Molecular Therapy
Methods & Clinical Development
In the Spotlight

The comparability tales: A phase-appropriate roadmap for CGT drug product development

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https://doi.org/10.1016/j.omtm.2023.101170

Cell and gene therapies (CGTs) have revolutionized patient outcomes and provided care options for previously untreatable conditions. The clinical and commercial progress of CGT therapies is hindered by chemistry, manufacturing, and control (CMC) challenges. This article summarizes recommendations from the 2023 Annual Meeting CMC sessions wherein speakers advocated for science-driven comparability strategies, proactive risk assessments, clearer regulatory guidance, and a shift from retrospective to prospective studies. Planning for manufacturing changes, statistical approaches, and consideration of multiple product versions also emerged as crucial elements to help sponsors navigate CMC hurdles for successful CGT clinical and commercial development.

INTRODUCTION

Cell and gene therapies (CGTs) have demonstrated remarkable clinical outcomes in patients around the globe. As of Q2-2023, according to the most recent landscape report by ASGCT and Citeline, globally there are currently 89 approved gene and cell therapies.[1] These therapies have ushered in new and potentially curative treatment paradigms for patients that previously had limited options. However, the development of these drug products has often been stymied by chemistry, manufacturing, and control (CMC) considerations.

Unlike traditional biologics, CMC is the cornerstone of drug product development for CGTs. The CMC challenges associated with the production and scaleup of these novel drug products have been well documented. Due to the complexity of CGT drug product production and composition and the rapidly evolving nature of the field, manufacturing changes are often required during the drug development life cycle. This entails designing a compelling comparability narrative that is phase appropriate, robust, and comprehensive, assessing the major drug product quality attributes (identity, strength, purity, and potency) between process changes throughout the drug development life cycle.

Recently, ASGCT sponsored a CMC symposium and workshop at the 2023 Annual Meeting[2] to provide a comprehensive overview and roadmap on how to conduct efficient and regulatory compliant comparability studies. The overarching goal of the workshop was to underscore the impact of timely and informed decisions throughout the drug development life cycle to avoid and overcome common CMC challenges. The main points related to comparability from both sessions are summarized here in "The Comparability Tales."

DISCUSSION

The speakers highlighted the challenges that have historically resulted from the lack of clear CGT-specific comparability guidance. While ICH Q5E[3,4] serves as the standard "go-to" reference, it does not address many of the unique challenges associated with comparability for CGT products, which include complexity of product characterization, high variability in product type, manufacturing and analytical methods, and limited number and size of batches available. Hence, speakers stressed that the upcoming draft guidance "Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products"[5] on the FDA's 2023 guidance agenda[6] was eagerly anticipated as an indispensable source of greater clarity on the FDA's recommendations on designing, executing, and interpreting CGT comparability studies. This guidance was released 2 months after the Annual Meeting in July 2023 and includes mention of many of the same topics discussed here.

A recurring recommendation was the need to follow the science through prospective consideration of product composition, mechanism of action (MOA), and critical quality attributes (CQAs) when setting comparability strategy. Potency assays form a critical component of any comparability strategy; thus, early development of a matrix of candidate potency assays for the product is a critical component of a successful comparability strategy. The candidate potency assays should, ideally, reflect the intended MOA(s), if known, or the biological activities of the product tested. Ultimately, selection of one or more candidate potency assay(s) for inclusion in the final product specification will be driven by information gathered on the MOA during development, as well as considerations such as assay robustness and suitability for validation.

Risk assessment should be performed to determine the likelihood of impact of the change on product safety and effectiveness,

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and a comparability plan should then be crafted with the identified risks in mind. It was noted that sponsors know their products better than anyone else and should leverage that knowledge to control their comparability narratives and make data-driven and scientifically justified proposals for their comparability study designs. Speakers also touched on the differences between prospective and retrospective comparability studies and the potential use cases, advantages, and disadvantages for each. Prospective studies, intended to support future implementation of a manufacturing change, can de-risk delays in clinical development but typically require more resources to perform split-stream and side-by-side analyses. Such studies are typically not required to be formally statistically powered. Retrospective studies, intended to support pooling of clinical data through analysis of historical product data, typically do require formal statistical powering and often involve greater risk to development timelines but often require fewer resources to perform and enable sponsors to leverage clinical data to support acceptance criteria.

Speakers also emphasized the importance of planning proactively for a product's comparability journey during its development life cycle. Specifically, sponsors should have a plan for the intended timing of process changes (ideally before initiation of clinical studies intended to support product efficacy), invest in process understanding and analytical methods to support future comparability goals, and save sufficient retains throughout development to support future analytical development and comparability testing needs, should they arise. Once comparability studies become required, key success criteria include establishing a prospective study protocol and acceptance criteria and engaging early and often with regulators,[7] as well as building sufficient time and budget for what may be lengthy comparability discussions into plans from the start.

Finally, it was noted that a successful comparability strategy must include giving careful consideration to the choice of statistical approach and acceptance criteria. In selecting statistical methods for demonstration of comparability, one needs to consider a variety of factors, including data normality, whether a paired or unpaired analysis is appropriate, statistical power, and what acceptance or rejection of the null hypothesis means in each case. Acceptance criteria for each attribute should be determined based on whether a quality range or equivalence range approach is more fitting, as well as what specific attribute ranges are appropriate in each case.

Ultimately, acceptance criteria for each attribute should be tied back to biological meaning, as statistically significant differences may not be biologically meaningful, whereas a lack of statistically significant differences may signal lack of statistical power rather than lack of a true difference between processes.

A related area to comparability testing is the concept of testing multiple versions of a drug product. Although this topic was not directly addressed at the May 2023 ASGCT CMC symposium and workshop, a November 2022 guidance by the FDA provides recommendations for studies that evaluate multiple versions of a cellular or gene therapy product, including how to organize and structure the INDs, submit new information, and report adverse events.[8] Testing multiple versions of a drug product is an active area of discussion and will likely have important implications for manufacturing and clinical trial design strategies.

CONCLUSION

Although comparability has been a significant challenge for CGT products historically, participants agreed that with careful attention to these important considerations, sponsors can position themselves for success. CMC comparability no longer needs to be a daunting task during the drug development life cycle for these innovative therapeutics. Several developments play a role in that shift: the recent release of the FDA's draft guidance on comparability, an increasing awareness of the need to plan for comparability during CGT development, improvements in knowledge and understanding of CGT products, and an increasing array of manufacturing and analytical tools becoming available to the industry.

ACKNOWLEDGMENTS

Conceptualization and foundational evidence was provided by speakers at ASGCT's 2023 Annual Meeting: Katie Miller, PhD; Tal Salz, PhD; Brian Collins, PhD; Katy Spink, PhD (moderator); John Tomtishen (moderator); Jessica Chery, PhD; Chris Cheng, PhD; Alison Holzer-Speed, PhD; Jingying Xu, PhD; Angela Whatley, PhD (moderator); and Dan Leblanc (moderator). Manuscript preparation support was provided by Caitlin McCombs, an employee of ASGCT.

AUTHOR CONTRIBUTIONS

Project administration, conceptualization, writing, review, and editing, N.C., J.T., and K.S.; writing support, review, and editing, D.L. and S.H.K.

DECLARATION OF INTERESTS

K.S. is an independent director of Single Use Support GmbH and MicrofluidX, Inc., and a member of ASGCT's Strategic Planning Committee. S.H.K. has consulting agreements, receives honoraria, and sits on the scientific advisory boards of Tome Biosciences, Oncternal Therapeutics, and Enara Bio.

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