Product Comparability in Cell Therapy: Approach to Managing Multifactorial Changes

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Overview

Purpose of this Talk

- Share key strategies for comparability in cell therapy products undergoing multifactorial changes

What I hope you will takeaway

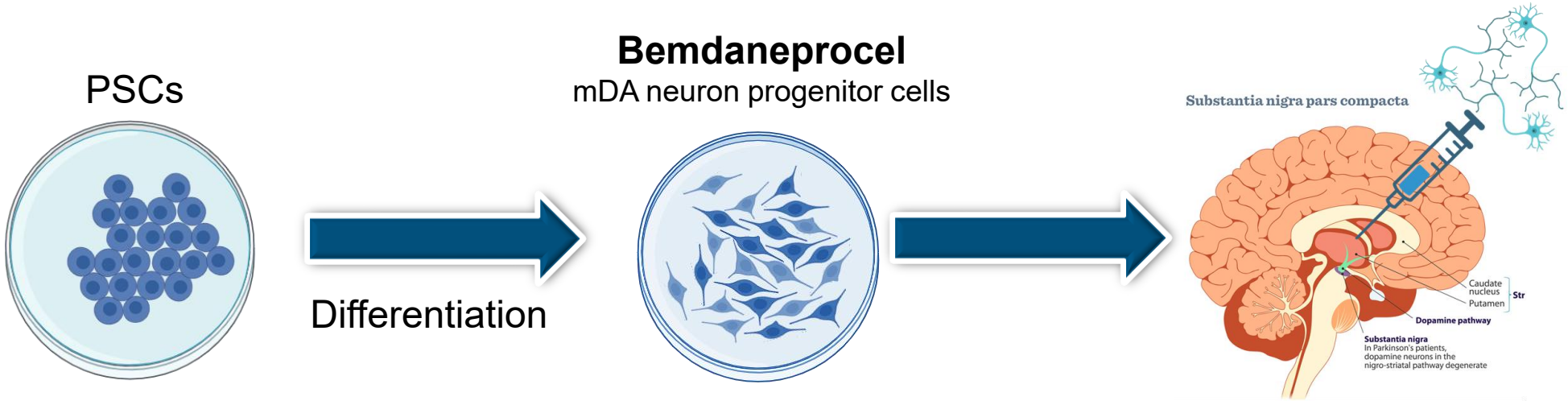
- Systematic approach to comparability incorporating risk-based evaluation
- How to de-risk comparability
- Role of advanced analytics like transcriptomics
- Challenges & Tips

Our mission

To discover and develop cell therapies that can change the way we treat disease and improve the lives of patients.

Bemdaneprocel Development:
mDA Neuron Progenitor Cells for Parkinson's Disease (PD)

Bemdaneprocel consists of allogeneic, engraftable midbrain dopaminergic (mDA) neuron progenitors derived from pluripotent stem cells (PSCs)[1-3]



An optimized differentiation protocol yields cells that express markers consistent with those of mDA neuron progenitor cells[1]

PD is characterized by loss of mDA neurons. BlueRock's cell therapy aims to replenish lost cells

1. Kim TW, et al. *Cell Stem Cell*. 2021;28(2):343-355.e5. **2.** Piao J, et al. *Cell Stem Cell*. 2021;28(2):217-229.e7. **3.** Kriks S, et al. *Nature* 2011;480:547-551.

Bemdaneprocel Phase I Results

- Well tolerated with no Serious Adverse Events related to Bemdaneprocel
- Demonstrated cell engraftment and survival after stopping immune suppression at 12 months
- Exploratory clinical efficacy endpoints are encouraging
- Phase 3 trial planned based on data and RMAT designation from FDA

*The phase 1 study enrolled 12 subjects diagnosed with Parkinson's disease who received surgical transplantation of 1 of 2 different dose levels of bemdaneprocel to the post-commissural putamen bilaterally, and administration of a 1-year immunosuppression regimen.

Tabar, V., Sarva, H., Lozano, A.M. et al. Phase I trial of hES cell-derived dopaminergic neurons for Parkinson's disease. Nature (2025). https://doi.org/10.1038/s41586-025-08845-y

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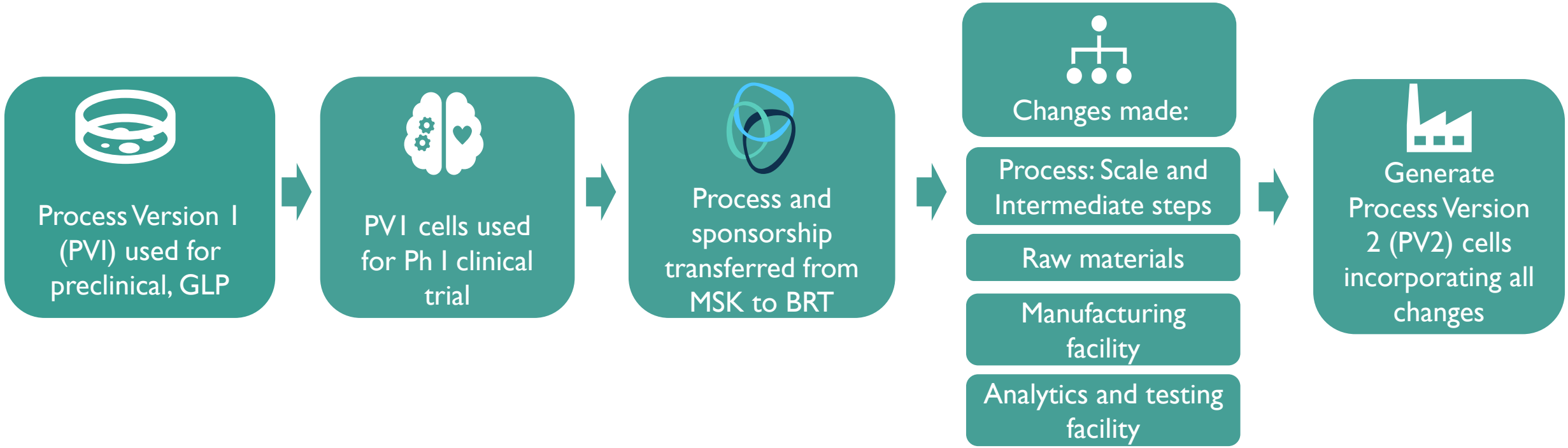
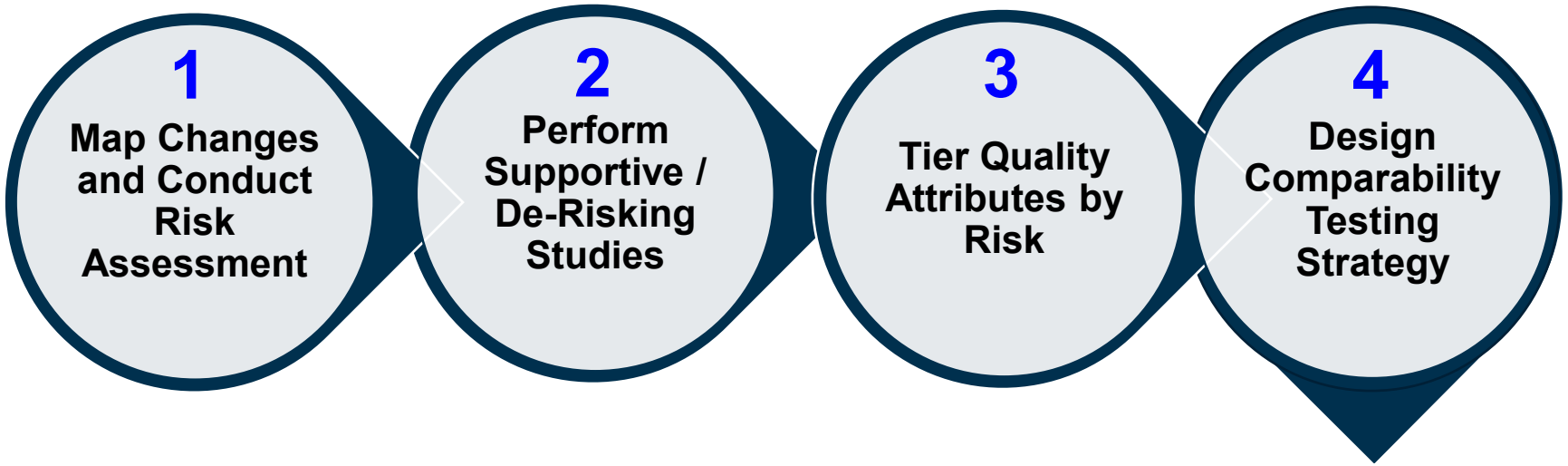
Simultaneous Changes Made to Bemdaneprocel to Enable Future Commercialization



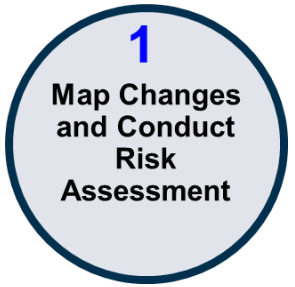
Changes were made to improve process, with improved GMP controls and robust analytics
As a result, we need to demonstrate comparability between PV1 and PV2 cells prior to use in subsequently planned clinical trials

Utilizing a Systematic and Risk-Based Approach to Guide Comparability



- Method Readiness & Testing Strategy
- Evaluate Statistical Approaches
- Select Material for Testing
- Advanced Tools & Characterizat-ion

Mapping Changes & Evaluating Risk of Change Enables Strategic Comparability Planning



- Not all changes carry the same **level of risk** to product quality
- Systematically identify and assess risks associated with changes.
  - analyze how changes could affect critical quality attributes (CQAs) and overall product performance
- Understanding the risk associated with a change helps determine the **scope, depth and type of comparability studies needed**
  - Minor changes may require limited assessment, while major changes necessitate comprehensive evaluation or supportive non-clinical studies

Tips

- **Evaluate attribute criticality early** to identify and prioritize critical quality attributes
- Summarize the **justification** of change, **rationale for ranking** and **outcome** in your comparability protocol or regulatory submission.
- Engaging with the FDA early in the process is crucial to discuss proposed changes and associated risk assessments and comparability plan

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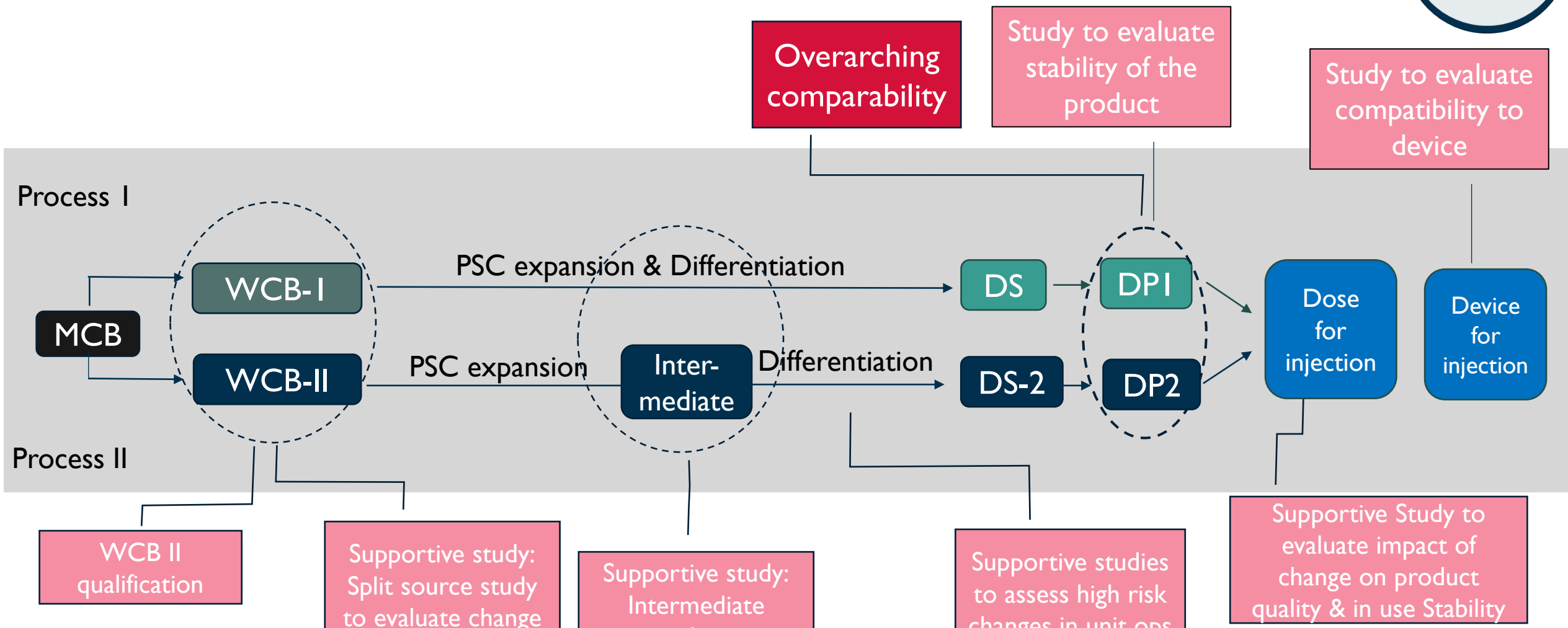
MCB – Master Cell bank; WCB – Working Cell bank; DS – Drug Substance; DP – Drug Product;

Multifactorial Changes Require an Overarching Comparability Study & Supportive De-Risking Studies

2 Perform Supportive / De-Risking Studies



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MCB – Master Cell bank; WCB – Working Cell bank; DS – Drug Substance; DP – Drug Product; CSI – Cell Suspension for Injection

Risk-Based Tiering Provides Framework and Context for Comparability Studies

- Tier attributes based on criticality to product quality, risk of change and the reliability of the analytical method
- Can be used to align testing strategy and statistical rigor with attribute importance
- Focuses resources on the attributes most critical to clinical safety and efficacy

Tier	Criticality for comparability	Example of Bemdaneprocel attributes in this tier
Tier 1	Essential to demonstrate comparability	All safety attributes*, viability, identity markers for target cell product, purity, residual PSCs
Tier 2	Informative for comparability but may not be critical as Tier 1	Maturity marker, apoptosis, process derived impurities, **Potency**
Tier 3	Added to characterize product to gather data for future. Quality attributes that are not routinely evaluated Also included descriptive attributes	Global Phenotypic/ transcriptomic analysis

* Attributes like sterility, endotoxin, mycoplasma may not be amenable to statistical analysis

Tips

- Depending upon the robustness of analytical method, some CQAs in early stages may be Tier 2 attributes
- Include tiering logic and test plans in comparability protocol in Regulatory interactions

Robust Overarching Comparability Assessment Encompasses Testing, Statistical Evaluation & Material selection

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Methods Readiness for Analytical Comparability

- **Method Readiness Drives Credibility**
  - Methods must be **sensitive** and **specific** enough to detect differences that could affect product quality
  - For Release Attributes → phase appropriate **qualification or validation**
  - Extended characterization assays → precise enough to detect meaningful differences
- **Analytical Changes**
  - Maintain analytical method consistency through comparability studies if possible
  - If method change is unavoidable:
    - Establish analytical equivalency/ transfer/ bridging studies
    - Or test **retained pre-change samples** with the updated assay
- **Pick a Testing strategy**
  - **Historical Comparison**: when assay variability is low & methods are consistent or bridged
  - **Side-by-Side Testing**: Needed when variability is high or methods/sites differ — helps isolate process impact but may be impractical for cell therapies.

Regulatory Guidance

- **ICH Q5E recommends** using "sensitive and appropriately validated analytical procedures to detect differences."

Tips

- Document clear rationale for change & evidence supporting method transition in regulatory submission.
- Ensure you retain sufficient precious pre-change material- particularly from clinical lots

Key Considerations for Statistical Analysis in Comparability

- Relying solely on established **release tests and in-process controls** is generally **insufficient** to assess the impact of manufacturing changes
- Select statistical methods based on:
  - Process and analytical variability, Sample size (n)
  - Study design (side-by-side vs. historical comparison)
- Tier 1 CQAs (critical to safety/potency):
  - Use Equivalence Testing or Simultaneous Prediction Intervals for stricter evaluation
- Simultaneous Prediction Intervals:
  - Help estimate range of future values
  - Useful with unbalanced pre/post-change batch numbers
  - Less effective with high method variability
- Not all CQAs are amenable to statistical testing:
  - Use minimum–maximum range, trend analysis, or descriptive comparisons
  - Visual analysis (e.g., boxplots, control charts) can support conclusions

Tips

- Engage biostatisticians early while designing comparability to ensure suitability of statistics approach for comparability
- De-risk comparability by performing similar statistical evaluation during process development
- Engage the FDA early & present your planned statistical analysis within the comparability protocol ahead of study execution

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Select the Right Material for Comparability

4
Design Comparability Testing Strategy

- Comparability studies should generally use full-scale manufactured lots
- If using full-scale lots is not feasible, perform risk assessment and characterization studies to justify that **scale-down still provides meaningful comparability** evaluation
- Justify each lot picked; ensure they reflect routine production
- Regulators may require use of **clinical** pre-change material for comparability, especially for complex changes.
  - Representative nonclinical material can be combined with statistical justification, particularly when sourced from different sites.
- Since material is limited, **coordinate** testing when possible

Tips

- Routinely retain material—including clinical material—for future comparability assessments.

Regulatory Expectations

- **FDA guidance on CGT comparability** (2023 draft) states: "Lots must be "representative of your typical manufacturing process"…."the sponsor should justify the choice of every comparability lot and (when relevant) the cellular source material"

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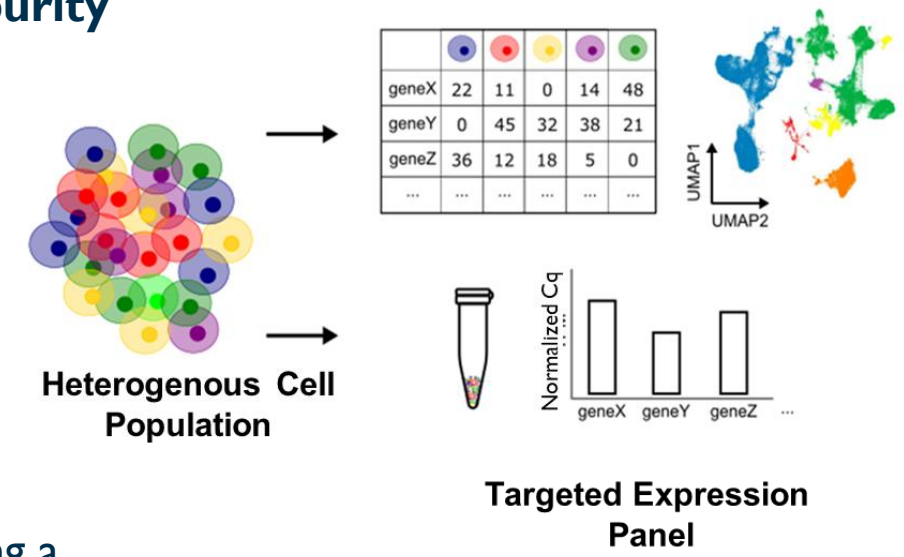
Advanced Characterization Tools Supports Comparability Assessments

4
Design Comparability Testing Strategy

Transcriptomic Profiling

- Support understanding of **product differences** in early stages
- Aid in **impurity characterization** and can support in identifying **novel impurity markers**
- Best applied as a **discovery, hypothesis-generating** tool in early stages
- Avoid reducing to a single metric; use descriptive, multidimensional analysis



Genomic Integrity Assessment

- Detect chromosomal aberrations, single nucleotide variants (SNVs), and structural variants.
- Typically, not suited for **statistical comparability analysis**—interpret using a safety, biological and mechanistic lens.
- Pre-define your analysis and investigation framework to avoid ambiguity.
- Be prepared for follow-up investigations.

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Bemdaneprocel Overarching Analytical Comparability Plan

4
Design Comparability Testing Strategy

Method Readiness & Testing Strategy

- All Tier 1 methods & Tier 2 were qualified; Extended characterization assays were deemed to be scientifically sound
- Tested retained PVI material and PV2 material with same analytical methods

Evaluate Statistical Approaches

- Set acceptance using Simultaneous Prediction Interval based on PV1 material data in advance of testing PV2 material

Select Material for Testing

- PV1 material used: Clinical Material & Full Scale PV1 material made in Process Development Lab
- PV2 material: representative full scale
- N=6 pre change lots
- N=3 post change lots

Advanced Tools & Characterization

- Included extended characterization using qPCR and scRNaseq
- Performed Genomic Integrity evaluation of WCB, hESCi and DP

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Key Comparability Challenges in Cell Therapy – and How to Tackle Them

Challenge	Mitigation / Considerations
Limited number of vials	➢ Coordinated testing, ensuring it doesn't impact performance ➢ Plan to retain limited/valuable early-phase material
Limited batch availability	➢ Combine with representative non-clinical material (justify statistically)
Limited product understanding	➢ Use broad characterization ➢ Treat more attributes as potentially critical until data says otherwise ➢ Support with nonclinical data
Potency assay not qualified	➢ Use orthogonal or surrogate assays to supplement or substitute ➢ Support with extended characterization like transcriptomic profiling
Testing site/method changes	➢ Perform assay bridging across sites ➢ Use consistent methods where possible to test pre- & post- change lots
Regulatory pressure + timelines	➢ Engage regulators early ➢ Include comparability in development strategy

It takes a village

- Bemdaneprocel CMC Team
- Bemdaneprocel Process Development & MFG Teams
- Analytical and Quality Control
  - Testing Team
  - Analytical Development team
  - Analytical Strategy Team
- Bioinformatics team

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Replace. Restore. Reimagine.

Striving to transform the treatment of disease by harnessing the power of cell therapy