Oribiotech

Manufacturing Brighter Futures

Experience IRO® - The New Standard of CGT Manufacturing

September 17, 2024

Boston, MA

Matthew Hewitt

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Charles River Laboratories

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Our mission is to create healthier lives

We currently operate

120+ Facilities **IN** **20+** Countries

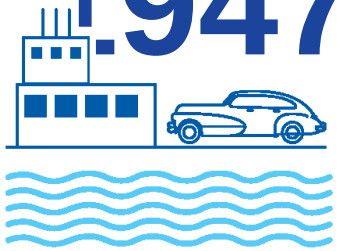
We supported the development of

86%

of novel FDA-approved drugs in 2021

Founded

1947

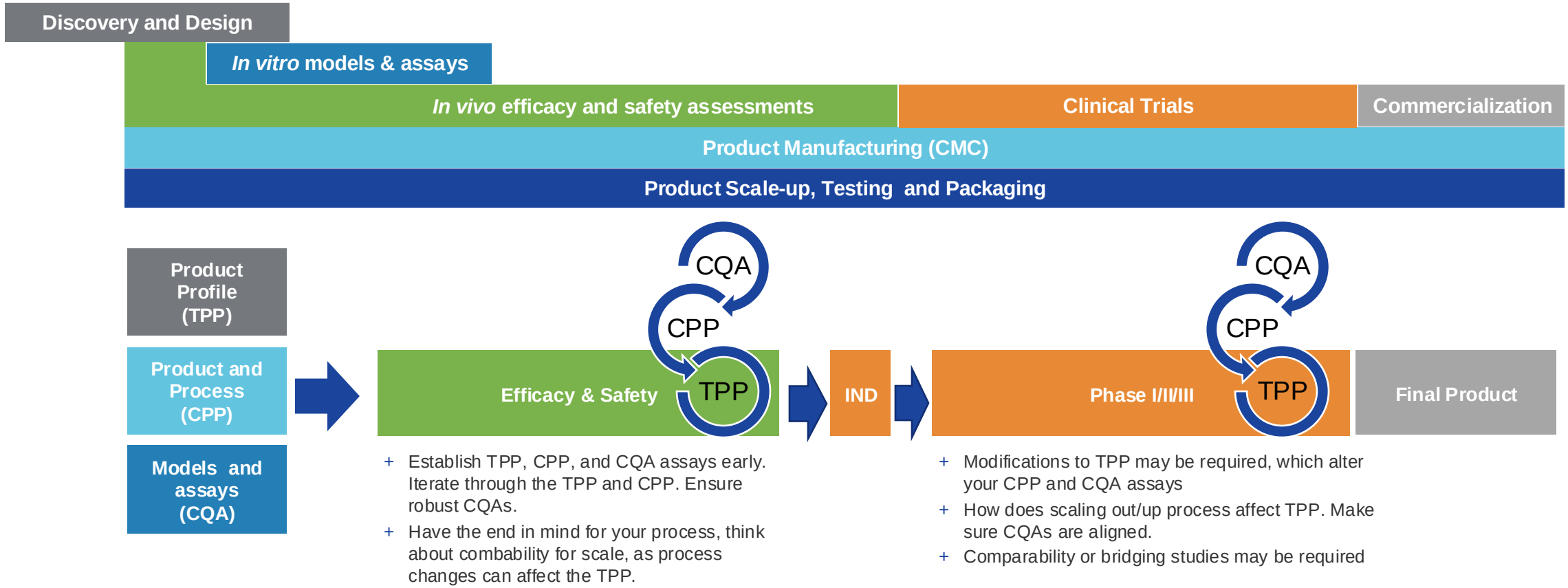


DIVISIONS

- RESEARCH MODELS & SERVICES
- DISCOVERY SERVICES
- SAFETY ASSESSMENT
- LABORATORY SCIENCES
- BIOLOGICS SOLUTIONS (CDMO AND TESTING)
- QC MICROBIAL SOLUTIONS

Interdependencies in CGT

Benefits of Integrated Portfolio



+ Establish TPP, CPP, and CQA assays early. Iterate through the TPP and CPP. Ensure robust CQAs.
+ Have the end in mind for your process, think about combability for scale, as process changes can affect the TPP.

+ Modifications to TPP may be required, which alter your CPP and CQA assays
+ How does scaling out/up process affect TPP. Make sure CQAs are aligned.
+ Comparability or bridging studies may be required

+ CGT assets have significant interdependencies between the TPP, CPPs, and CQAs
+ One partner that can handle the discovery, safety, assay development, process development, and manufacturing creates significant efficiencies as TPP or CPPs change
+ One team, focus on entire project = increased speed, reduce costs

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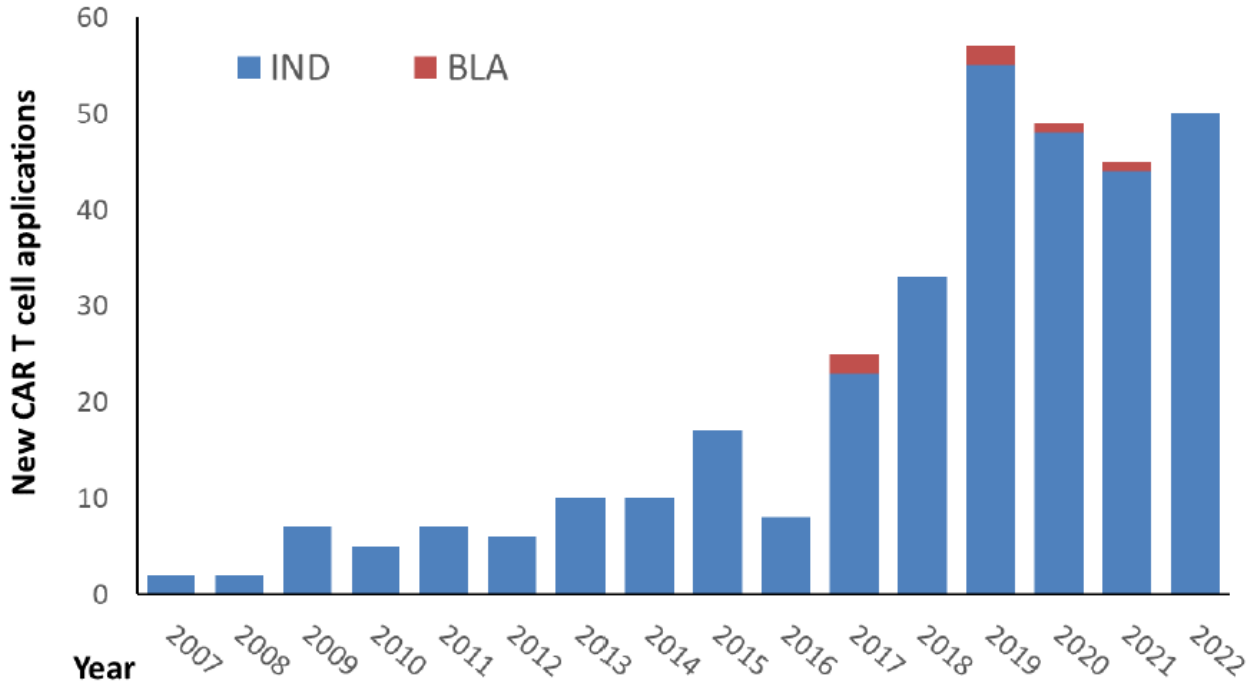
INDs for Cell Therapy Continue to Climb

FDA increasingly signaling they are open to discuss how to increase manufacturing



- Approximately 327 CAR T cell research INDs*
  - 62% are for hematologic malignancies
  - 86% are autologous products
  - >60 antigen targets
- 6 licensed autologous CAR T cell products

- Field continues to expand:
  - New targets
  - New indications
  - New manufacturing strategies
- FDA support:
  - Guidance
  - Town Halls
  - Workshops

Adapted from FDA slides from ISCT NA 2023, Kimberly Schultz, PhD

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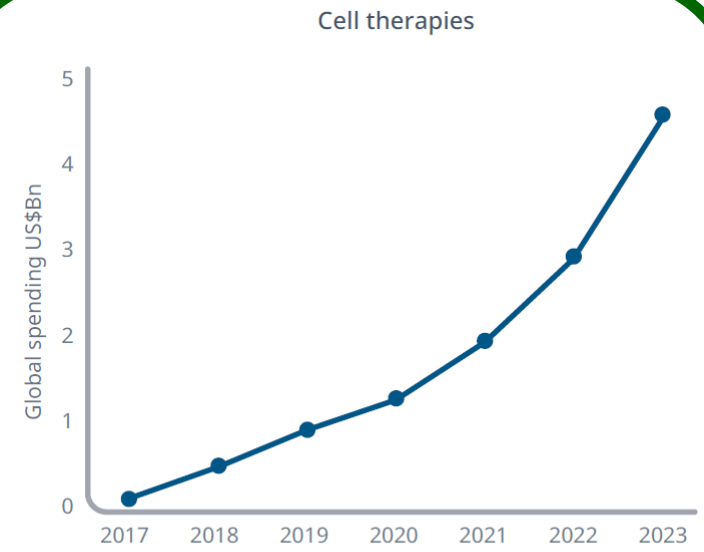
Cell Therapy Demand is Outstripping Supply

Comments from Christi Shaw and an academia-led survey suggests therapies are in short supply

"After 5 years post-approval for diffuse large B-cell lymphoma, even today only 2 out of 10 patients who are eligible are actually receiving the therapy…43% of patients are alive five years after receiving this therapy"



Source: Company Financials; IQVIA Institute, Dec 2023.
Notes: Spending estimates based on company reported sales.

Medscape

News > Medscape Medical News > Features

Patients Waiting Months for 'Last Chance' CAR T-Cell Therapy

Roxanne Nelson, RN, BSN
July 14, 2022

Patients eligible for a Commercial Cell Therapy,

- Six (6) month median wait time
- 25% received a commercial CAR T-cell therapy
- Another 25% enrolled in a CAR-T clinical trial
- The rest (50%) either enrolled in a different type of clinical trial, entered hospice, or died.

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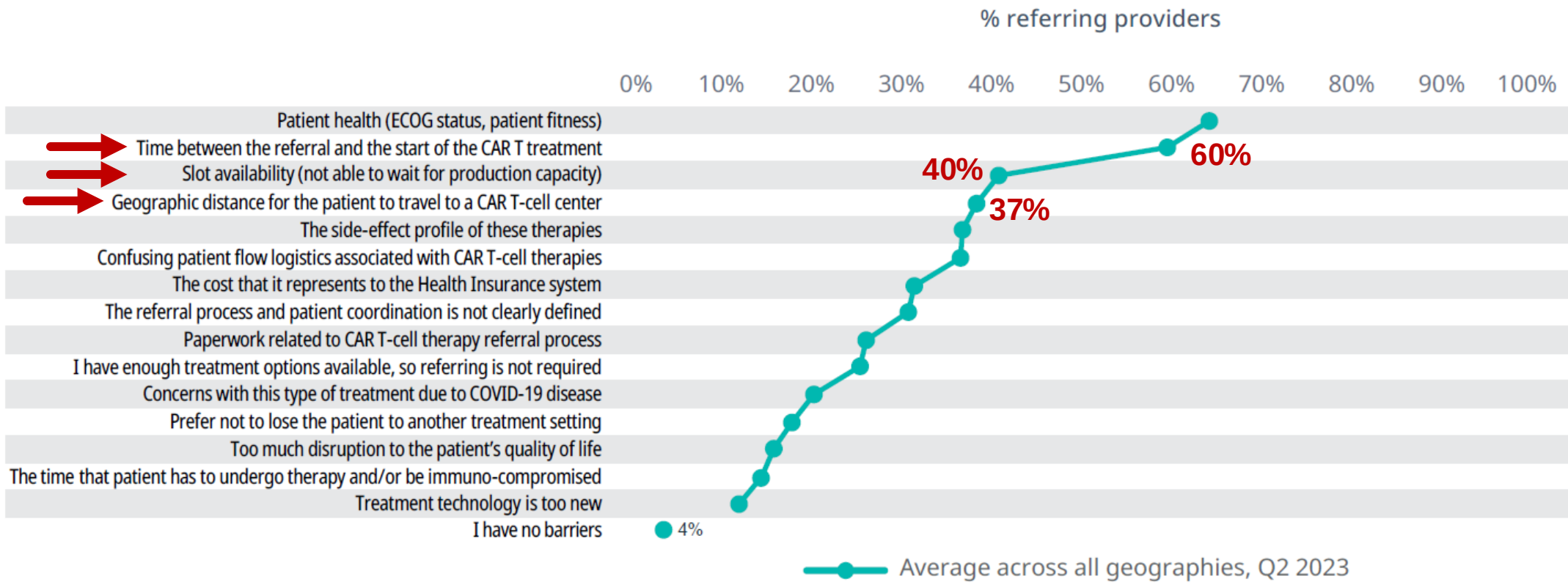
Patient/Provider Barriers to Accessing Commercial CAR-T

Three (3) of the top (4) barriers have links to manufacturing & analytics



Source: IQVIA CAR T-cell Monitor, Jun 2023.

Notes: Share represents providers who rated the barrier as "very" or "extremely" important. Includes providers from Brazil, Canada, France, Germany, Italy, Japan, Korea, Spain, and UK.

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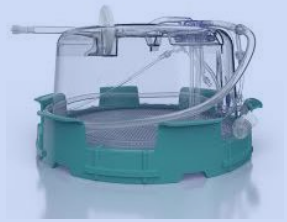
The blending of manufacturing and analytics automation

CRL is examining options for strategically investing in manufacturing automation

Gen 1

Manufacturing



Open, manual processing

Release Analytics

Gen 2

Manufacturing

Closed, automated & scalable processing

Costs ↓ **40%** vs Gen 1

Release Analytics

Gen 3

Manufacturing

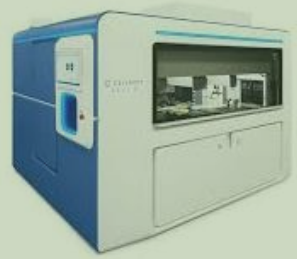
Fully automated in-process sampling

Costs ↓ **50-55%** vs Gen 1

Release Analytics

Gen 4

Manufacturing w/ Integrated Analytics



Costs ↓ **65-70%** vs Gen 1

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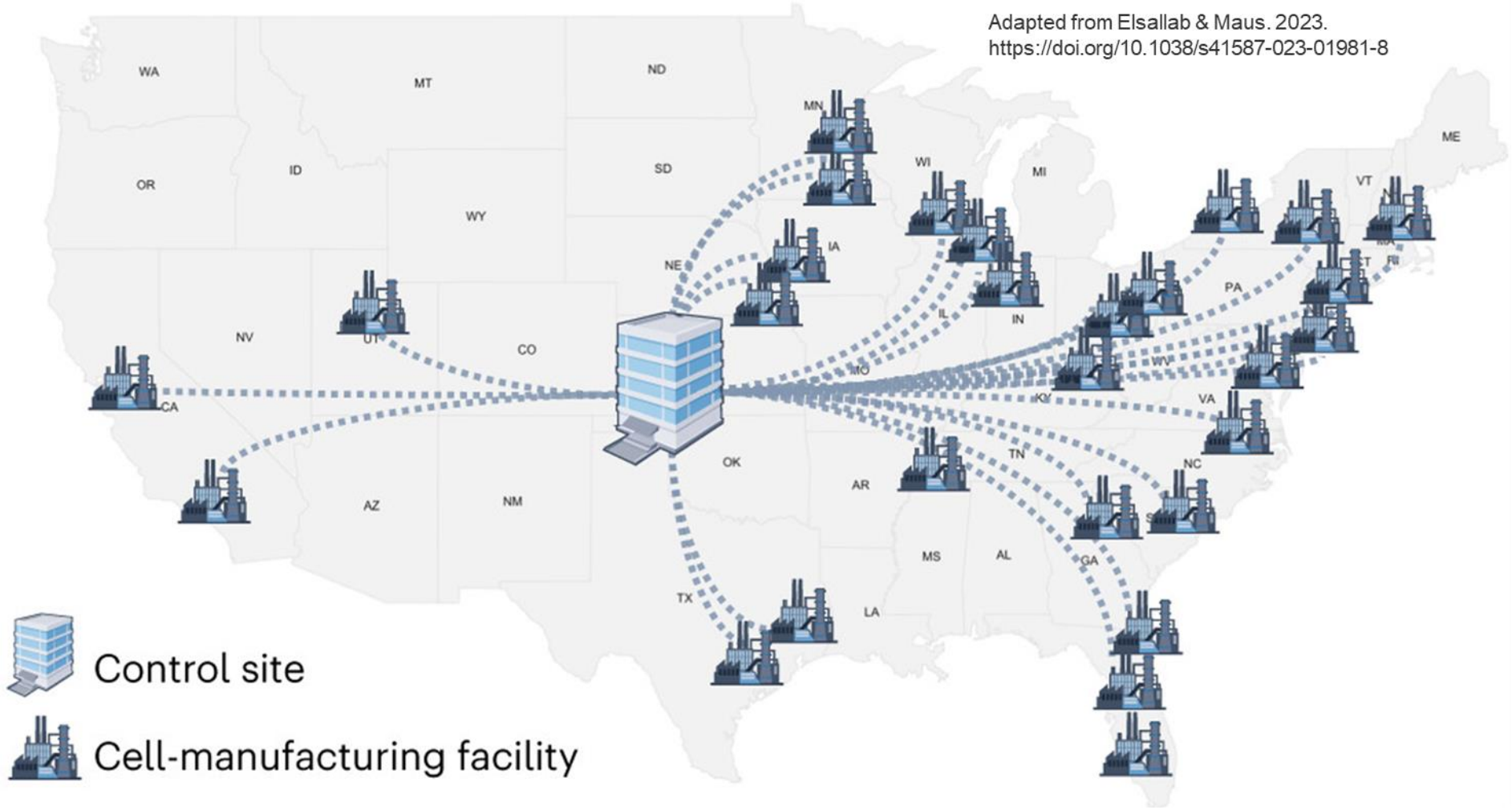
Biggest Changes for CGT CDMO in 5 Years

Decentralized manufacturing is the topic of conversation in the US and EU; FDA/MHRA/EMA are talking about potential structures, CRL is well positioned to step in as a leader



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1st Level

Central Quality Oversight with Aligned Digital Systems

LABWARE Results Count

SAP

pilgrim an IQVIA company

SmartSolve®

APPRENTICE

2nd Level

Duplicate Equipment; Standardized BOE

3rd Level

Standardized Procedures; General Protocol Methods

- Sterility (BacT/Celsis)
- Endotoxin
- Mycoplasma
- Viable Cell Counts
- VCN Platform (qPCR/ddPCR/dPCR)
- ELISA/Ella (Potency)
- Flow Cytometry (BD FACSLyrc, etc)
- Plate Reader

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Workforce Training

A workforce competent in key areas is critical to the success of the CGT field

Move GMP manufacturing from 4-year degree to a trade (i.e. LabCorp)

Exact Instructions Challenge - THIS is why my kids hate me. | Josh Darnit

https://www.youtube.com/watch?v=cDA3_5982h8&t=25s

Key Skills Needed:

1) Gowning in and out of cleanrooms

2) Aseptic Technique

3) Basic Cell Culture

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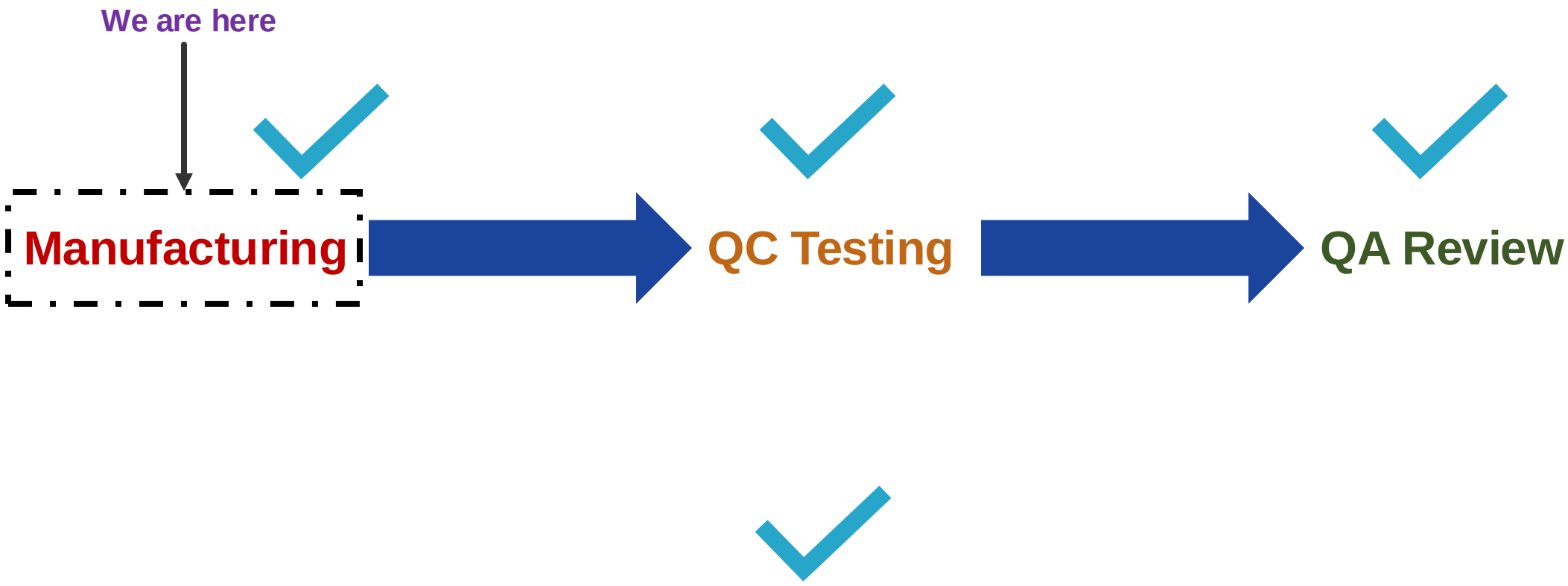
Manufacturing is just 1 Challenge Facing the Field

Must get more proactive on solutions going forward to lower costs and increase patient access



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Scientific Testing of Ori's Platform by CRL

Optimized process using the Prodigy was assessed against the Ori platform using Ori's internal T-cell TransAct™ protocol

Process Overview:

- Ori's internal T-cell TransAct protocol was run against a CRL optimized process (using an industry standard technology) to assess the performance of the Ori platform
- A fresh leukopak was negatively for CD4/CD8+ T-cells on the Prodigy® from three healthy donors and subsequently seeded into the Ori and Prodigy for the three runs. A different donor was used for each run

Process Details:

  - Starting Viable Cells: 300M in 60mL
  - Activation on D0: 0.6mL RUO TransAct
  - Transduction on D1: CD19-LV, MOI = 1.75
  - Culture Medium: TexMACS,™ 100IU/mL IL2, 0.1% Pluronic

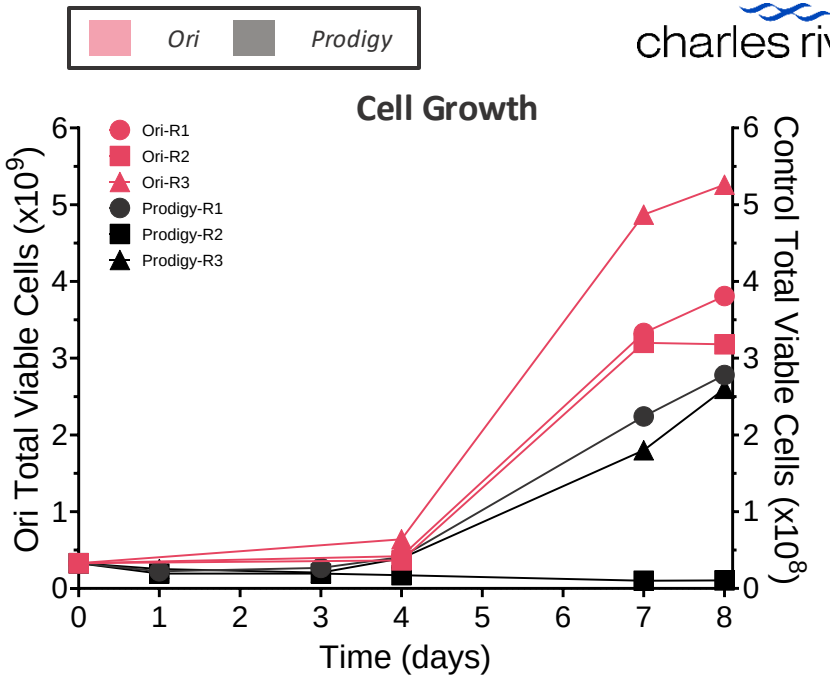
- Multiple samples were taken throughout the process to track cell growth and viability. Flow analysis was performed on final cell product

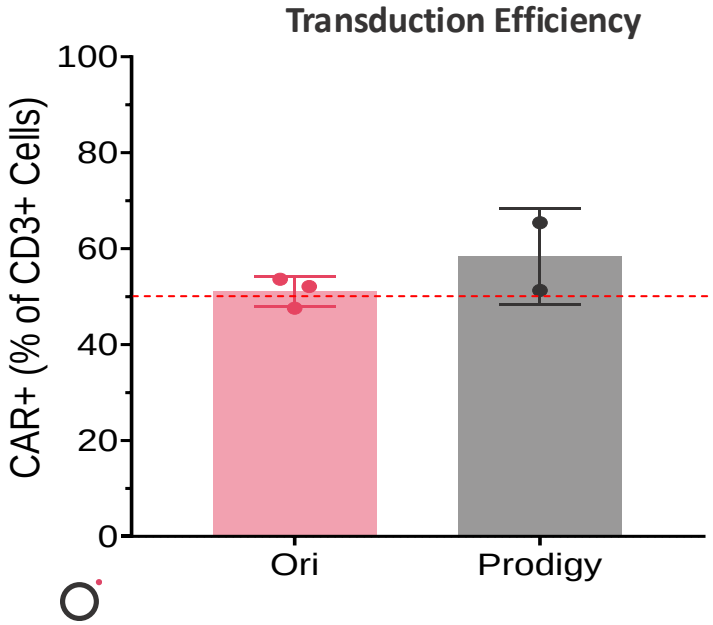
Qualitative Goal	CQAs
# of T-Cells (Ori vs. Control)	> 4B T-Cells
CAR+ Cell Yield	> 2B CAR+ Cells
High Level of Viability	> 90% Viability
Similar Transduction Efficiency	~50%
Similar Phenotype of Final Product	Similar to Current Process

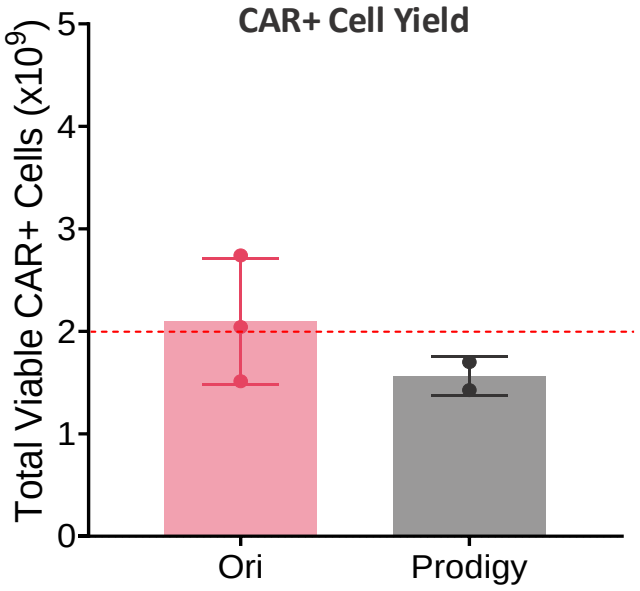
Charles River Prodigy Comparison Runs

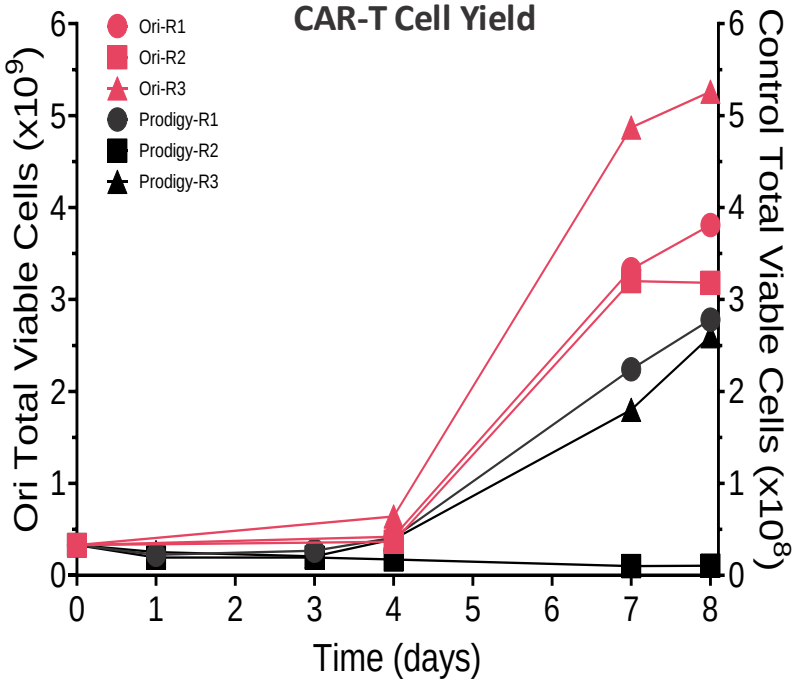
Key Takeaways

- **Ori consistently outperformed the Prodigy control** in both **cell growth and total CAR+ cells**
- Ori achieved an average of 51% CAR+ expression and **2.1B total CAR+ cells compared to 1.6B total CAR+ cells**
- The Prodigy completed only two full runs, **as it had a critical error in run 2**, resulting in the low output shown here









Results Summary of the Scientific Testing of Ori's Platform by CRL

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Ori platform outperformed an optimized CRL process using a standard technology out of the box

Qualitative Goal	CQAs	Ori Outcome	Control Outcome
# of T-Cells (Ori vs. Control)	> 4B T-Cells	Exceeded 1/3 runs (Met 1/3 runs)	All 3 below
CAR+ Cell Yield	> 2B CAR+ Cells	Exceeded 2/3 runs	All 3 below
High Level of Viability	> 90% Viability	Exceeded	Met 2/3 (one critical run failure)
Similar Transduction Efficiency	~50%	Exceeded 2/3 runs	Exceeded 2/3 runs (one critical run failure)
Similar Phenotype of Final Product	Similar to Current Process	Similar	N/A

Ori consistently outperformed or matched the control
on all key metrics out of the box against a CRL process that had been optimized for 2 years

"The test of Ori's new IRO platform using head-to-head process transfer runs shows promising results and provides therapeutic developers another option for manufacturing and helps to address the manufacturing bottleneck challenge."

Matthew Hewitt, B.A. PhD

Vice President, CTO Manufacturing Business Division, Charles River