples of when the lack of potency would introduce "unreasonable and significant" risk to patients at each phase of a clinical trial (lines 102-105).

C. Current Good Manufacturing Practice

ASGCT again notes the reference to using multiple potency assays in this section. Developing an *in vitro* potency assay which mimics closely the MOA of CGT products is important, but as the Agency noted, should be a part of a comprehensive strategy. Potency assays are also used to develop *ex vivo* genetically modified cells such as CAR-Ts, and non-modified cell therapies such as tumor-infiltrating lymphocytes. There are well-documented challenges for cell therapy products with multiple modes of action, e.g. immune cell products that may secrete a wide range of immunomodulatory factors or act through a range of synergistic mechanisms. For these reasons, ASGCT recommends a risk-based approach which includes the development of one strong potency assay addressing the main MOAs of the final drug product for product release. The Society suggests that additional measures of potency could be continued throughout development, but rather as general characterization assays without acceptance criteria.

[5] Quality risk management is a systematic process for the assessment, control, communication, and review of risks to the quality of the drug product across the product life cycle. See: Food and Drug Administration. (May 2023). *Guidance for Industry: Q9(R1) Quality Risk Management.* https://www.fda.gov/media/167721/download

The guidance for an effective pharmaceutical quality system (PQS)[6] includes information on the design, development, documentation, and processes for products. The Society notes that the evaluation/ assessment of the potency attributes of a drug product are inherent in a good PQS. We respectfully object to the creation of a new layer of quality systems that is specific to potency. If the Agency would like to see greater attention to potency in the existing quality system, we recommend that the finalized potency assurance strategy guidance be clear about how to do that rather than requesting separate systems, documentation, and justifications.

IV. DEVELOPING A POTENCY ASSURANCE STRATEGY

As reflected in the Society's general comments, we have concerns about the scope of the potency assurance strategy, specifically phase appropriateness, quantity of assays being requested, integration with existing standards, etc. While we agree with the goal of utilizing process and product knowledge to contribute to overall understanding of potency, some of the requirements in this section add a layer of complexity and undue burden. With this overarching comment in mind, we did include some suggestions below.

A. Quality Risk Management and Assurance of Potency

The Agency references "acceptable levels" of risk to product potency at all stages of the lifecycle. The Society also supports a risk-based approach. For Phase I trials, using a limited number of well-defined CQAs rather than statistical potency assays is more appropriate given the data limitations on small clinical sample sizes. CQA specifications could then be added/tightened over time as more knowledge of the attributes, and their impact on clinical data, is gained. Using characterization assays without acceptance criteria can provide important and relevant qualitative but difficult-to-quantify data to inform the overall assessment of comparability for attributes that are not expected to impact safety. This flexibility would help developers meet the needs of underserved patient populations.

B. Applying Prior Knowledge and Experience

ASGCT appreciates the ability to leverage prior knowledge and experience from manufacturing and testing of a similar product, published information, etc. when developing a potency assurance strategy. We request clarification on when the use of characterization strategies and risk assessments for product specific manufacturing is necessary, and when sole use of prior knowledge is not. Information on phase-appropriate use is requested in this regard. Although companies developing similar products to those currently approved seek such information through literature, it may not be published or disclosed in approval documents. The Society requests that the Agency consider how to provide general approaches to classes of products when approved.

C. Gaining Product and Process Understanding

There are instances when the MOA is not fully understood, but the clinical and nonclinical results are clear. The Society requests guidance on how to develop a

[6] Food and Drug Administration. (2006). *Guidance for Industry: Quality Systems Approach to Pharmaceutical CGMP Regulations.* https://www.fda.gov/media/71023/download

potency assurance strategy in these cases. For example, lines 588-589 state that it is not essential for a bioassay to mimic the product's MOA. We request examples of how potency can be expressed when the MOA is not understood.

As referenced earlier, more information is requested on how CQAs are used during different phases of development. In early-stage development a product's characterization data are not fully understood, and therefore it may not be possible to identify and define CQAs. In later stages of development, will it be necessary to identify some CQAs as potency related – or will it be sufficient to understand they are CQAs?

For many CGT product developers, critical process parameters (CPP) are only developed for later-stage products. The Society suggests that the Agency consider CPPs a Phase III activity due to the limited acceptance criteria in early-phase manufacturing products and processes.

D. Risk Assessment

In the draft guidance, lines 307-310 reference going beyond lot release for product risk assessment by including container closure, conditions for drug storage, shipping, and handling, etc. Currently, the stability and viability of a product is measured after making these assessments. The measurements include a potency test, but it is one component rather than the only component measured. For investigational products, initial shelf life is often provisional with little to no long-term data at IND opening and is supported by accelerated or other stability data studies. Accelerated stability studies performed under stress conditions may be useful for identifying stability-indicating attributes. ASGCT suggests the use of stability studies as a metric supporting potency.

Referencing lines 318-320, further discussion is needed to understand how the guidance's risk assessment recommendations fit into the existing quality plan. The draft guidance states that risks to product potency should be assessed prior to implementing manufacturing changes. However, potency is already a component of quality and assessed prior to manufacturing changes.[7] Therefore, as previously suggested, the Society requests clarity on how the FDA foresees these systemic approaches integrating or being utilized separately.

F. Control Strategy

The overarching question in this section is how the development of a potency assurance strategy relates to the overall product control strategy. Many of the steps outlined in the control strategy are currently being done prior to lot release. The Society requests clarity on whether the Agency views this as an integrated approach, and how or if this changes current documentation processes.

[7] When implementing a manufacturing change for a licensed product, an assessment of the effect of the change on potency is required before distributing the post-change product. See: U.S. Congress. (2024). *Code of Federal Regulations.* 21 C.F.R. § 601.12 (a)(2). https://www.ecfr.gov/current/title-21/chapter-I/subchapter-F/part-601/subpart-C/section-601.12

Cell death and differentiation is referenced in process parameters. In instances of decreased potency, the limit of the CPP should be reassessed throughout the product lifecycle as more information becomes available.

The guidance states in-process testing is required as a part of the control strategy but does not specify if testing is for characterization of the product or potency. However, in FDA's public webinar on the draft guidance the presenter stated, "You should have potency tests in place for in-process and lot release testing, and these tests should have both suitable performance characteristics and appropriate acceptance criteria."[8] Due to potential challenges with implementation for CGT products, which often have limited samples, we suggest that potency testing should not be a part of in-process testing.

ASGCT appreciates FDA's efforts to look at expanded metrics to measure potency. We note that in some instances, components of the strategy will be reviewed more stringently and extensively. Conversely, the Society respectfully requests clarification on the elements of enhanced flexibility for lot release testing.

G. Progressive Implementation of a Potency Assurance Strategy

As noted in prior comments, there is limited knowledge and acceptance criteria in early phase manufacturing of products. Therefore some aspects of a potency assurance strategy may be better suited for late-stage development. The Society requests clarity of the expectations of potency assays at different developmental stages and phase-appropriate expectations for other aspects of a potency assurance strategy.

This section also discusses the use of multiple assays developed to measure known, or potential, CQAs. The guidance recommends use of these assays in parallel during early clinical investigations unless deemed redundant. Assays developed in parallel may be significantly different from assays developed in the early stages of product development. We request additional information on FDA's expectations for evaluating the results of early- and later-stage assays.

H. Requesting FDA Advice on Potency Assurance Strategy

We noted conflicting guidance on the MOA in lines 509-511 and lines 587-590, for example. In the latter part, the guidance states that a bioassay does not need to mimic the product's MOA. However, in the earlier section sponsors are asked to "explain how the attribute measured by the assay is relevant to the product's MOA and the desired therapeutic effect" (lines 509-511). The Society respectfully requests guidance on FDA's expectations for the MOA.

ASGCT members strive to interact with the Agency early and often, as is often encouraged by FDA leadership. Given the importance of potency assays in the development of CGT products, we request that this guidance provide information on the

[8] Klinker, M. (2023). *Introducing Draft Guidance for Industry: Potency Assurance for Cellular and Gene therapy Products* [presentation]. https://fda.zoomgov.com/rec/play/sio00ZZ27mnDZabNW6wrm2GjRDAIlu7RGhYnhKGjatcMVlwdjhN7_aipv4j8XG-HspUww2HSSjS2gyZI.4bmk95suGraJdV7z

type and timing of meetings that are best used to discuss these questions, preferably in person. We suggest that the milestone End of Phase II meeting is an appropriate venue.

For questions earlier in development, FDA suggests an IND amendment. We are concerned that without PDUFA timing goals associated with such correspondence, this may not be a timely or productive mechanism. We suggest that the Agency provide an understanding of expectations for how and when FDA will respond to such requests or make recommendations as to the type of meeting request, e.g. Type C, Type D meetings, etc.

V. POTENCY ASSAYS AND ACCEPTANCE CRITERIA

B. Assay Selection and Design

Earlier in the guidance, the Agency notes that for lot release "most [not all] CGT products should include at least one bioassay that measures a biological activity related to the intended therapeutic effect of the product..." (lines 174-176). We recommend adding examples and/or scenarios of when it is not necessary to include a bioassay. In addition, we request phase-appropriate guidance on lot release potency bioassay expectations.

This section references the need for "multiple release assays" (line 583) which may include a bioassay. ASGCT recommends that FDA employ a least burdensome approach which would include one bioassay for the purposes of measuring potency for lot release, or an acceptable physicochemical assay. Furthermore, we respectfully request examples of situations in which a single release assay is not sufficient.

Attempting to define an at-risk CQA can cause confusion as every CQA is at risk. The quality principle is to ensure that CQAs are met. ASGCT requests the Agency remove the term "at risk" as it relates to CQAs (line 584, line 588).

We appreciate FDA's efforts to provide flexibility in assay selection in order to reduce regulatory requirements which may lead to redundancy. We understand that each assay can measure unique properties of a product. However, those may not be the most relevant metrics for determining potency. Therefore, we request examples of the proper selection of relevant assays, and how they will be measured for redundancy and ultimately removed from consideration.

D. Acceptance Criteria

We suggest the potency acceptance criteria should be established based on the potency of the product rather than manufacturing experience. Therefore, ASGCT recommends removing lines 870-872.

Conclusion

ASGCT believes that addressing the overarching concerns with FDA's outlined potency assurance strategy through these comments will enhance the value of the final guidance

document to assist CGT product developers as they address product potency. Potency assays are a key part of product development that need to be incorporated in a way that reflects the nature of the mechanism of action and manufacturing of these complex products. This is critical to ensure effectiveness for patients. Deriving a framework that strikes the correct balance of critical data collection with scientific plausibility and regulatory need is essential to advancing the field. We welcome the opportunity to provide any additional detailed information the Agency may be interested in considering.

Thank you for the consideration of these comments. If you have any questions, please do not hesitate to contact Margarita Valdez Martínez, Director of Policy and Advocacy, at mvaldez@asgct.org.

Sincerely,

David Barrett, JD
Chief Executive Officer