

# Recommendations on CMC Expectations for Gene and Cell Therapy Products

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# Disclosures

- Jan Thirkettle is CEO of Transine Therapeutics, an oligonucleotide platform therapeutics company utilizing AAV as one of its delivery modalities
- J Fraser Wright is a co-founder of Spark Therapeutics, a scientific co-founder of Kriya Therapeutics, and an inventor on patents relating to methods to make viral vectors

# Topics

- Introduction
- Product specifications
- *In vitro* potency assays
- Additional product characterization
- Manufacturing process comparability
- Concluding observations

# Introduction

- Advances in manufacturing and analytical techniques have improved control and characterization of cell and gene therapy (CGT) products, but the link between product characteristics and clinical performance is still evolving.
- Small clinical trial populations that are characteristic of CGT product development make statistical analysis of CMC data from CGT batches challenging.
- The CGT category is wide, and the challenges presented by complex cell products (that may have multiple modes of action) and viral vector products may be different.

**Rapid innovation in the CGT field warrants a CMC framework that remains flexible, risk-based, and correlated with the extent of clinical experience.**

# Challenges related to CGT product specifications

- Sponsors have experienced an expectation from FDA of setting specifications for complex assays for CGT products in very early-stage clinical trials even for parameters which are not known/confirmed CQAs.
- The overall objective of product developers is to improve product quality and clinical potency over the course of clinical development.
  - Specification 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).
    - Lack of mechanistic understanding.
  - CQA specifications should be added/tightened over time as more knowledge of the attributes and their impact on clinical data is gained.

# ASGCT recommendations for specifications

- Take a pragmatic approach to the application of statistical analyses of specifications early in development. With limited data, these may not be as meaningful as robust qualitative analysis.
- Focus early-stage specifications on the limited number of well-defined CQAs at that stage.
- Allow characterization assays performed throughout development to inform the product specifications applied in late-stage development.
- Use available data and science-based risk assessment to guide the evolution of specifications at the appropriate point of development (including post-marketing if so justified).

# Challenges related to *in vitro* potency assays

- ASGCT members who are sponsors agree with FDA that developing *in vitro* potency assays which mimic closely the mechanism of action (as far as it can be understood) of CGT products is an important, but very challenging goal.
  - Development of such assays suitable for a QC/GMP environment is a significant undertaking that may take many years.
    - These are highly complex assays with intrinsic limitations of precision and robustness and analytic methods.
    - These assays may need to be qualitative early in development until multi-batch experience is available to set specifications.
  - Challenges are heightened for cell therapy products with multiple modes of action e.g., immune cell products may secrete a wide range of immunomodulatory factors, or act through a range of synergistic mechanisms.
  - Full (quantitative) linkage between a potency assay and clinical effectiveness may require post licensure experience as clinical trial sizes are limited.
- ASGCT members who are sponsors have noted a trend through reviewer interactions towards requiring multiple potency assays on the product specification, for instance:
  - Infectivity assays for viral vectors in addition to a bioassay.
  - Requirements for potency assays for lentiviral vectors used to make gene modified cell therapies, which themselves have a potency assay.
- ASGCT members who are sponsors have noted a trend through reviewer interactions towards requiring extensive assay validation and statistically-driven specification setting approaches at the start of pivotal development even when there is insufficient data to support such approaches.

# ASGCT recommendations for potency assays

- That FDA allow a risk-based approach in the context of the unmet medical need of the patient population in its requirements for potency assays of CGT products.
- The development of one strong potency assay addressing the main mechanism of action(s) of the final drug product should be sufficient for product release, obviating the need for other potency assays as product release tests.
  - For example, eliminate AAV infectivity or potency testing of rLV when these vectors are used to create a final genetically modified cell product which has its own potency assay.
- Additional measures of potency should be continued throughout development, but rather as general characterization assays with no acceptance criteria.
- Expectations for potency assay qualification and specification setting need to take into account the complexity of the assay, known correlation with clinical outcomes, and data availability.
- Allow 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 or those that have especially complex modes of action).



# Challenges related to product characterization

- ASGCT members who are sponsors agree with FDA that maximizing use of available analytical tools to increase product understanding and quality is imperative; however, such methods are not always amenable to being deployed as specification assays.
  - Implementation of some complex characterization assays and validation in a GMP environment is not possible due to compliance challenges.
  - Biological assays possess inherent variability.
  - Information generated may be complex/not single-dimensional and so not amenable to setting specifications
  - The greatest value of characterization assays are not the specific results, but rather the role they play in increasing product understanding and risk assessment.
- ASGCT members who are sponsors are concerned that some reviewer requests increasingly drive towards moving assays from characterization to batch release assays (and therefore needing validation) even in cases where these challenges are manifest.

# ASGCT proposals related to product characterization

- FDA should develop broad, *high-level* guidance for the CQAs that should be the focus of characterization studies for each product class (i.e., rAAV, rLV, CAR-T cells, etc.).
  - This helps sponsors better understand the rationale and prioritization for characterization assays for each class of CGT product and develop appropriate methods to address them.
- FDA should provide feedback to sponsors in early-stage meetings regarding characterization expectations through the course of product development.
- Acceptance criteria should not be required for characterization assays (including when these support comparability assessments); rather, the results obtained should be used for science-based risk assessments.
- The focus of performing characterization assays should be to gain a deeper understanding of product CQAs during product development; while the focus of performing quality control assays is to ensure lot to lot consistency of *known* product CQAs within acceptable ranges.

# Challenges related to manufacturing process comparability

- Multiple changes to the manufacturing process may be required during product development, often with limited batch datasets at each stage.
- ASGCT members who are sponsors believe the goal of studies to compare products before and after a process change is to prospectively ensure comparable safety and efficacy of an investigational product within bounds supported by risk assessments, rather than ensure identical performance on all measured characteristics.
- ASGCT members who are sponsors:
  - Have indicated that the agency has requested quantitative acceptance criteria and validation for characterization assays used for process comparability studies, which is sometimes not possible given the complexity of these assays.
  - Have interpreted agency data requests as indication that processes should be identical in comparability studies.
  - Feel agency expectations regarding similarity to the “pre-change” comparator(s) can be unclear or unrealistic, in effect requiring identicalness because of limited clinical trial sizes, in which there may be only one or few batches to compare.
  - Do not have clear guidance on what constitutes a manufacturing change requiring a comparability assessment.
- FDA moving toward requiring statistical analyses in setting comparability acceptance criteria is often not realistic given:
  - the lack of sufficient batch numbers that can realistically be generated during clinical development.
  - insufficient understanding of the clinical impact of biological variation.

# ASGCT recommendations on comparability

- FDA should allow a more flexible and pragmatic approach to manufacturing process changes and comparability assessment, providing further guidance on principles for decision making.
- It is acceptable for characterization assays without acceptance criteria to provide relevant but difficult-to-quantify data to inform the overall assessment of comparability for attributes that are not expected to impact safety.
- Statistical analysis expectations should consider that low-replicate batches are an inherent feature of CGT investigational products. We propose greater weighting of science- and risk-based arguments and decision making that includes qualitative data.
- ‘Identicalness’ cannot be demonstrated in a comparability study given current assay limitations, natural biologic variation of complex (sometimes ‘living’) cell products, and poorly defined links to clinical benefit.
- Further guidance/clarity is required on the expectation for comparability testing of viral vectors used in genetically modified cell therapy products.
- Further guidance is needed on the parameters that FDA believes define a “change” in manufacturing that warrant comparability studies.
- The appropriate comparator for contemporaneous comparability testing following a process change should be the product manufactured using the preceding process, not all historical products and processes.

# Concluding observations

- **ASGCT appreciates the ongoing partnership and opportunity to engage in a scientific dialogue with FDA.**
- **ASGCT appreciates FDA's ongoing engagement with the community to share and discuss its thinking, such as the recent CTGT Advisory Committee meeting.**
- In addition to the specific regulatory recommendations presented, we suggest the following CMC policy approaches be considered:
  - Keeping CMC guidance consolidated to increase clarity in the Agency's views and avoid risks of divergence between therapeutic areas.
  - Greater coordination between OTAT and other offices with less experience in CGT to assist with product review consistency.
  - Continuing engagement with the scientific community at conferences and meetings, including sharing case studies – where possible, these should include blinded datasets representing broad areas/large samples to provide context and assist cross-field collaboration.
  - Continued engagement across HHS agencies, such as with the Bespoke Gene Therapy Consortium (BGTC).

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Thank you !