2024 CASSS CGTP Summit

Analytical Comparability for Autologous CAR-T Products

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Bristol Myers Squibb™

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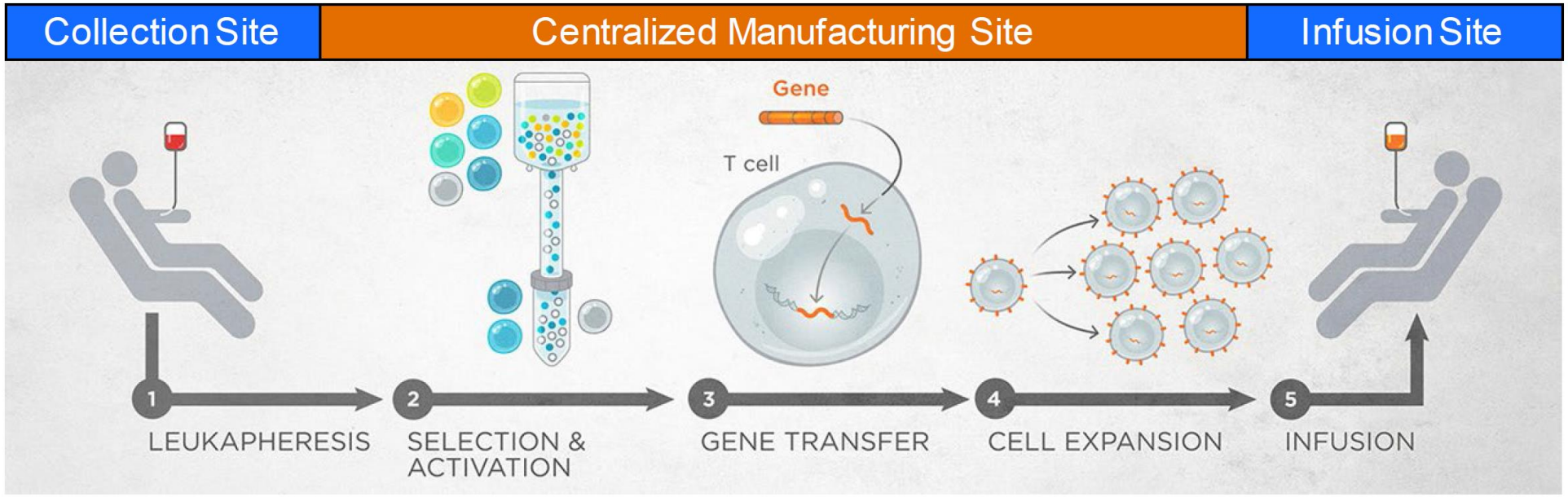
Autologous CAR T Cell Therapy Product At Bristol Myers Squibb



Abecma™ (idecabtagene vicleucel) SUSPENSION FOR IV INFUSION

FDA approved March 2021
EMA approved August 2021

Breyanzi™ (lisocabtagene maraleucel) SUSPENSION FOR IV INFUSION

FDA approved February 2021
EMA approved January 2022

In the pipeline: https://www.bms.com/researchers-and-partners/in-the-pipeline.html

Key Cell Therapy Product Approval and Guidance Documents Timeline

1996: FDA: Comparability guidance for biological products

2006: FDA: ICH Q5E

2017: *First commercial cell therapy product (Kymriah, 3L+ LBCL, CD19+) followed by Yescarta approvals in US*

2019: EMA: Q&A on comparability for ATMP

2021: *Abecma (multiple myeloma, anti-BCMA) approval in US*

2021: *Breyanzi (3L+ LBCL, CD19+) approval in US*

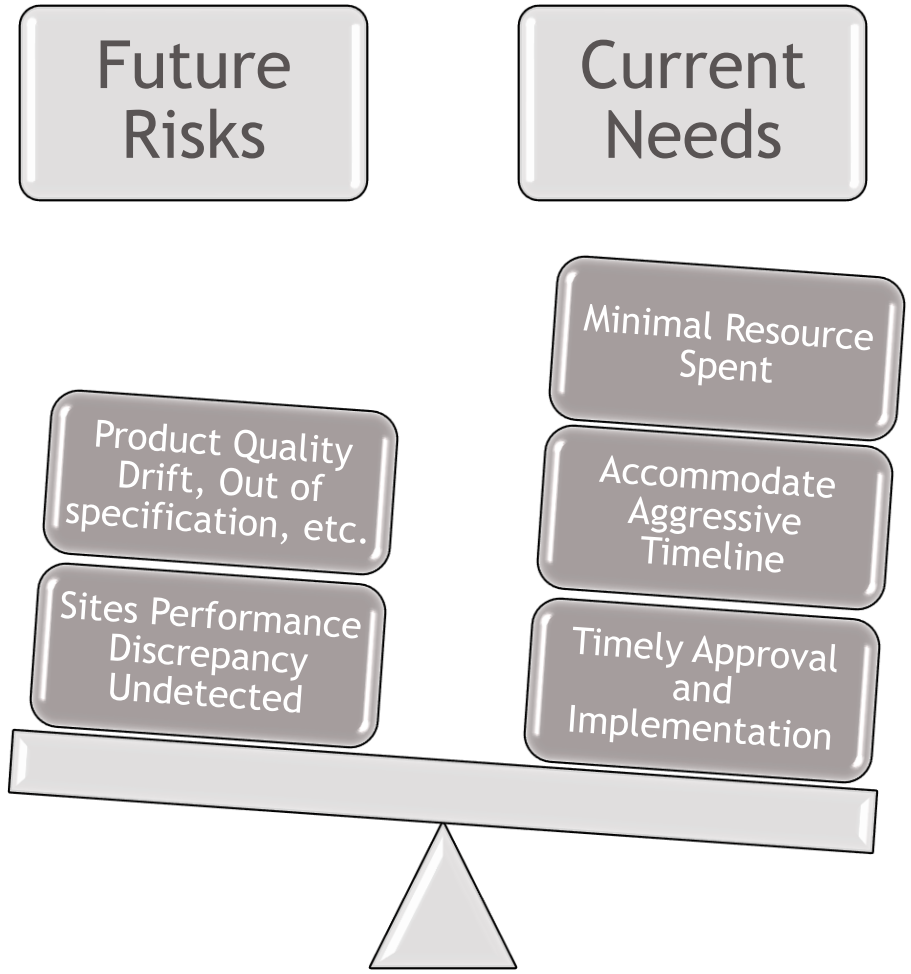
2022: *Carvykti (multiple myeloma, anti-BCMA) approval in US*

2023: ***FDA: draft, Manufacturing changes and comparability for human cellular and gene therapy product***

2024: FDA: Considerations for the Development of CAR T Cell Products

Business Purposes of Comparability

- Mitigate future risks of product quality drift after a major change, i.e., vector change, new sites, etc.
- Enable business priorities, e.g., capacity expansion, cost reduction
- Timely regulatory approval to implement process improvement



Comparability: what we can learn from the review of advanced therapy medicinal products

Table 4. Comparability-related issues evident during initial review.

Type	Theme	Example
Site change	Inadequate comparability data provided for a change of manufacturing site	Kymriah
Surrogate material	Requirement to show that donated starting material used in lieu of patient material is suitably representative for CQAs studied	Libmeldy, Kymriah
Potency assay	Changes and variability in potency test resulting in difficulties for comparative analyses	Zolgensma
	Acceptance criteria not considered suitable for adequate control	Zynteglo
Efficacy data	In the absence of comparability data, some efficacy data was excluded from consideration (primary data)	Kymriah
Non-clinical data	Requirement to show suitable comparability for product used for non-clinical studies and intended for commercial supply	Yescarta
	Limited value of comparative *in vivo* pharmacology studies in the context of data to support a comparability assessment	Kymriah
Major objection†	Acceptance criteria for potency assay not adequate for mitigating risk of a treatment failure	Zynteglo
	Insufficient comparability information for medicinal product from proposed commercial process and earlier versions of product	Spherox
post-approval measures required	Continued monitoring (trending) of analytical results, e.g., as part of process verification	Libmeldy
	Requirement for additional analyses post-approval	Zolgensma
	Re-evaluate clinical data to understand whether release specification acceptance criteria can assure efficacy and safety	Zynteglo
	Develop an assay to monitor a vector impurity	Strimvelis

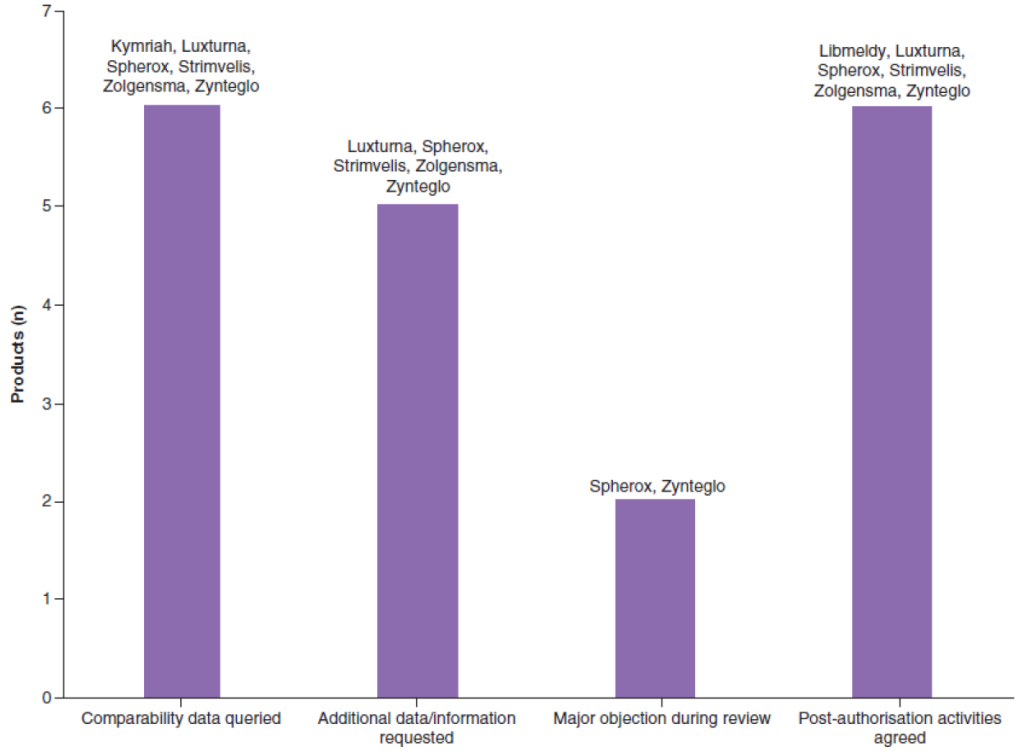


Figure 1. Extent of regulatory concerns identified in relation to comparability for 12 recently approved advanced therapy medicinal products. The source of the information used was the European Public Assessment Reports [39] and

Cockroft A, Wilson A. Comparability: what we can learn from the review of advanced therapy medicinal products. *Regen Med*. 2021 Jul;16(7):655-667

Major Manufacturing Changes Through Product Lifecycle and Comparability General Workflow

- Substantial changes to the manufacturing process, e.g., vector change, process automation, etc.
- New facility for manufacturing, e.g., tech transfer to new commercial manufacturing site, etc.
- Manufacturing suite addition at an existing approved facility
- General workflow:

Change Summary

Summarize the *proposed changes*:

- **Process**
- **Facility**
- **Equipment**
- **Raw materials**
- **Analytics**
- **Etc.**

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Risk/Impact Assessment

Assess the ***level of risk*** due to the *proposed changes against process controls and product quality* and assign criticality tiers:

Scoring of 1 to 9 (low - high risk)

Tier 1: High risk; may use equivalence test with split runs
Tier 2: Medium risk; may use quality range (tolerance interval) using historical clinical and/or commercial data
Tier 3: Low risk; may use graphical or tabular comparison against process control strategy, release specification, etc.

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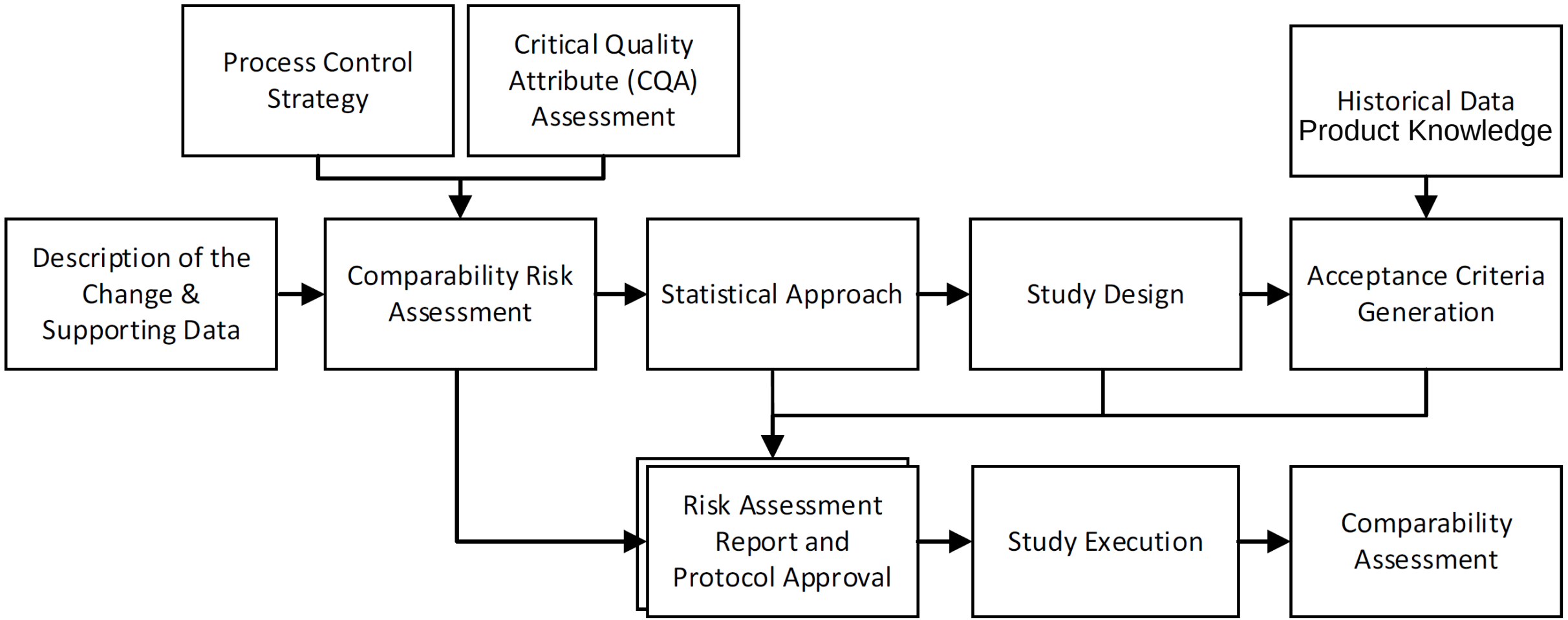
Comparability Study, If Required

- Generate risk-based comparability strategy and acceptance criteria for each attribute
- Ensure study execution aligns with strategy
- Assess results
- Author regulatory submission documents

Risk-based Comparability Approach



Brust, Erica "Risk-based Approaches for Autologous CAR T-cell Therapy Comparability", Cell & Gene Therapy Bioprocessing & Commercialization, Virtual (October 2020)

Scenario #1: CAR T Cell Manufacturing Major Changes – Late-Pivotal/Commercial Program

- **Process Change**: Vector production process change
- **Comparability Risk Assessment**:
  - Initial risk level - High
    - Per existing product and platform knowledge, the change will impact vector and potentially DP CQAs
    - Multiple development studies are planned to address the expected risks
  - Revised/final risk assessment after development studies outcome with pre- and after-change vector and DP - Medium
    - Vector CQAs changes but toward positive direction: e.g., increased titer, reduced impurity levels
    - Confirmed minimal impact to DP attributes: e.g., similar transduction frequency and vector copy number pre- and post-change
- **Comparability Study Design**:
  - Vector comparability: pre- and post-change CQAs/CPPs comparison against historical ranges
  - DP comparability: CQAs/CPPs assigned tiers and comparison with healthy donor based split studies and against historical ranges
  - Additional characterizations: for both vector and DP in-process and final product characteristics to assure detectability of meaningful shift
- **Regulatory Strategy**:
  - Within acceptable timeline, a Post-Approval Change Management Protocol (PACMP) may be submitted to reduce risk for commercial programs LCM changes

Scenario #2: CAR T Cell New Manufacturing Site Tech Transfer – Late-Pivotal/Commercial Program

- **Process Change:** Drug Product capacity expansion via new site addition
- **Comparability Risk Assessment:**
  - Initial risk level – Medium/Low
    - Minimal process change to impact DP CQAs
    - Past experiences with new sites addition demonstrate effectiveness of the tech transfer process
    - New staff members and site need to accumulate more experiences to handle complex autologous CAR-T manufacturing process
  - Revised/final risk assessment after TT runs - Low
    - TT runs (engineering, GMP, etc.) demonstrated comparable process performance between sending and receiving sites
- **Comparability Study Design:**
  - DP comparability: CQAs/CPPs assigned tiers and comparison with healthy donor based split studies (may pair with transfer runs) and against historical ranges
  - Additional characterizations: for DP in-process and final product characteristics to assure detectability of meaningful shift
- **Regulatory Strategy:**
  - Different health authorities may have different requirement for comparability study design and acceptance criteria

Phase-appropriate Comparability Considerations

	Main Risk to Mitigate	Key Constraint	Points to Consider
Pivotal	• Clinical and CMC data poolability	• Lack of knowledge on process/product variability • Limited clinical manufacturing experiences	• Acceptance criteria should not be too stringent to limit clinical development • "Comparability assurance": TT + Comparability + Monitoring
Commercial	• Product quality drift • Out of specification (OOS)	• Commercial DP release specifications may be "too tight" (relative to traditional drug)	• Understanding process and analytical variability • Consider balance the risk of OOS and meeting patients need by continuous process and product improvement

Comparability Acceptance Criteria Considerations

- Per ICH Q5E: *A determination that a product is "Comparable" indicates that products before and after a manufacturing change are **highly similar** and that **no adverse impact** on the quality, safety or efficacy of the drug product has occurred ….. And **does not mean that pre-and post-change products are identical or indistinguishable***
- When commercial specifications are set too tight (e.g., < 99% coverage tolerance bounds), comparability in commercial LCM may practically become a test for the "sameness" and potentially favor more variable processes in clinical study
- Nonclinical animal model data may be used to assess impact from differences observed in post-change product quality attributes. However, it maybe difficult to use for setting acceptance ranges
- Scientific knowledge of CQAs and link with clinical safety and efficacy should be considered in setting comparability acceptance criteria

Thank you

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