Bristol Myers Squibb®

CASSS CGTP Summit 2026

Rethinking Product Release Specifications for Autologous CAR T Cell Therapy

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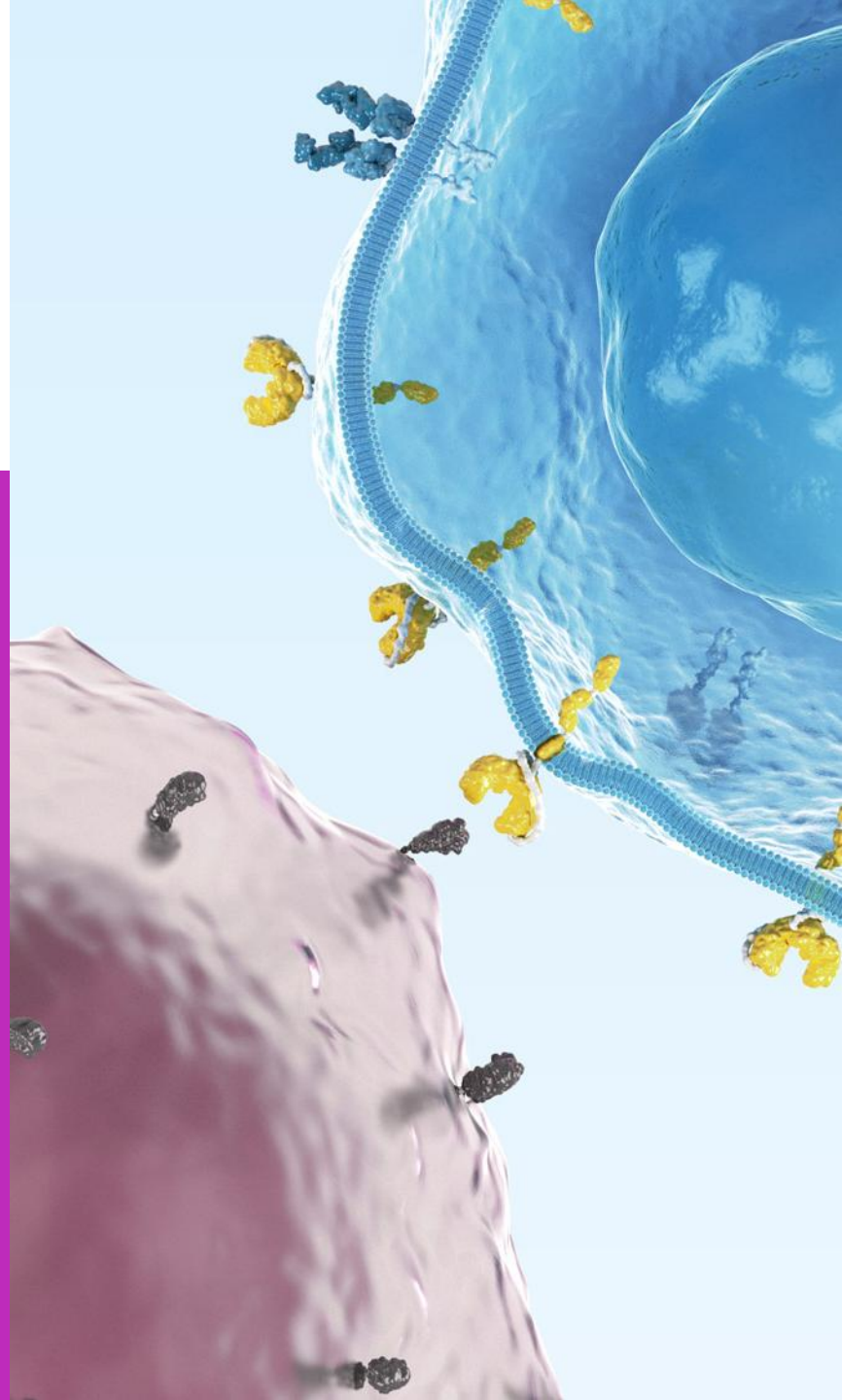
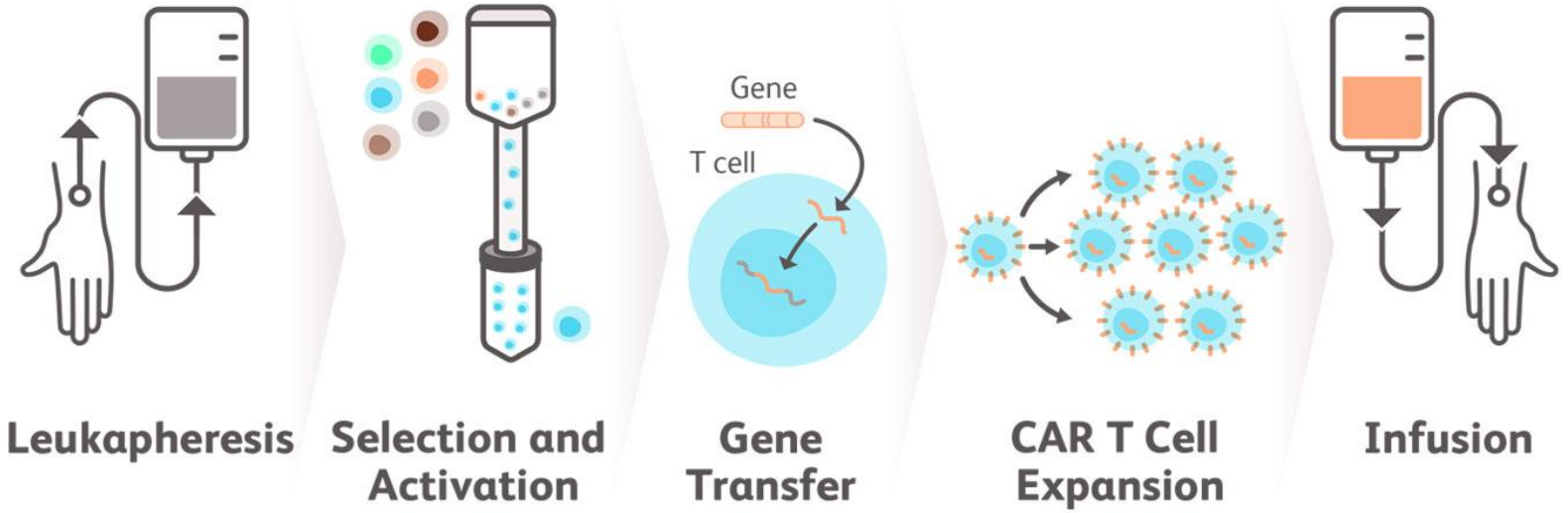
June 8, 2026



Autologous CAR T Cell Therapies at Bristol Myers Squibb



Abecma™ (idecabtagene vicleucel) SUSPENSION FOR IV INFUSION

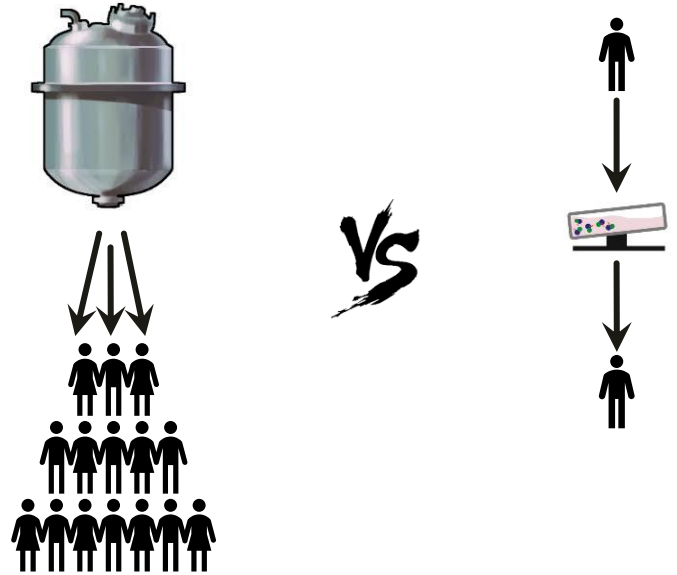
FDA approved March 2021
EMA approved August 2021

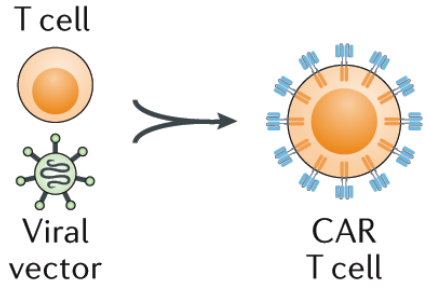
Breyanzi™ (lisocabtagene maraleucel) SUSPENSION FOR IV INFUSION

FDA approved February 2021
EMA approved January 2022

Unique challenges for CMC Control Strategy:
Contrasting traditional pharma & biologics v/s autologous CAR T

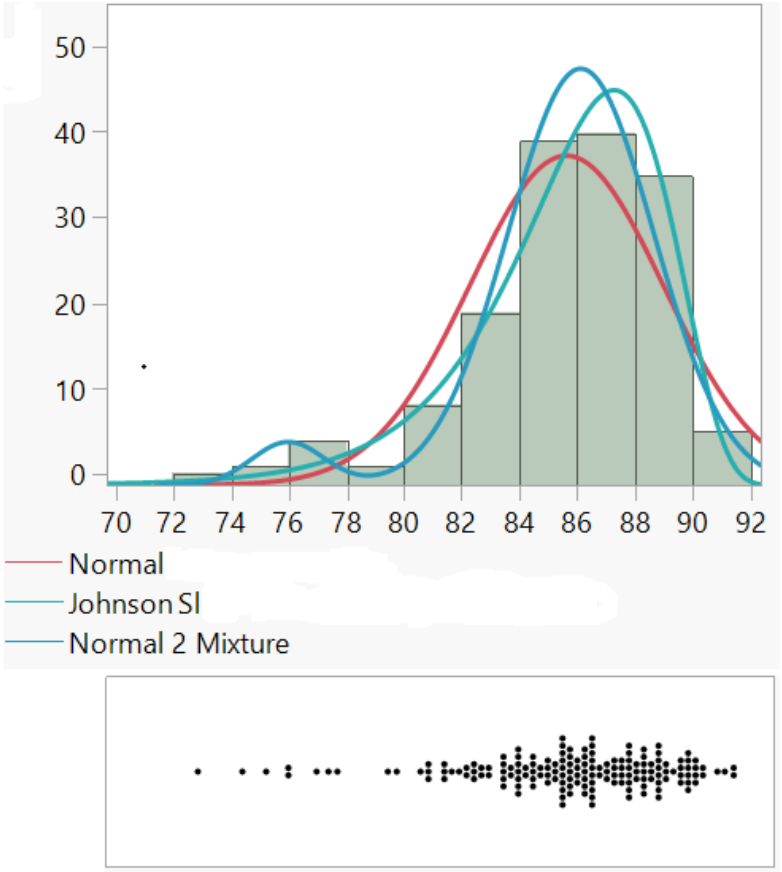
- Each patient is a drug product batch, each batch is a dose
- Complex MoA, multiple pathways
- CMC and clinical elements are highly interconnected
- Starting material is usually the most dominant source of variability[1]
- Viral vector for gene delivery manufactured separately
- Release specifications for DP are often, relatively “too tight”
  - based on larger sample sizes (large number of at-scale clinical batches at the time of PPQ / commercialization)
  - using 95% confidence, but less than 99% coverage Tolerance Bounds
  - high Out-Of-Specification (OOS)[6] rates even under common cause variability could become a *de facto* patient selection mechanism





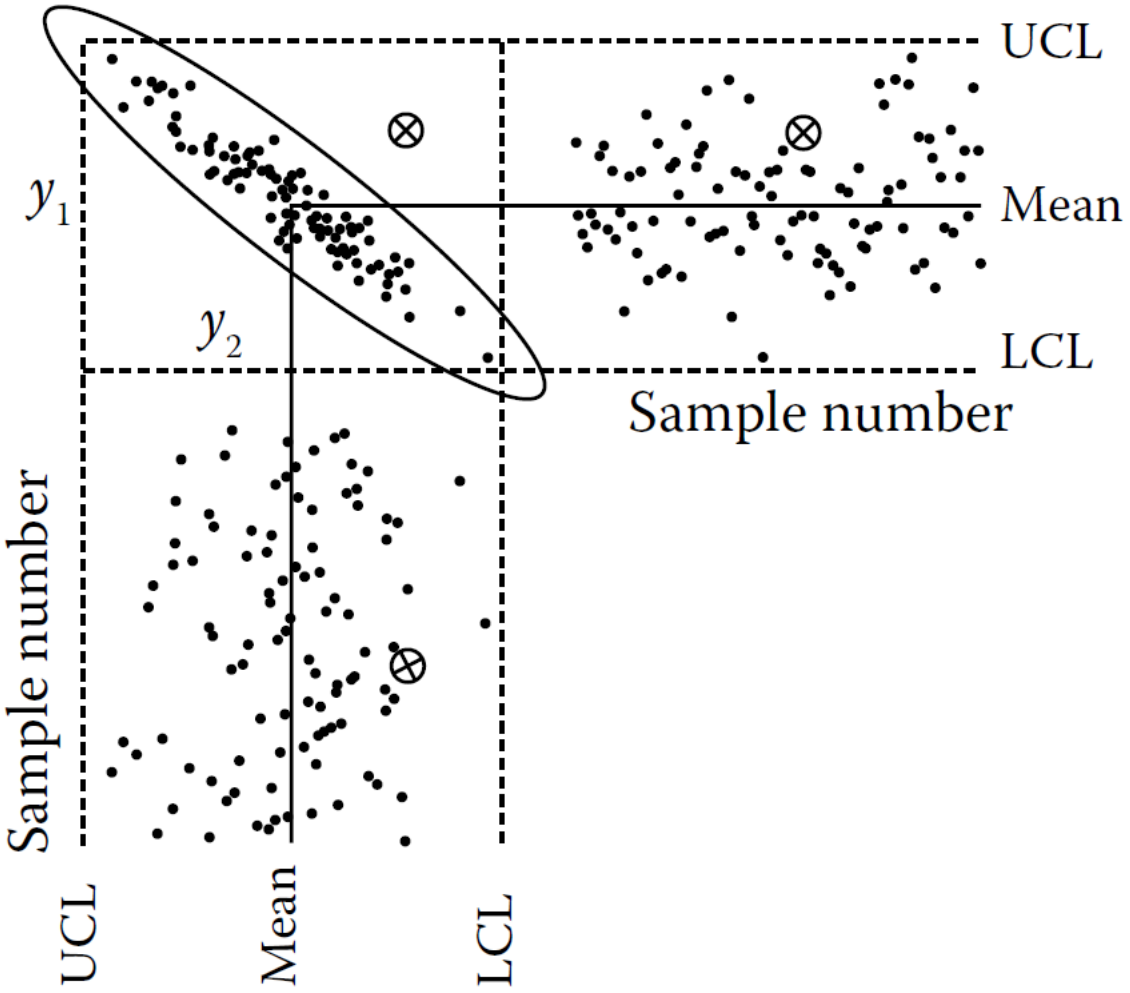
Lessons learnt

- BMS has extensively shared their experience gained over the years[1, 4, 15, 17]
- Impact of OOS:
  - Financial viability[13], compliance risks and possibly health outcome (- Nocebo effect[2])
- Typical interactions with health authorities:
  - “Indication-specific” or ”Lines of therapy” specific release criteria?
  - Representativeness and homogeneity of data sets
  - Consistency of manufacturing
  - Holistic assessment of the Control strategy[8]
  - Clinical outcomes for patients at the tails (extremities) of the data distribution
  - Statistical details – distribution model fitting, coverage levels, example calculations
- An evolving paradigm



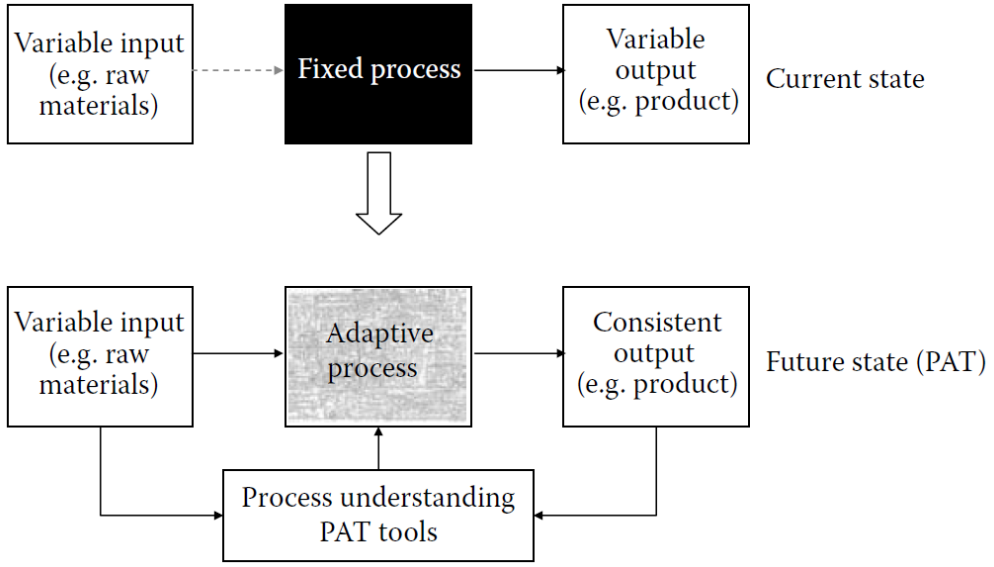
Some thoughts on the road ahead

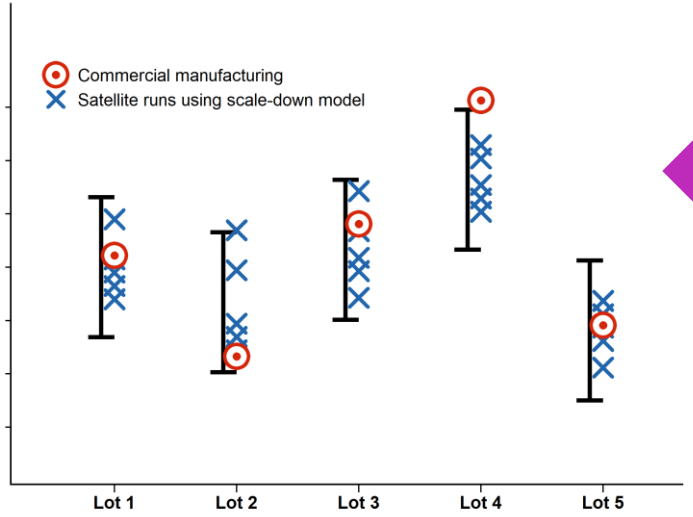
- Design of Experiments[10]
  - Maximize the information gained in the presence of constraints
  - Framework for causal models
  - Variance Components Analysis
- Bayesian approaches[7]
  - Before and after modeling
  - Framework for incorporating prior knowledge
- Multivariate approaches[12,14,16]
  - Model measurements collectively
  - Framework for incorporating large dimensions, correlations, noise



Some thoughts….(contd.)

- Systems thinking
  - Model-driven, adaptive manufacturing[11, 16] processes
- Patient-centric specifications[5, 9]
  - Personalized quality standards
  - Marginal Design Spaces and Marginal Release Specifications
- Scale-down models
  - Satellite runs for lot release[3]





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