# Approaches for Establishing Comparability for Cell Therapy Products

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# Why Should We Plan on Comparability?

## Various Factors Necessitate Process Changes During Product Lifecycle

- During early stages of product lifecycle, there may be insufficient data to identify upfront underlying issues with process robustness and / or facility fit that may come to light as additional manufacturing runs are executed
- Given the highly variable nature of starting material for autologous cell therapy, processes initially developed using healthy donor cells, may not work well with patient derived cells
- A process change may benefit patients by simplifying their experience and addressing pain points
- Advances in the science and understanding behind cell therapy may drive a process change especially if early in product lifecycle

# Regulatory Guidance On Comparability For Autologous Cell Therapy

## FDA, EMA and Other Regulatory Agencies Have Provided Clear Guidance on Comparability

- EMA/CAT/123573/2024 (Draft Guidance on ATMPs): *"Manufacturing processes and their control strategies are continuously being improved and optimised, especially during early phases of clinical trials and later development towards marketing authorization…..In general, these improvements and optimisations are considered as normal development work"*

- Non comprehensive list of regulatory guidance for comparability of cell therapy products:
  - *FDA Draft Guidance: "Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products" (2023)*
  - *EMA Draft Guidance: "Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials" (2019, 2024)*
  - *EMA: "Questions and answers: Comparability considerations for ATMPs" (2019)*
  - *ICH-Q5E: Comparability of biotechnological/biological products subject to changes in their manufacturing process (2004)*

# High-Level Approach to Establish Comparability

## Like Other Biologics, A Stepwise Structured Approach Recommended By Health Agencies

- *"The comparability exercise should be conducted stepwise, starting with the physico-chemical and biological properties of the product. This will be based on analytical testing e.g., routine batch analysis, in-process controls, process validation/evaluation data, characterization and stability studies, as applicable."*

- *"The investigation should focus on the manufacturing process steps most appropriate to detect a change. This may require an evaluation on all critical steps/in-process controls/materials of the manufacturing process downstream of the change."*

- *"Analytical methods should be suitable for purpose and sufficiently sensitive to ensure the detection of differences/modifications. Any observed analytical difference should be evaluated in relation to its impact on the product quality, safety and efficacy."*

- *"If required due to non-comparable results that can have impact on the relevance of the safety and/or efficacy data gathered so far, the comparability exercise should proceed with the generation and evaluation of comparability non-clinical and/or clinical data as necessary to contribute to the conclusion of comparability of the product."*

ICH Q5E, EMA "Questions and answers: Comparability considerations for ATMPs", EMA/CAT/499821/2019

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# Specific Methodology To Establish Comparability

## The Specific Quantitative Approach Depends On Risk Level of Proposed Process Change

- *"It is not necessary for the measurements of pre- and post-change CQAs to be identical to reach a conclusion of comparability if there is evidence demonstrating that there is no adverse impact of the change on product quality."*
- *"A split-source design limits the impact of cellular variability by splitting individual cellular source materials into two equal portions."*
- *"Your risk assessment should also inform the statistical approach to comparability. Higher risk attributes typically warrant a more stringent statistical analysis than lower risk attributes."*
- *"The absence of a statistically significant difference between the pre- and post- change products (e.g., p-value >0.05) does not demonstrate comparability."*

FDA Draft Guidance on "Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products", July 2023

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# Process Change During Early Stages of Product Lifecycle

## Less Rigorous Approach for Comparability Especially if Process Changes Pose Low Risk

*"Side-by-side or graphical presentations (such as dot plot) to allow visual comparison, in lieu of statistical analysis, may be sufficient for characterization of attributes at low risk of being impacted by a manufacturing change."* - FDA Draft Guidance 2023

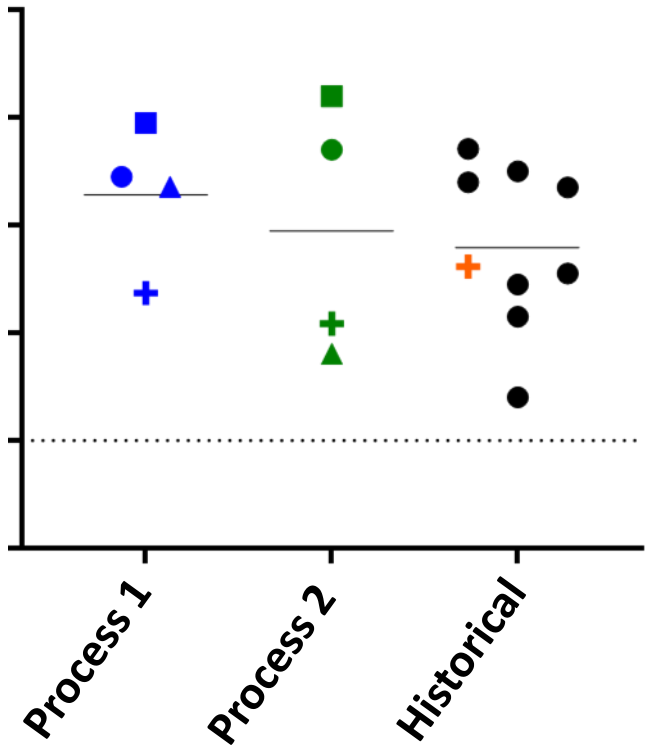
**A phase 1a CAR-T manufacturing process initially developed using healthy donor derived materials, was found to be insufficient to support patient derived materials in a consistent manner upon initial clinical manufacturing, and therefore improvements were made to T-cell activation, transduction and expansion steps**

- Low risk process changes and early phase of clinical development
- Comparability assessed through tabular and graphical comparison of final product attributes

# Side-by-side Graphical Presentation of Critical Quality Attributes

## Comparability Assessment Based on Scientific Arguments Accompanying Graphical Representation

### CAR Expression (%)

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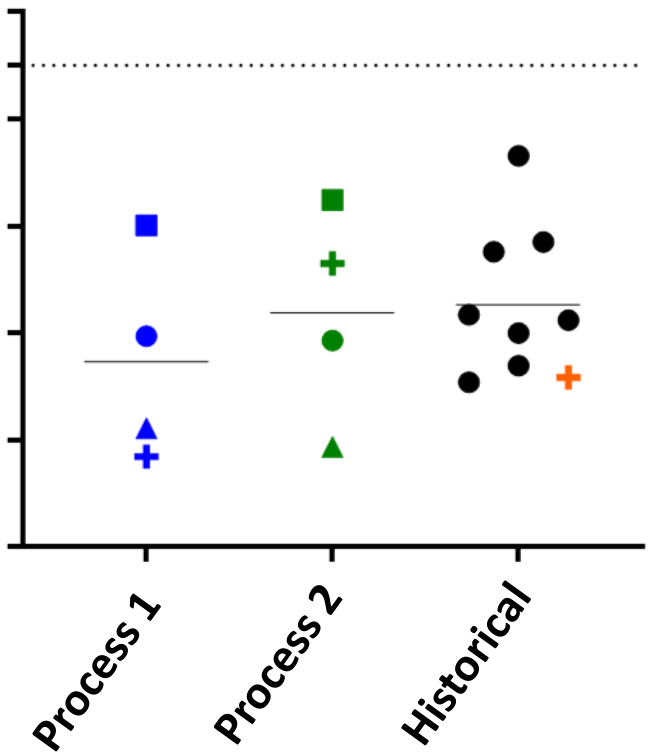
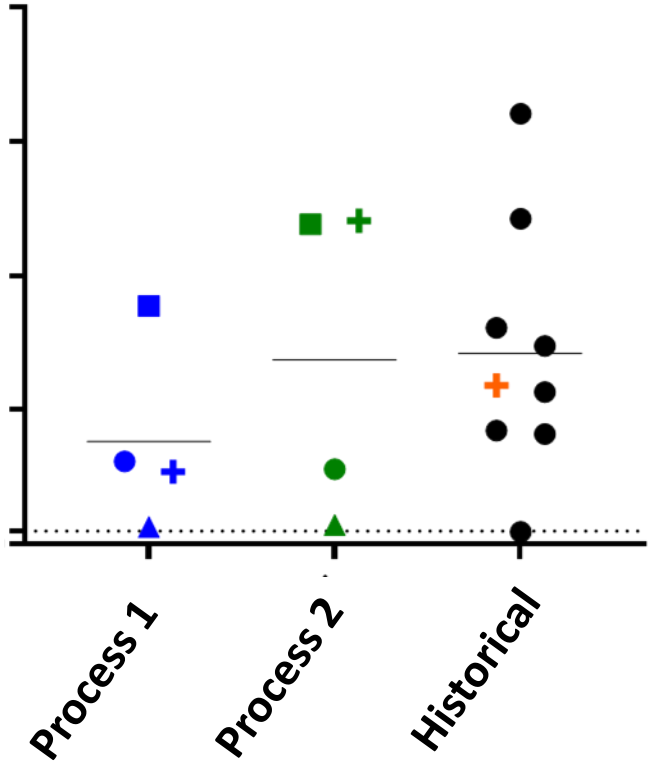
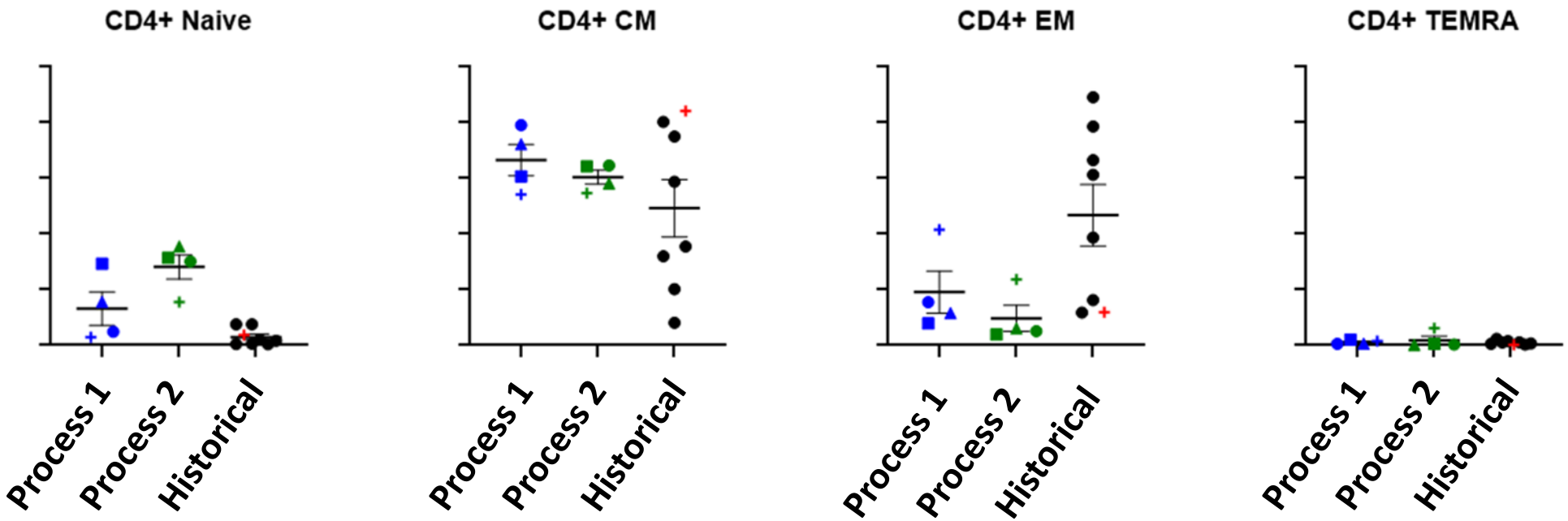



### Potency



# Additional Characterization Data on Biological Attributes

## Comparability Assessment Based on Scientific Arguments Accompanying Graphical Representation




*"The comparability program for these complex products cannot be based solely on the characterisation of the phenotypic markers related to purity confirming a heterogeneity profile. The dynamic nature of the product reflecting its metabolism, differentiation stage, structural organisation and interactions should be part of the comparability assessment"* - EMA/CAT/499821/2019

# Statistical Approaches For Establishing Comparability

## Quality Ranges versus Equivalence

- *"The quality range approach can potentially be used for attributes with various risk levels, but higher-risk attributes should be evaluated using the more rigorous equivalence approach."* - FDA Draft Guidance 2023
- Quality ranges are established using statistical tolerance intervals on historical data from current process
  - One approach may be to use 95% confidence, 99% coverage tolerance intervals
  - A significant majority of individual results from new process should fall within these quality ranges for successful comparability
- Equivalence approach requires that the means from the two processes fall within a window of no practical relevance
  - Acceptance criteria based on scientific understanding that the development team possesses

# Quality Range Approach for Late-Stage Product

## Medium Risk Process Change

- For a late-stage or commercial process with ample process data, a simple side-by-side graphical presentation is not sufficient for purposes of comparability

**Quality range approach was utilized for a medium risk process comparability assessment for a late-stage product**

- Quality ranges were based on 3 standard deviations of original process data
  - For a normal distribution ±3 standard deviations contains 99.73% of the population.
- Comparability was deemed acceptable if >99% of new process results for each quality attribute fell within the quality ranges

# Quality Range Approach for Late-Stage Product

## Comparability Established By Demonstrating >99% Within Quality Ranges

| Parameter | Quality Ranges Based on Original Process | New Process Sample Size | % Within Quality Range | Outcome |
|---|---|---|---|---|
| CD3+ | 0.83 - 1.00 | 229 | 99.56% | Comparable |
| Harvest Transduction | a - b | 232 | 99.57% | Comparable |
| Harvest Viability | 0.78 - 0.99 | 233 | 99.14% | Comparable |
| Potency | X – Y | 229 | 99.13% | Comparable |
| Vector Copy Number | x – y | 188 | 99.47% | Comparable |

# Equivalence Approach for Late-Stage Product

## Higher Risk Process or Method Changes Require Equivalence Approach

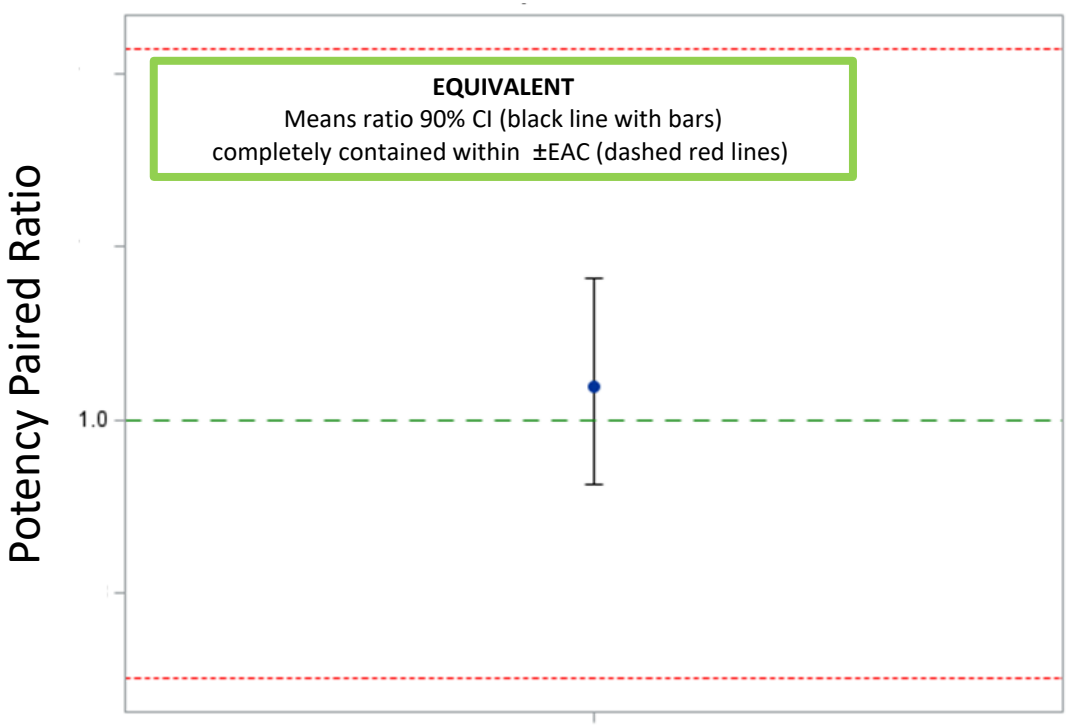
- For a late-stage or commercial process with ample process data, a simple side-by-side graphical presentation is not sufficient for purposes of comparability

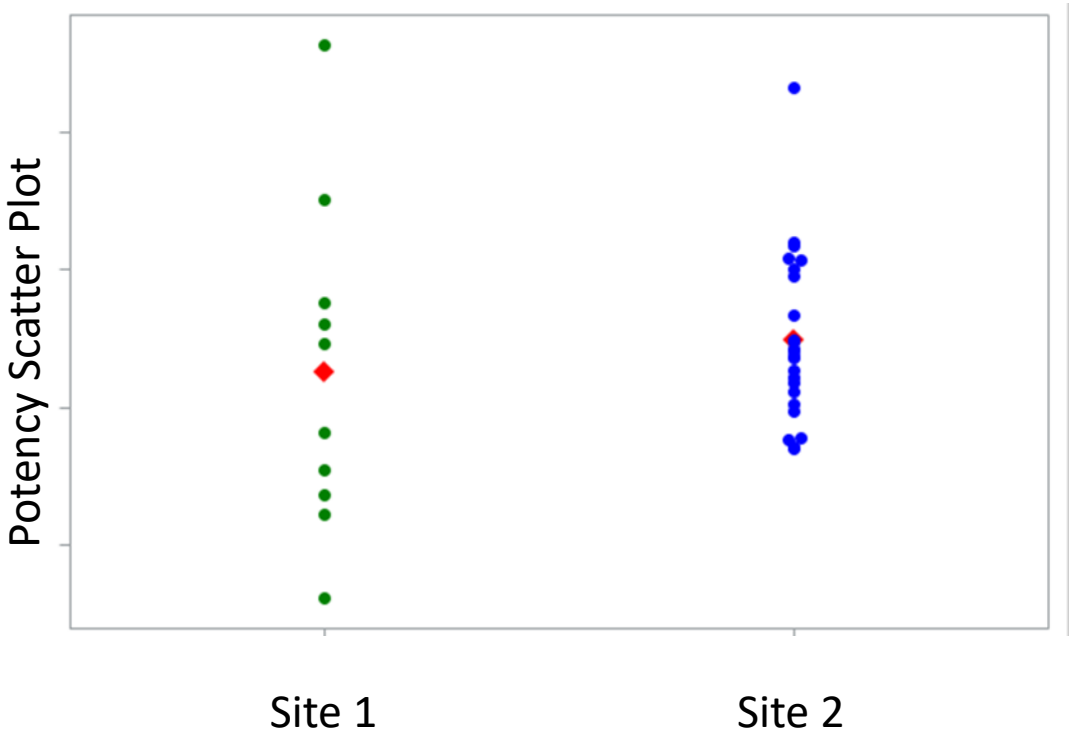
**Equivalence approach was utilized for a high-risk method comparability assessment for a late-stage product. A potency method was transferred from one manufacturing site to another**

- Equivalence acceptance criteria (EAC) set based on method characterization
- Comparability was deemed acceptable if mean of new method including 90% confidence intervals were within EAC

# Analytical Method Transfer Between Manufacturing Sites

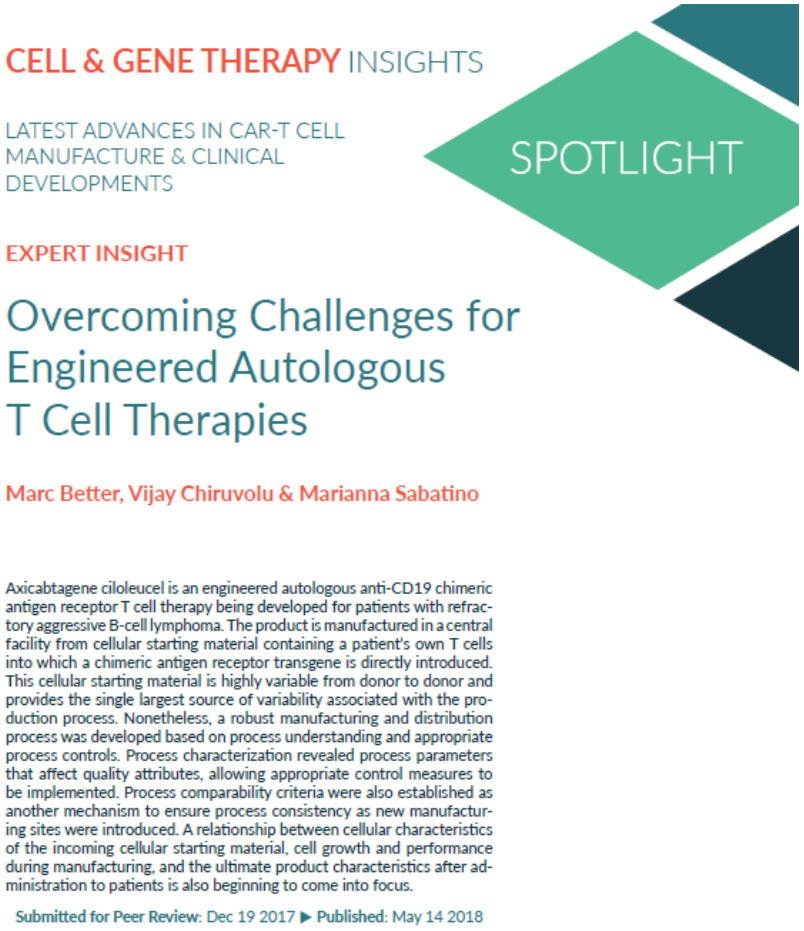
## Method Comparability Established Based on Equivalence Approach




Red diamonds denote means

# Historically Kite Has Leveraged These Approaches To Establish Comparability



CELL & GENE THERAPY INSIGHTS

LATEST ADVANCES IN CAR-T CELL MANUFACTURE & CLINICAL DEVELOPMENTS

SPOTLIGHT

EXPERT INSIGHT

## Overcoming Challenges for Engineered Autologous T Cell Therapies

Marc Better, Vijay Chiruvolu & Marianna Sabatino

Axicabtagene ciloleucel is an engineered autologous anti-CD19 chimeric antigen receptor T cell therapy being developed for patients with refractory aggressive B-cell lymphoma. The product is manufactured in a central facility from cellular starting material containing a patient's own T cells into which a chimeric antigen receptor transgene is directly introduced. This cellular starting material is highly variable from donor to donor and provides the single largest source of variability associated with the production process. Nonetheless, a robust manufacturing and distribution process was developed based on process understanding and appropriate process controls. Process characterization revealed process parameters that affect quality attributes, allowing appropriate control measures to be implemented. Process comparability criteria were also established as another mechanism to ensure process consistency as new manufacturing sites were introduced. A relationship between cellular characteristics of the incoming cellular starting material, cell growth and performance during manufacturing, and the ultimate product characteristics after administration to patients is also beginning to come into focus.

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CA. Was product produced at each of these sites comparable?

Two approaches have been used to assess comparability and answer this question:

1. Equivalence, performance with split starting material

2. Expectation, performance within prespecified tolerance intervals

# Summary

- Comparability approach should be selected based on:
  - Risk assessment for the proposed process change on safety and efficacy of final product
  - Clinical development phase for the program and availability of sufficient representative data for existing process
- Acceptance criteria to be set based on deep understanding of the process and methods and the underlying science
- In certain situations (for e.g. when utilizing quality ranges), comparability acceptance may be determined using statistical analysis of empirical process data
- Visual side-by-side comparison may be a viable approach in lieu of statistical analysis for lower risk process changes, however for late-stage programs with sufficient data, usually a more rigorous approach based on quality ranges or equivalence is warranted

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- The authors would like to acknowledge the scientific and biotech community who are constantly paving the path for cell therapy

- Last but not the least, the authors would like to acknowledge regulatory agencies across the world for providing clear guidance and support for enabling cell therapy

# THANK YOU

The opinions presented are my own and not necessarily representative of Kite Pharma or Gilead.



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