Jason Bock

CEO, CTMC

About Jason Bock:

- Jason brings **20+ years** of previous biologics development and commercialization experience gained from MD Anderson Cancer Center,
  Teva Pharmaceuticals, CoGenesys, and Human Genome Sciences.

About CTMC+:

- Connects cell therapy development and industrial manufacturing with MD Anderson's clinical trial capabilities
- Leverages proprietary TIL and CAR-T platforms to improve productivity and quality while reducing costs.
- Cleared six INDs, without delay, for its academic and industry partners.

CTMC | Cell Therapy Manufacturing Center

A joint venture between Resilience + MD Anderson Cancer Center

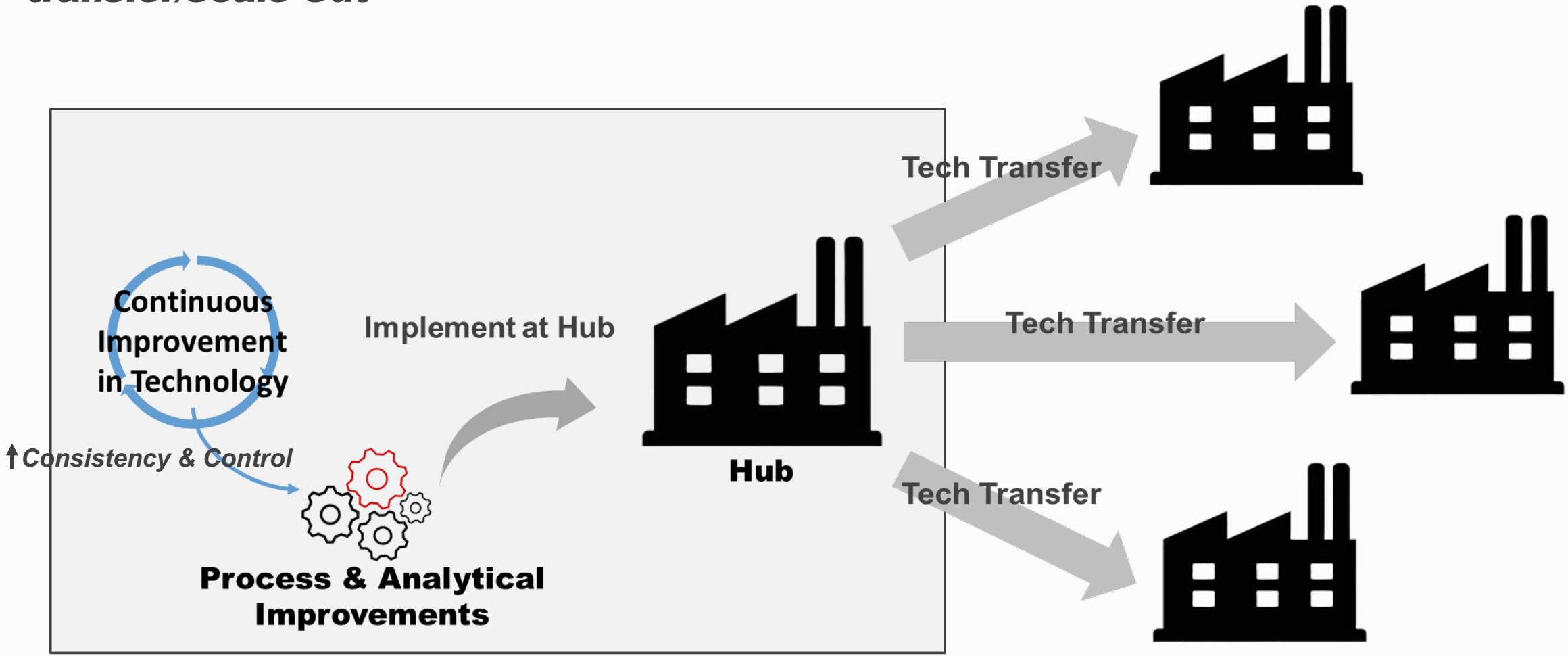
What Got Us Here, Won't Get Us There

Maturing of the Cell Therapy Field

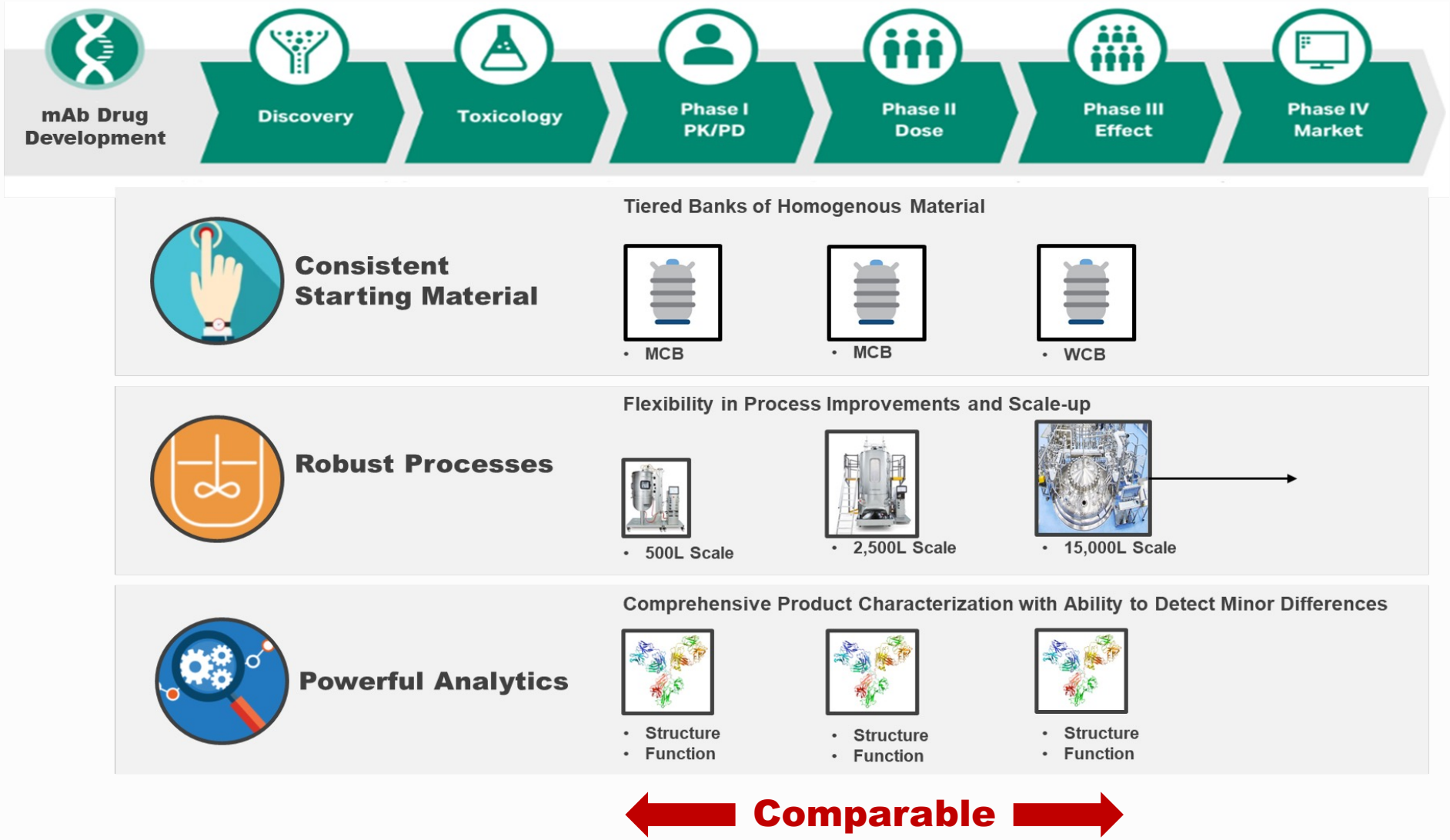
Dr. Jason Bock

Key to Maturing the Cell Therapy Field & Improving Access

Process Control and Understanding→ Process Improvements + transfer/Scale Out



Process & Product Understanding and Control



Variability in Cell Therapy Makes Comparability Challenging

Where We Are…

Variable Starting Material

Donor-to-Donor Variability

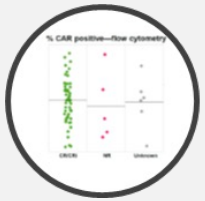
Variable Processes

Manual Processing

Poorly Defined CPPs

Variable Analytics

Complex Handling with Inability to Detect Minor Differences



Poorly Defined CQAs

Lack of Process & Product Understanding

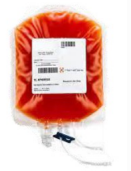
Strategic Approaches and Technological Innovations Facilitate Comparability

What Will Get Us There…

Variable Starting Material

Donor-to-Donor Variability

Split Starting Material



Variable Processes

Manual Processing

Automation
Innovative Manufacturing Methods

Variable Analytics

Complex Handling with Inability to Detect Minor Differences

Side-by-Side Testing
Advanced analytics

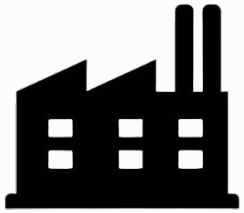
Alignment on comparability strategy with FDA

CTMC+

CTMC Well Positioned to Advance Manufacture of Cell Therapies

Innovative Partnership Model

- **Speed to Clinical PoC:** Fostering partnerships with biotech companies and academic institutions to accelerate transition from lab to clinic
- **Eye Towards Commercialization:** Positions partners for flexible transition to commercialization
- **Extended Capabilities:** Integration of R&D, industrial manufacturing, regulatory strategy, clinical trial support tailored to unique needs of each partner



State-of-the-Art Facility

- **Scalable Production of Cell Therapies:** 60,000 sq ft manufacturing space
- **Assurance of Product Safety & Efficacy:** 14 GMP-compliant clean rooms complemented by QC laboratories
- **Viral Vector Supply:** 3,500 sq ft for manufacture of viral vectors

Strategic Integration of FDA Interactions

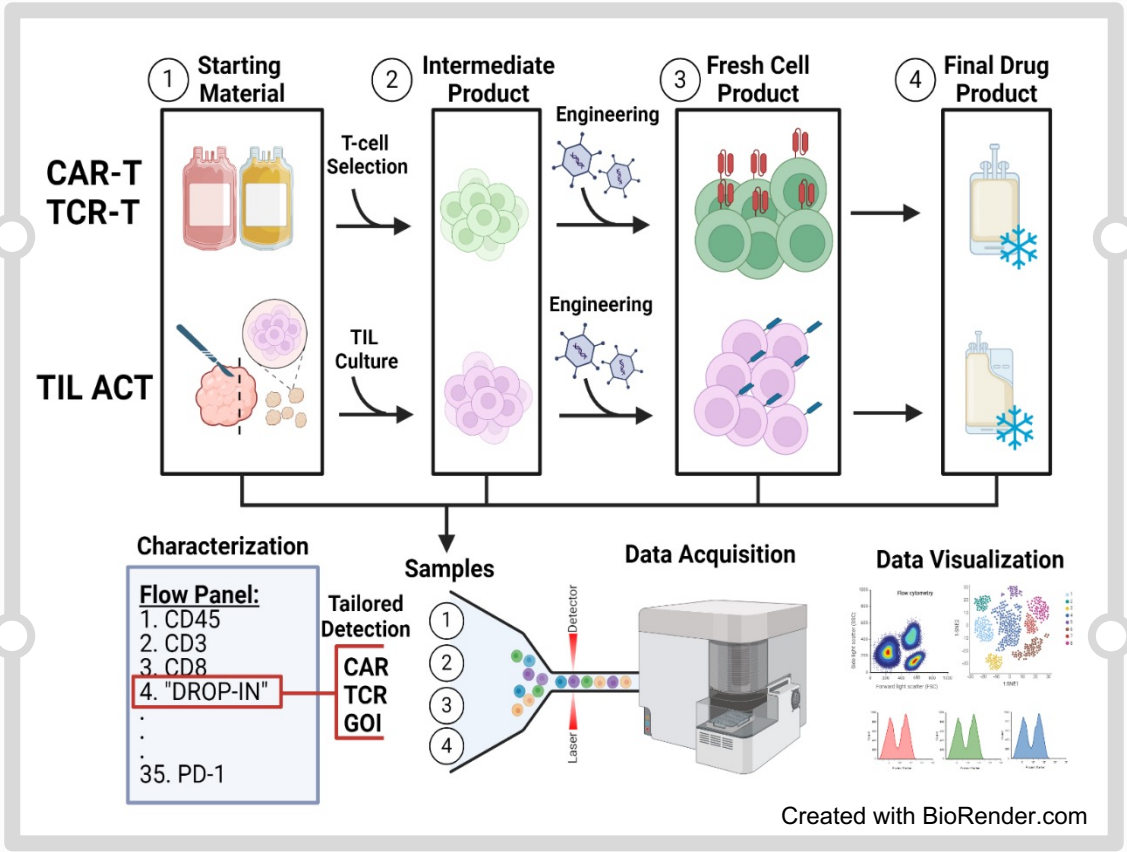
- **Pre-IND:** Laying the groundwork with an initial FDA interaction
- **IND:** Adapting the regulatory strategy based on feedback from FDA
- **Post-IND:** Managing ongoing dialogue with FDA during conduct of the clinical study (e.g., requests for designation, manufacturing improvements, FDA meetings)

Advanced Analytics Being Evaluated at CTMC

35-color Flow Cytometry Panel

Largest T cell-specific flow cytometry panel

Immunophenotyping of multiple T cell modalities



Analysis at various steps of the manufacturing process

Ability to detect impact of manufacturing changes

CTMC/MDACC's Advanced TIL Manufacturing Platform

Robust extraction and expansion of infiltrated TIL from starting tumor material

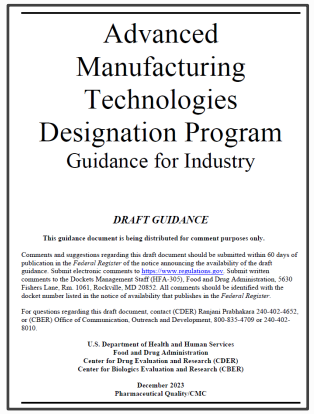
Starting Tumor Material from Core Needle Biopsies
Robust TIL extravasation from less tumor material

Reduced Patient Dropouts
Shorter time for production

Reduced Manufacturing Failures
More robust cell numbers

Greater Assurance of Expected Performance
More consistent phenotype

Indication Expansion Without Major Process Changes
High probability of success across various tumor types



Advanced Manufacturing Technologies Designation Program
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Ranjani Prabhakara 240-402-4652, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

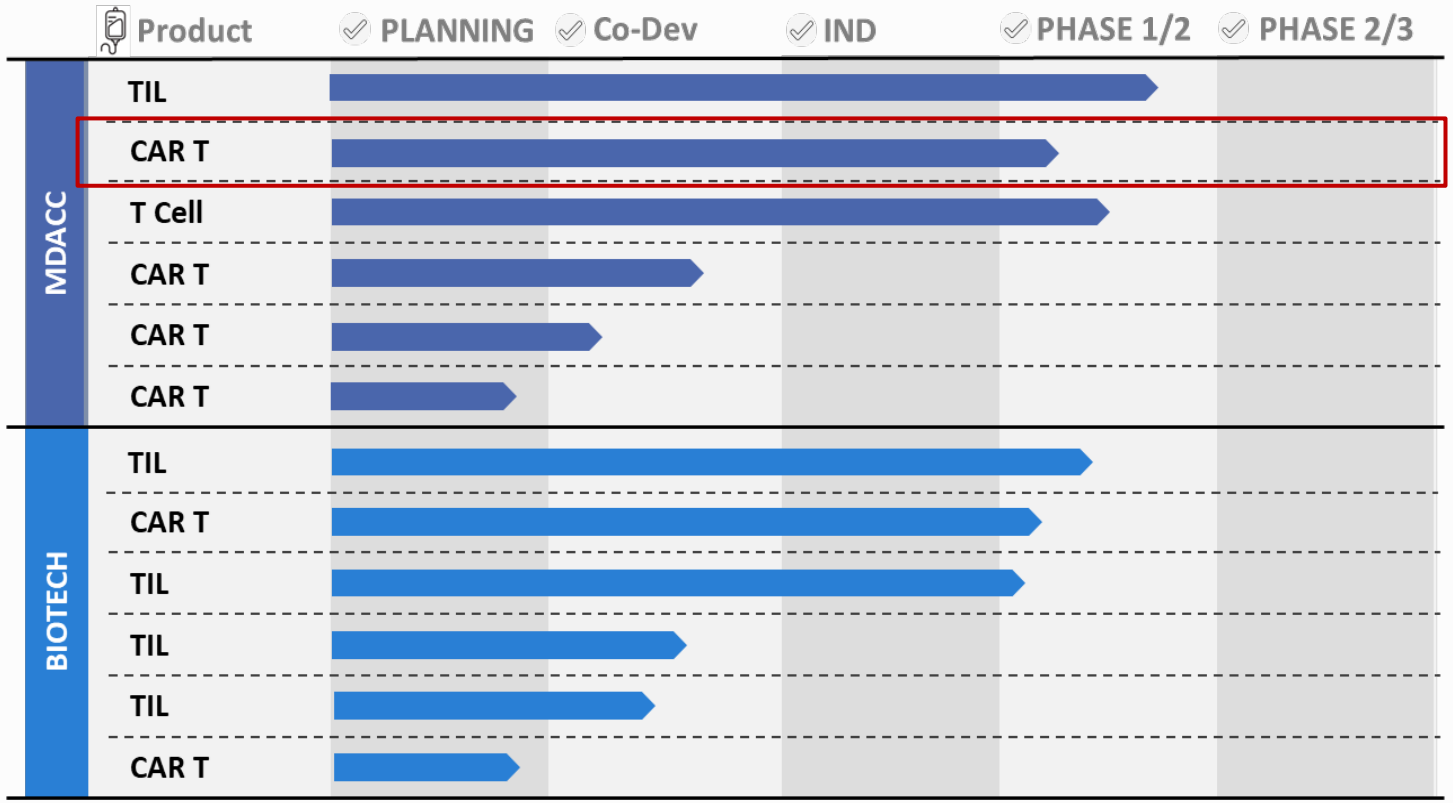
December 2023
Pharmaceutical Quality/CMC

Request for AMT Designation

CTMC+

Case Study: Advancing Manufacture of a Clinical CAR T Product

CTMC Product Portfolio



Autologous CAR T Product at MDACC

- *MDACC-invented CAR T product with promising target*
- *Co-developed & industrialized at CTMC*
- *Clinical proof of concept in patients with R/R BCLs at MDACC*
- *Continued process development at CTMC*

Implementing Automation via the Ori to Improve Consistency & Control

G-Rex Process

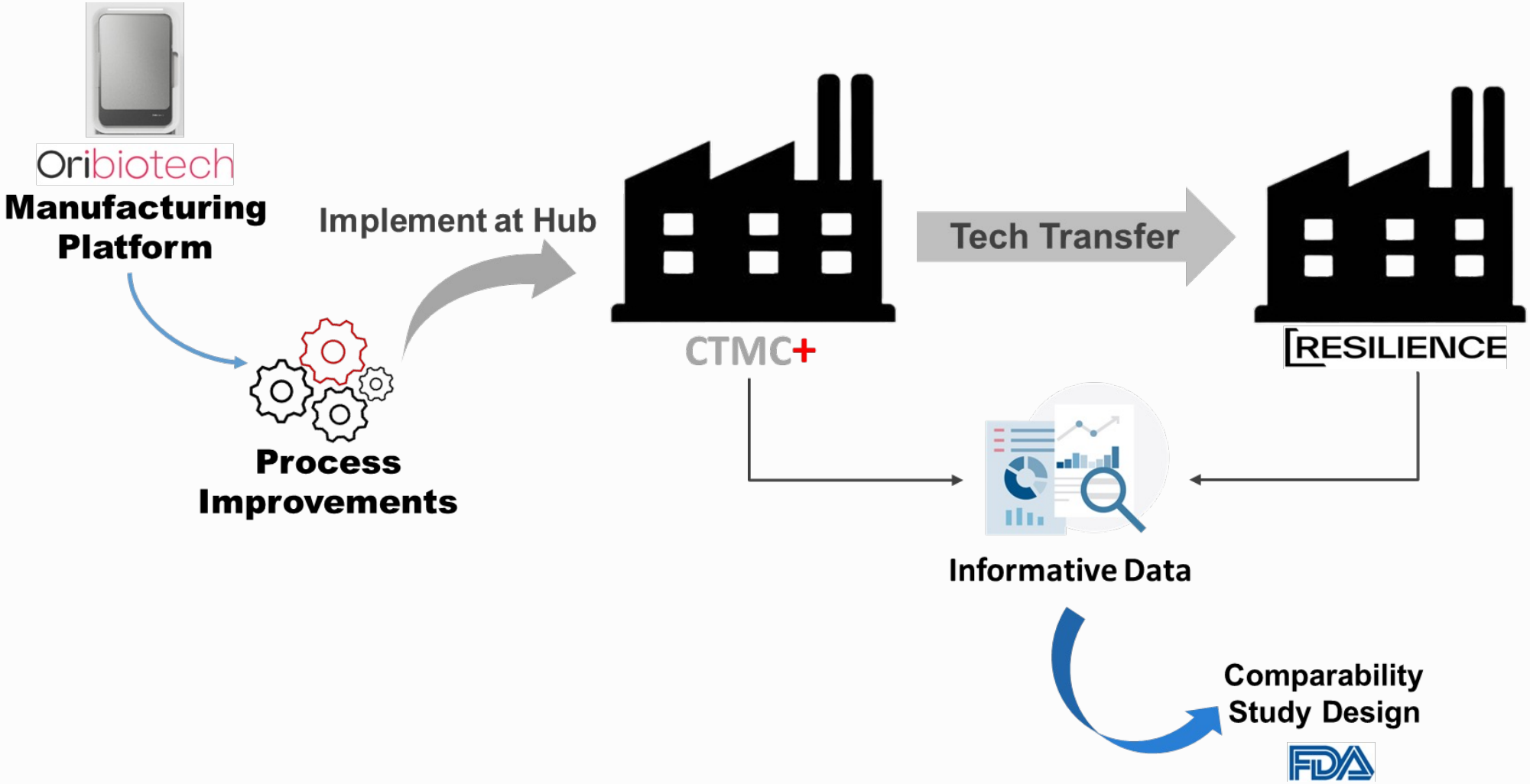
~~Manual Processing~~

Automated Processing

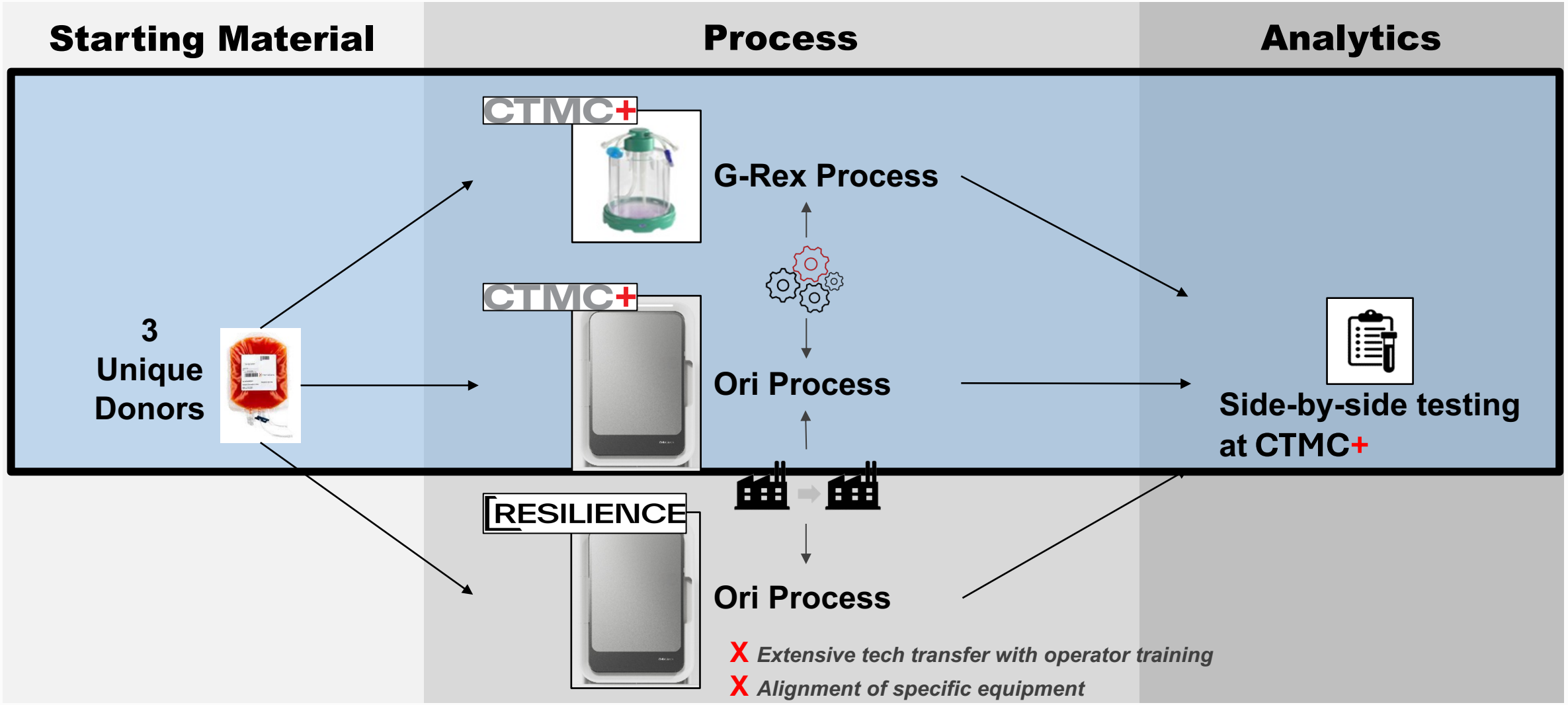
Ori Process

↑ *Consistency & Control*

Feasibility Study to Inform on Potential Comparability Strategy



Study Design Enabling Speedy Generation of Tangible Data



CAR-T Process Transfer Runs

Tech transfer from optimized GRex process onto the Ori Platform

The first step in this partnership was to evaluate the suitability of the Ori platform to run CTMC's existing optimized CAR-T process. These runs were done by CTMC staff, in their labs with their process / reagents on Ori equipment.

Process Overview:

- Cryopreserved positively isolated CD4/CD8+ T-cells from healthy donors
- Starting Viable Cells: 200M in 75mL
- Activation on D0: GMP TransAct
- Transduction on D1: CAR-LV

Objectives:

- Train process development personnel on independent use of the Ori platform
- Demonstrate that the CAR-T transduction and expansion process developed by Ori can be executed successfully at CTMC
- Optimize process parameters as needed to improve yield of CAR+ T cells

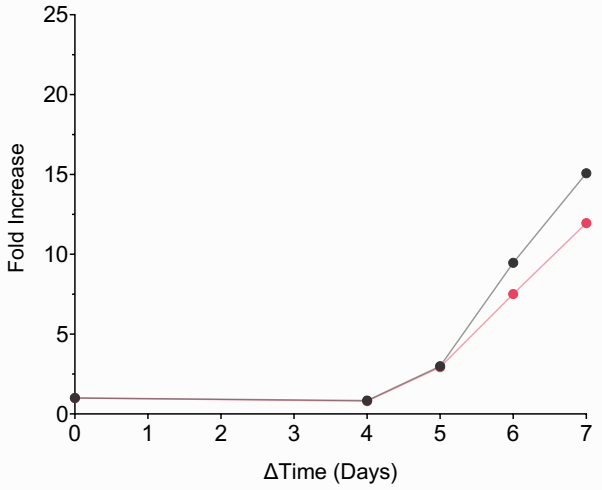
Qualitative Goal	CQAs
High Total CAR+ Yield	Greater than 700M CAR+ cells
High Viability	Greater than 70%
Vector Copy Number (VCN)	Less than 5

CAR-T Process Establishment in Ori

Key Takeaways

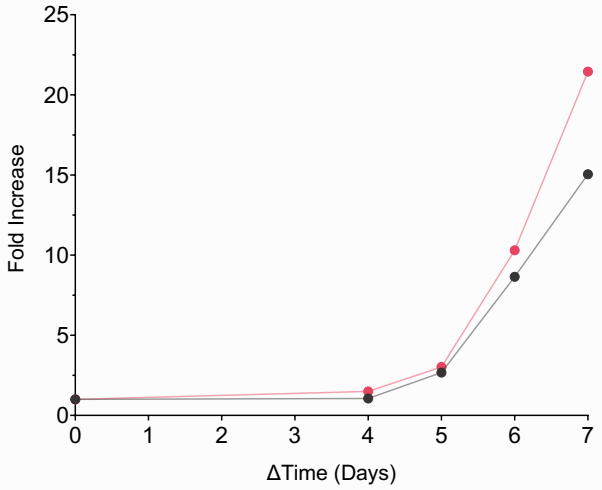
- Process establishment time onto the Ori platform was **< 5 weeks** from kick off
- **Run 1** had a lower total cell yield in the Ori system than the GRex control
- The protocol was adjusted for a repeat run with the same donor in **Run 2**. Changes were made to mixing speed and base height during the compression phase of culture to improve cell resuspension. The outcome was a **significant increase in fold expansion** in the Ori system
- **Run 3** used the updated protocol with a second donor and saw a **similar improvement with a slower growing donor**

Run 1: Donor A, Protocol A

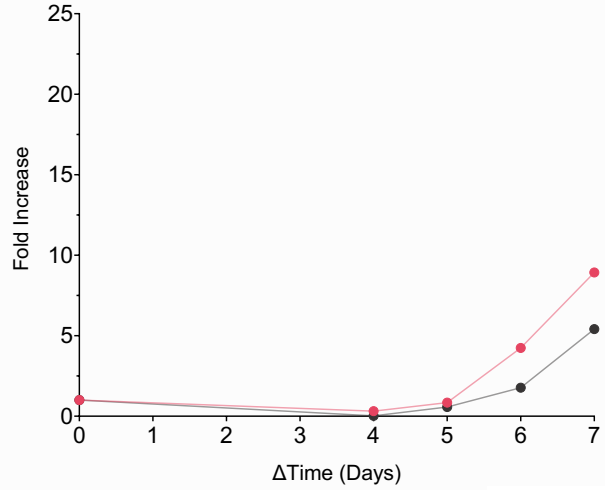


Improved mixing conditions

Run 2: Donor A, Protocol B



Run 3: Donor B, Protocol B

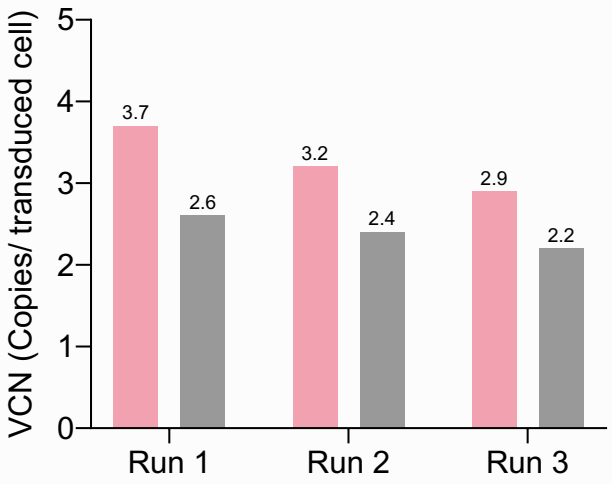


CAR-T Process Transfer

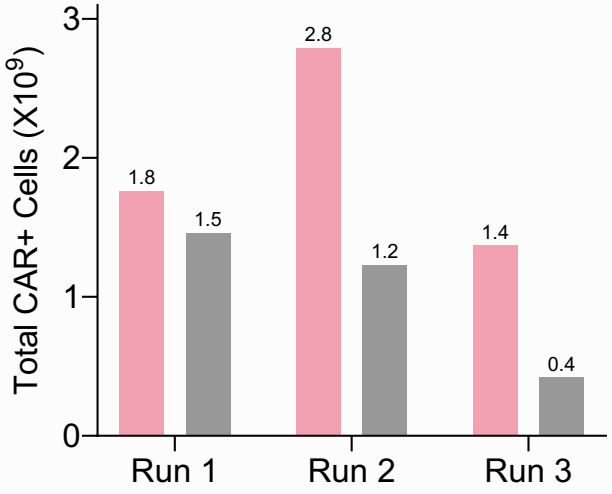
Key Takeaways

- Ori delivered a **21%, 127%, and 226% increase in CAR+ yield** vs GRex control
- Transduction efficiency averaged at **~69%** in Ori vs **~45%** in the control, with VCN remaining below the FDA recommended **< 5 per transduced cell**

Vector Copy Number



CAR-T Cell Yield

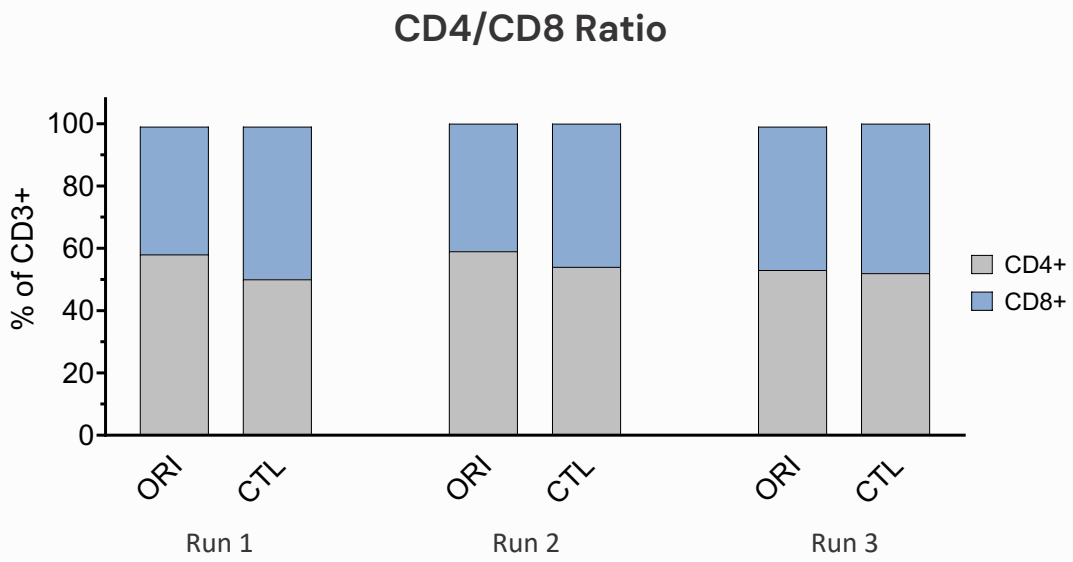


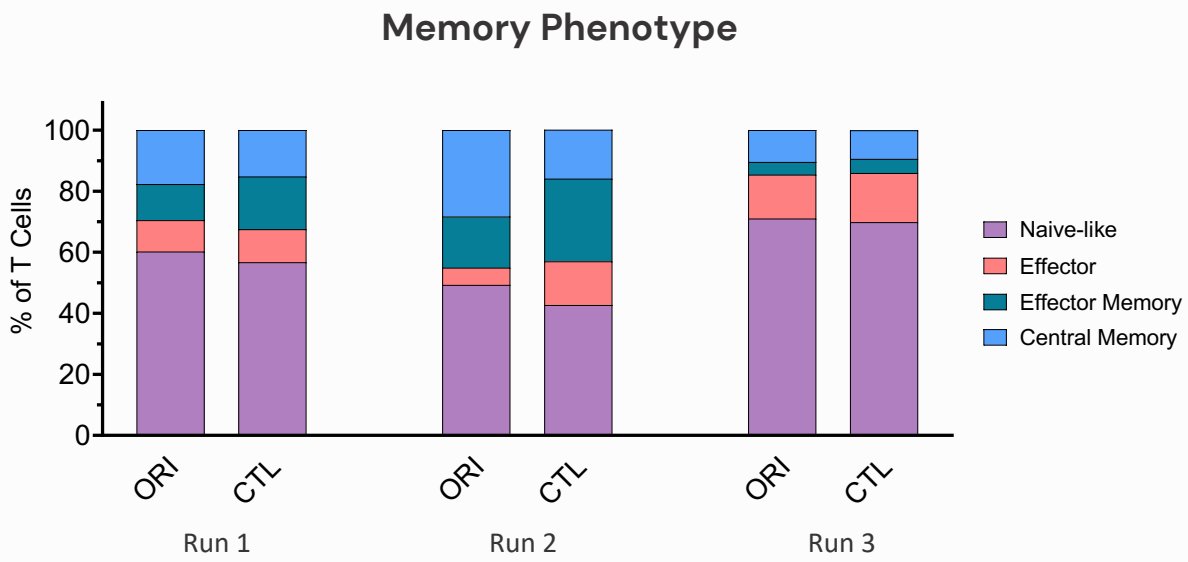
Ori Control

CAR-T Process Transfer

Key Takeaways

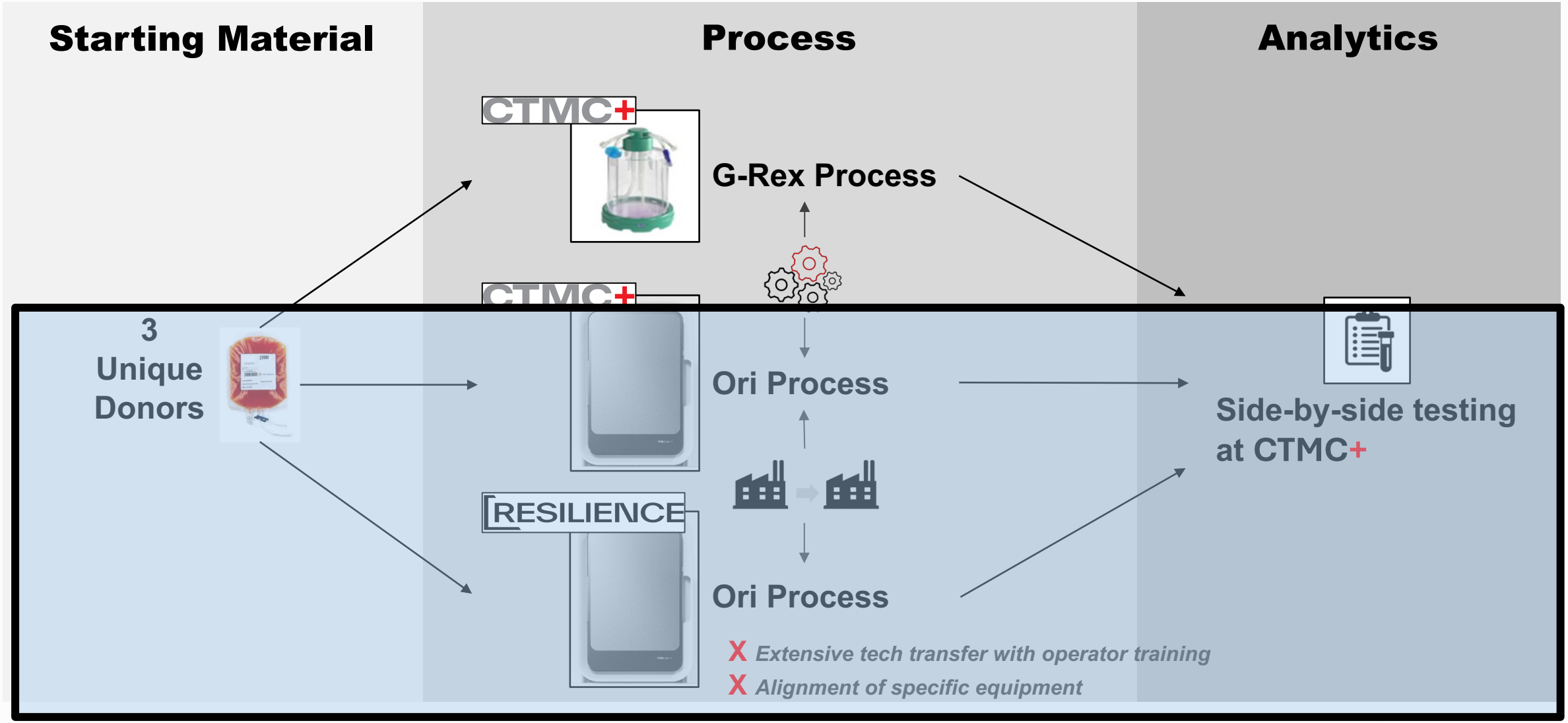
- **No trends** were observed in CD4/CD8 composition between each run
- **No trends** were observed in memory phenotype between each run





CTMC+

Study Design Enabling Speedy Generation of Tangible Data



Multisite Process Runs

- Parallel runs to demonstrate clinical process comparability and multi-site manufacturing

CTMC's optimized clinical process was then ran head-to-head with the Ori system and then tech transferred from Houston to Philadelphia to demonstrate a PoC for multi-site manufacturing

Process Overview:

- Cryopreserved negatively isolated CD4/CD8+ T-cells from healthy donors
- Starting Viable Cells: 200M in 75mL
- Activation on D0: GMP TransAct
- Transduction on D1: CAR-LV

Objectives:

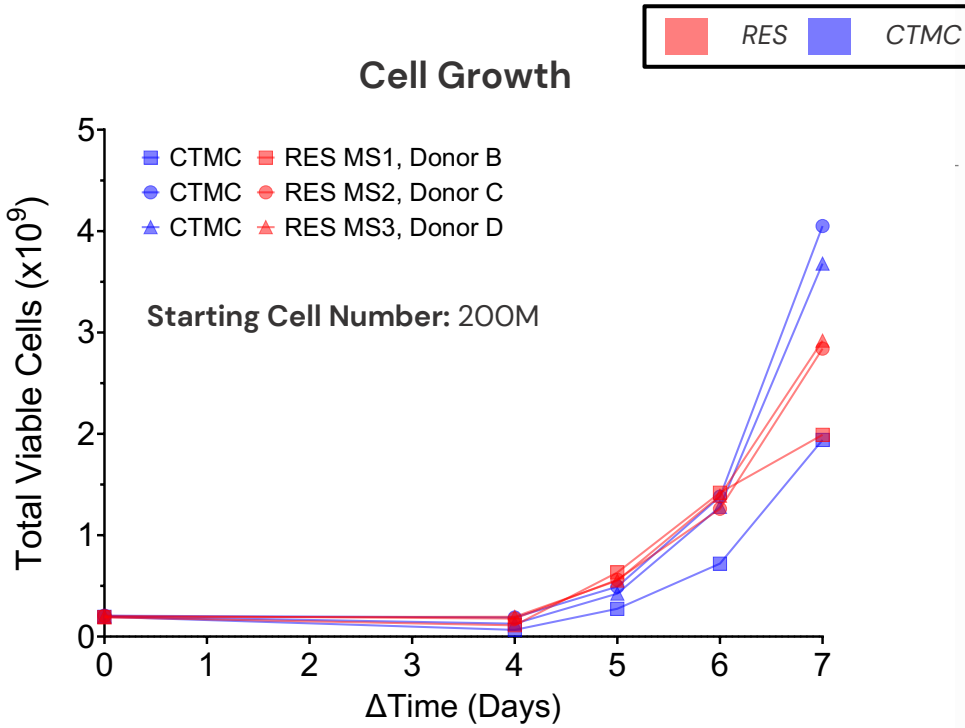
- To generate data for FDA feedback on implementation of the Ori system in clinical manufacturing of a CAR-T product and to evaluate the potential impact of adapting the process to change the culture platform.
- To evaluate the ease of tech transfer and potential impact of manufacturing the product at National Resilience's manufacturing facility.

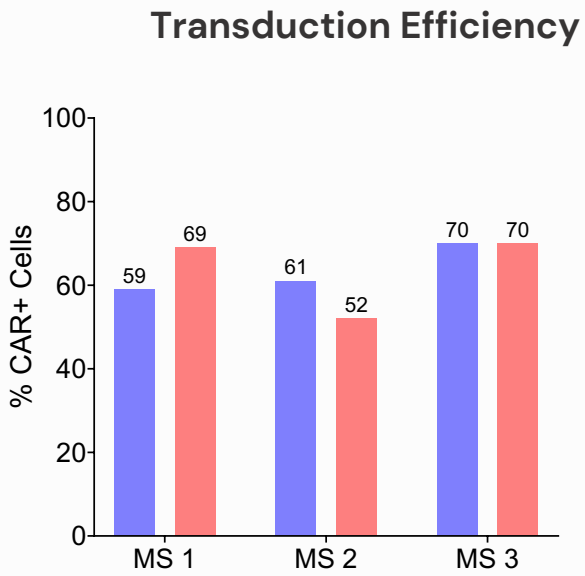
Qualitative Goal	CQAs
High Total CAR+ Yield	Greater than 700M CAR+ cells
High Viability	Greater than 70%
Vector Copy Number (VCN)	Less than 5
High % CAR+ Transduction	Greater than 20%
Phenotype + IFN-γ Secretion	Comparable to current process

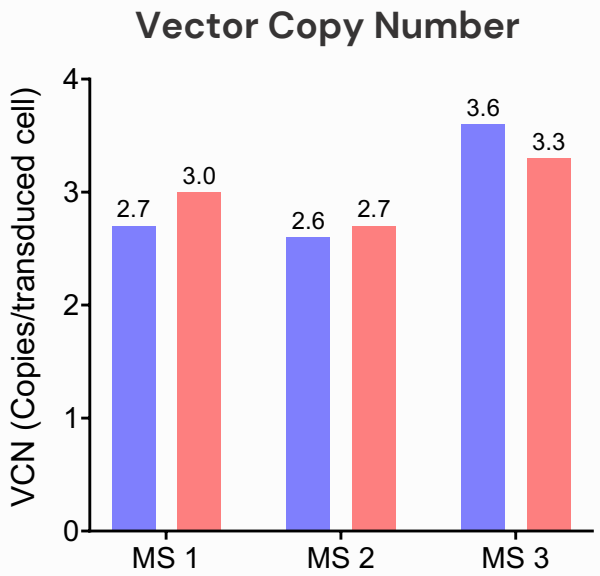
Multisite Manufacturing

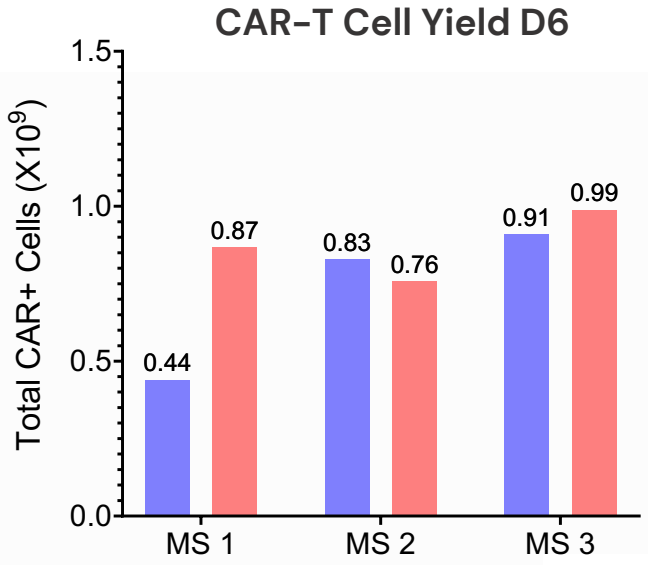
Key Takeaways

- The Ori platform **met all target release criteria by Day 6** across two independent sites with a **protocol establishment time of <2 weeks**
- Post-thaw product **viability was ≥80%** across both sites
- Transduction efficiency averaged well **above target at ~64%**
- VCN **remained below FDA recommended <5** per transduced cell







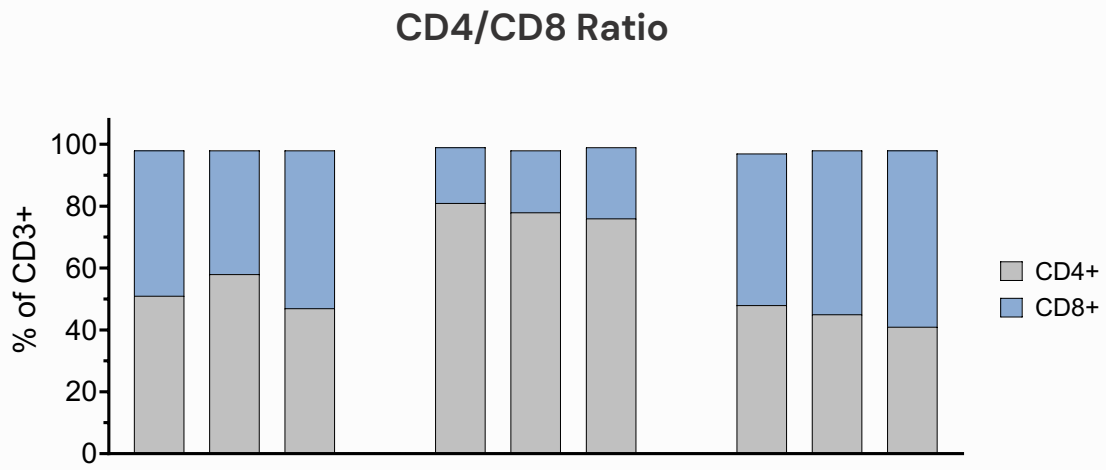


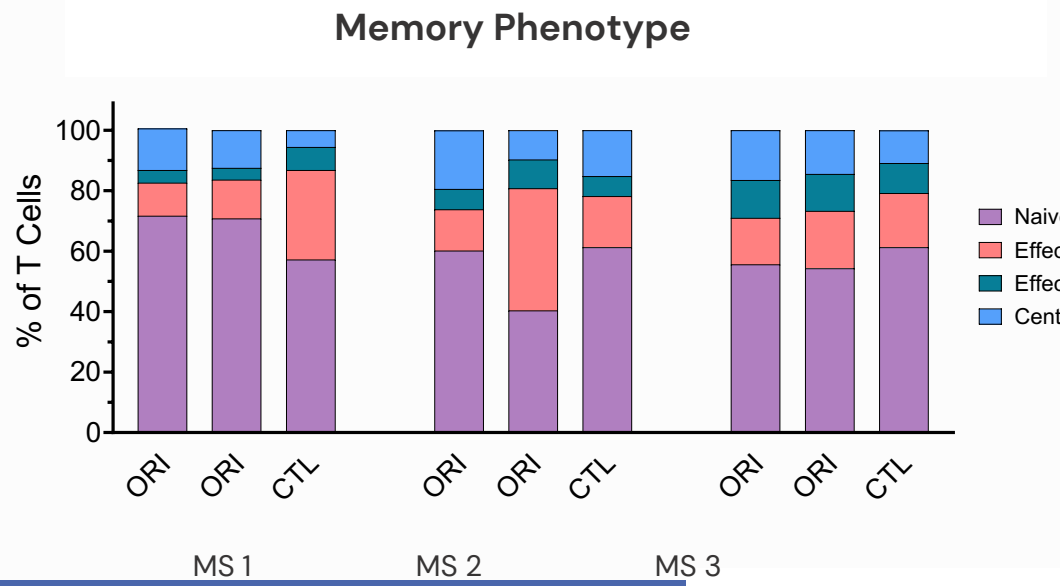
CTMC+

Multisite Manufacturing

Key Takeaways

- The Ori system **met all target release criteria** across two independent sites with a protocol tech transfer time of <2 weeks
- **No trend was observed** in CD4/CD8 composition between sites
- **No trend was observed** in memory phenotype between sites





CTMC+

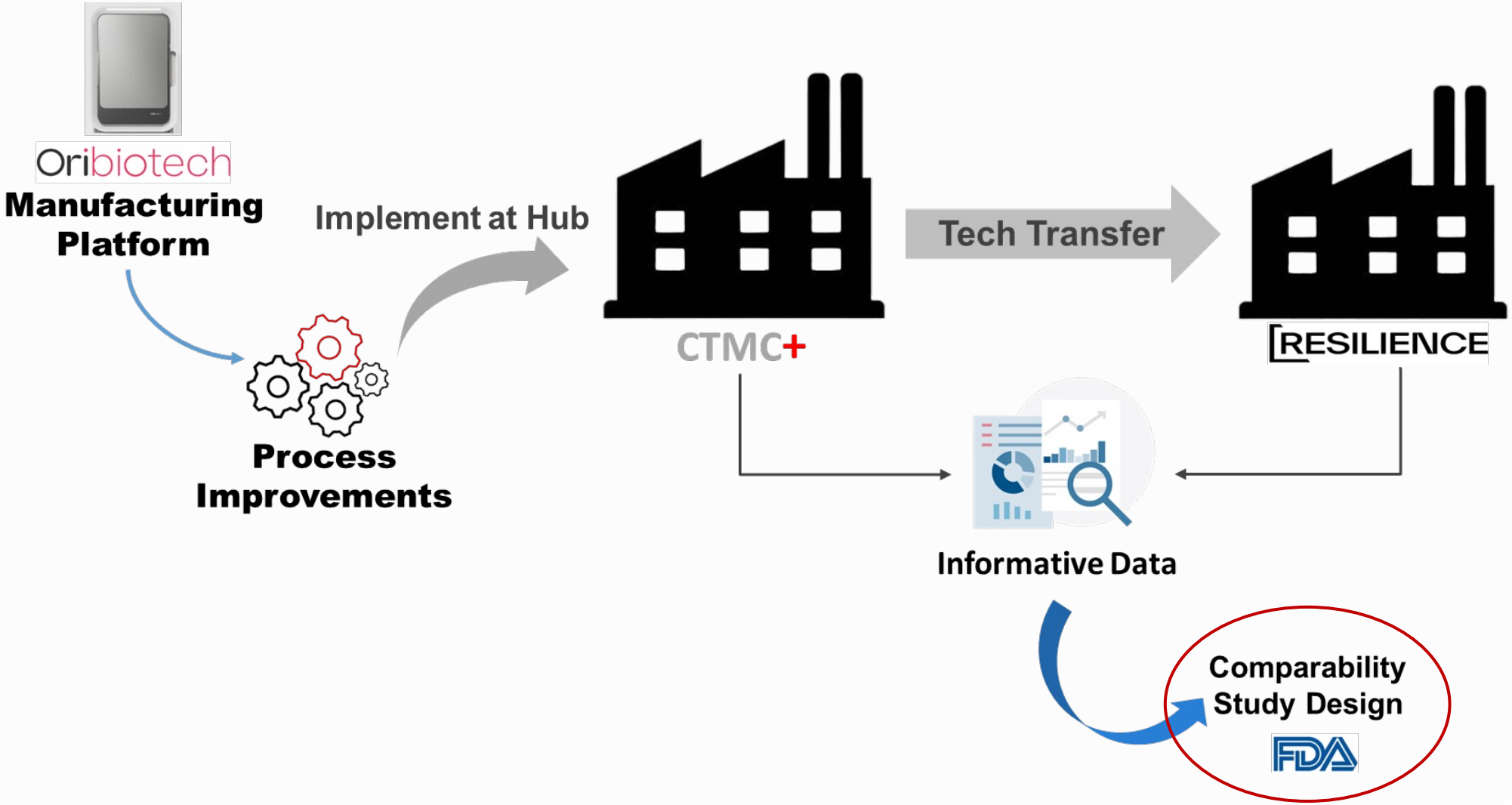
Ori Run Summary

Ori platform demonstrated capability to execute rapid tech transfer and multi-site manufacturing

- Demonstrated fast process establishment times (~2 weeks to transfer from Houston to Philadelphia)
- Faster cell growth and higher transduced cell yields than current clinical process
- Run-to-run consistency in Ori across sites

Qualitative Goal	CQAs	Outcome
High Total CAR+ Yield	Greater than 700M CAR+ cells	Exceeded
High Viability	Greater than 70%	Exceeded
Vector Copy Number (VCN)	Less than 5	Exceeded
High % CAR+ Transduction	Greater than 20%	Exceeded
Phenotype + IFN-γ Secretion	Comparable to current process	Exceeded

Type D Meeting with FDA on Comparability Study Designs



Isolate the Impact of the Changes on Product Quality

Minimize Sources of Variability Not Related to the Changes

Variability in Starting Material

Use of split starting material.

Differences in Testing

Consider testing sites, analytical procedures, qualification status, operators, etc.

Differences in Processing

Consider scale, unit operations, raw materials, equipment, operators, etc.

Variability in Acceptance Margins

Consider variability in historical data.

Confirm Reduced Variability from Automation

Accumulate reproducible and consistent data to reduce risk of tech transfer.

Prioritize the Big Picture, Aim for Overall Comparability

Attributes "Failing" Comparability Acceptance Criteria ≠ Not Comparable

Make Improvements

Optimization is encouraged when making major changes.

Risk Assess and Justify

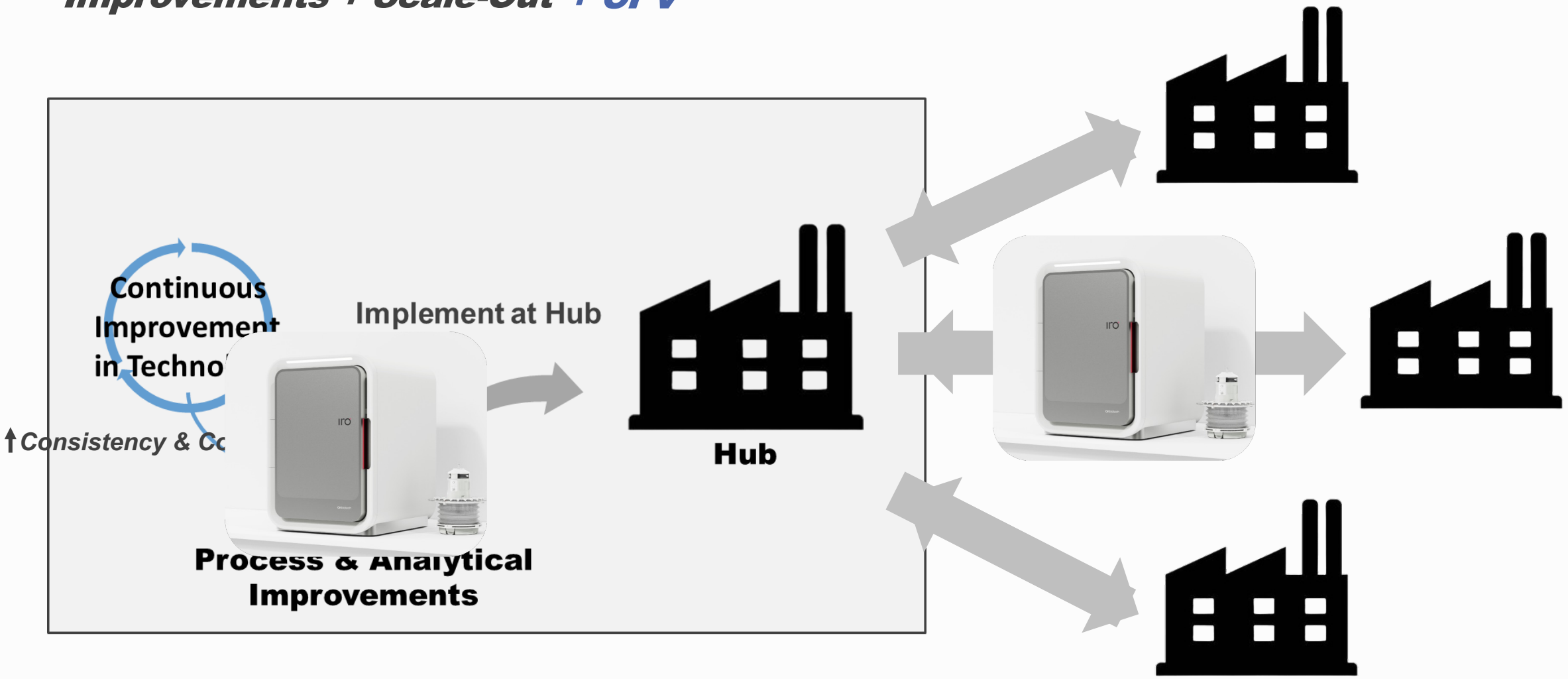
Provide risk assessments and justifications for attributes that fail to meet calculated acceptable limits you feel should not impact the overall conclusion of comparability.

Pool Clinical Data

Clinical data from patients treated with product manufactured pre- and post-change may be pooled if an overall conclusion of comparability is reached.

Key to Maturing the Cell Therapy Field & Improving Access

Improvements + Scale-Out + CPV



Thank you.

www.ctmc.com

CTMC+

The Ori has the Potential to Impact the Cell Therapy Field