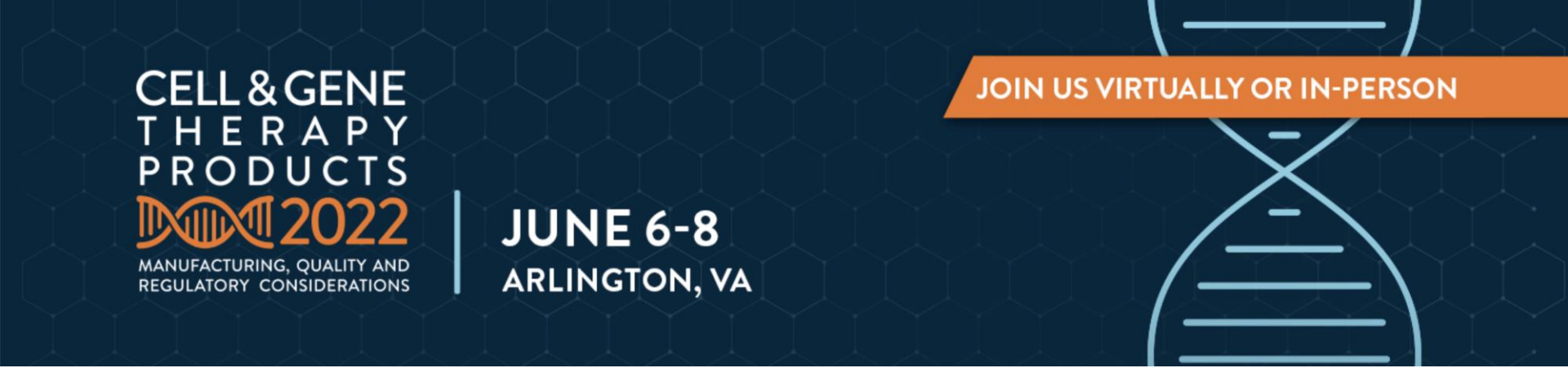

Supply Chain Challenges of Fully Individualized Therapies

Unique Challenges of ATMPs in regards to COI/COC, Patient Safety, Supply Chain Management and Treatment Site Engagement

Andy Case
Genentech, A Member of the Roche Group
06 June 2021

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A Member of the Roche Group

Agenda

- Supply Chain Challenges
- Chain of Identity/Chain of Custody
- Additional Challenges of Highly Individualized Therapies
- Orchestration Systems
- The Need for Standardization
- Lessons learned – things you may not have considered

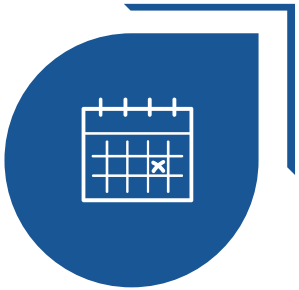
Biggest Supply Chain Challenges for Cell-Based Therapies

Maintaining COC/COI

The supply chain is complex with multiple CDMOs involved, but maintaining COI/COC is absolutely critical for patients.

Long Turnaround Times (TAT)

Having multiple stakeholders around the world can lead to long TATs and longer waiting times for patients.



Scheduling Challenges

Sample collection, pickup, manufacturing, and final product delivery all have to be coordinated and scheduled in specific slots. Missing a slot can be extremely costly (both time and money).

High Variation

Very little standardization currently exists across vendors and customers since we are working with multiple CDMOs and a large number of hospitals across the country.

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Individualized Therapies* present unique supply chain challenges

(*custom made “make to order”; highly specific to an individual patient)

- Patient safety depends on a robust Chain of Identity/Chain of Custody designed with **ZERO tolerance for failure**.
- The patient is the source of the critical (input) material.
  - Patients are inherently unreliable suppliers (dispassionate supply chain view of the world)
  - Manufacturers in this space must deal with upwards of 200 to 300 treatment center supply partners.
- **Standards** for labeling, quality management and product specs are not well established for the tissue samples and cell collections that are the starting (or critical) material.
- Treatment centers are finding it increasingly difficult to deal with all the different Biotech's and Bio-pharma companies in the space.
- Visibility across the supply chain is critical for the treating physicians and treatment teams.
- A single patient journey can pass through multiple CMO’s and integrated manufacturing plants adding complexity to the process.

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Establishing/maintaining COI/COC

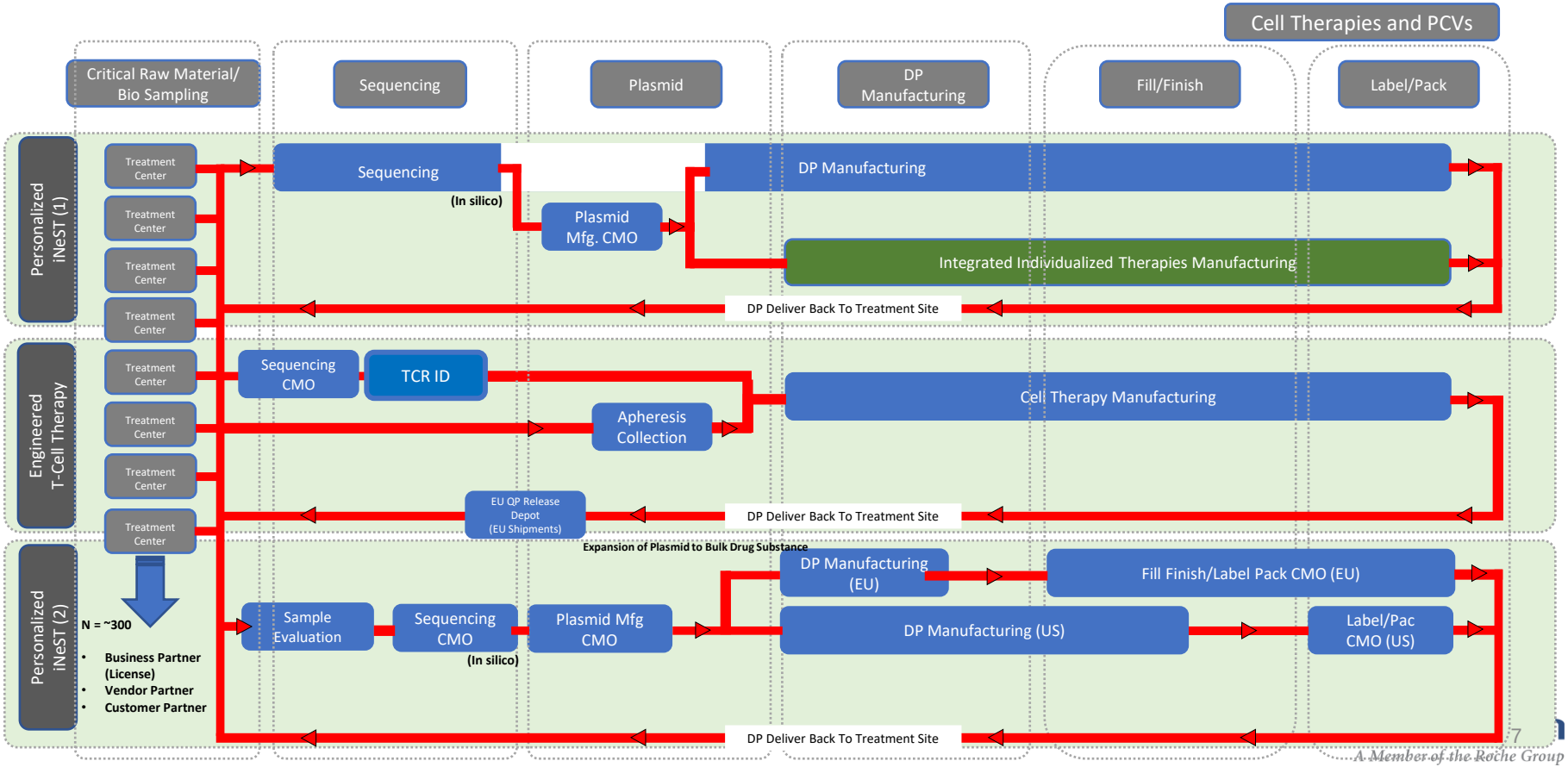
- ZERO tolerance for failure is the only acceptable goal here.
- Also, Health authorities drill deeply into your process during audits.
- System/process validation records will be heavily reviewed.
- The conflict between patient safety and patient data privacy is still being resolved.
  - For Commercial products, full name and date of birth (DOB) are accepted as key COI identifiers for autologous therapies.
  - Certain countries have established extraordinary data storage requirements when patient identifiers are used (France).
  - Use of name and DOB is not currently permitted for clinical batches in the EU, but is accepted in most other countries with active clinical trials.
  - The clinical trial Subject ID combined with an additional unique identifier (separate from the COI ID) is the alternative practice for EU clinical batches.

Special Focus – Challenges presented by Individualized Neoantigen Specific Therapies (iNeST) – individualized mRNA iNeST products

- Complex supply chain coordination
  - Tumor tissue sample.
  - Tissue + reference blood sample sequencing.
  - In Silico output defines custom de novo plasmid (two plasmids per patient).
  - Drug product manufacturing
  - Fill/Finish
  - Drug product returned to treatment center
  - Therapy requires a multi-month treatment regimen (+/- on dose/month over 9 – 12 months)

- Key challenges
  - Coordination of multiple independent complex process steps
  - Throughput time needs to be minimized
  - Multiple failure modes
  - Treatment lifecycle adds to supply chain complexity
  - Immature supplier network
  - Lack of standardization of tumor tissue sampling and identity labeling

Highly individualized therapies at Genentech/Roche increase supply chain complexity



Orchestration Platform Key Scope Considerations

- A robust validated computer system is essential to establishing a Chain of Identity/Chain of Custody process that ensures patient safety maintains control of the therapies from “vein to vein”.

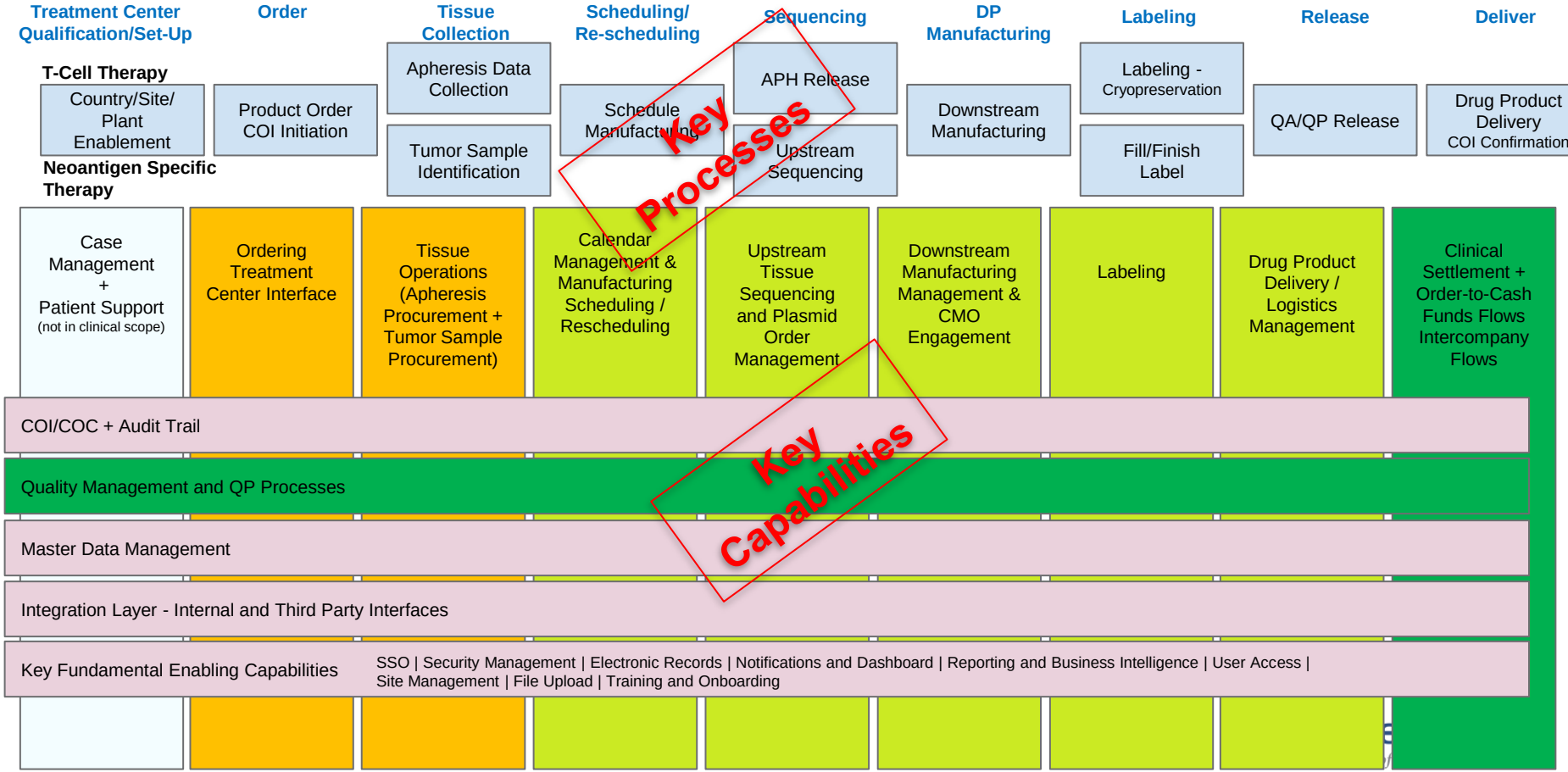
- An Orchestration Platform to support Chain of Identity and the End-to-End business processes for Personalized Therapies can be built incrementally starting with the front end Treatment Center Interface suitable to manage early stage clinical trials. Later stage clinical and the move towards commercial launch requires the implementation of a system architecture that is **scalable, modular, and flexible.**

- Required use of Protected Health Information and associated data security requirements require a very robust master data model as well as user role profile flexibility. Compliance with Title 21 CFR Part 11 and its ex-US equivalents is required and you will be audited on this.

- Robust integration capabilities are necessary as there can be multiple systems in scope which are key sources and consumers of data. i.e. : LIMS, MES, Case Management, Labeling, IxRS

Orchestration System Capability Map

High Level Individualized Therapy Business Process



Orchestration platform architecture – Modular, Scalable, Adaptable

- recognize that development of this platform is never done

Interface to Hospital Partners Chain of Identity

Treatment Center Platform

Capabilities (Views)

- Ordering
- Tissue Collection
- Supply Chain Visibility
- Chain of Identity
- COI Confirmation

Personas:
- Pharmacist/ HCP
- Aph Ctr
- Cell lab
- Patient Operations
- Admin

Integration Internal Orchestration Management

Treatment Management Platform

Capabilities (Views)

- Order Management
- Task Management
- Make to Order Scheduling/Rescheduling
- CMO Engagement
- Quality Management
- Chain of Identity

Personas:
- SC Operations
- Patient Operations
- Quality
- Admin
- CMO

Master Data | Quality Management | Order to Cash

Core ERP System(s)

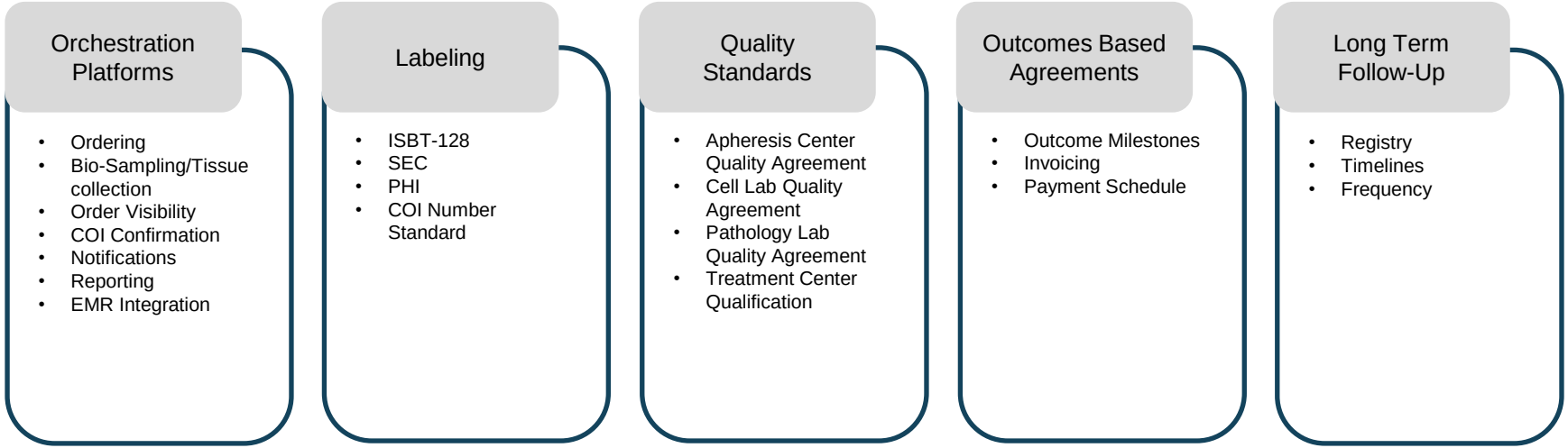
- Materials Management
- Intercompany Flows and Flow of Funds (O2C)
- Master Data Management
- Manufacturing Management
- Tissue/Apheresis Procurement
- Batch Management
- Quality Management
- Chain of Identity

Enabling Systems

- Manufacturing Execution
- LIMS
- Data Informatics

The Call for Standardization in CGT

Treatment sites struggle to manage interactions with CGT developers



The opportunity for differentiation in this space is driven by efficiency and execution - Not through proprietary systems and processes.

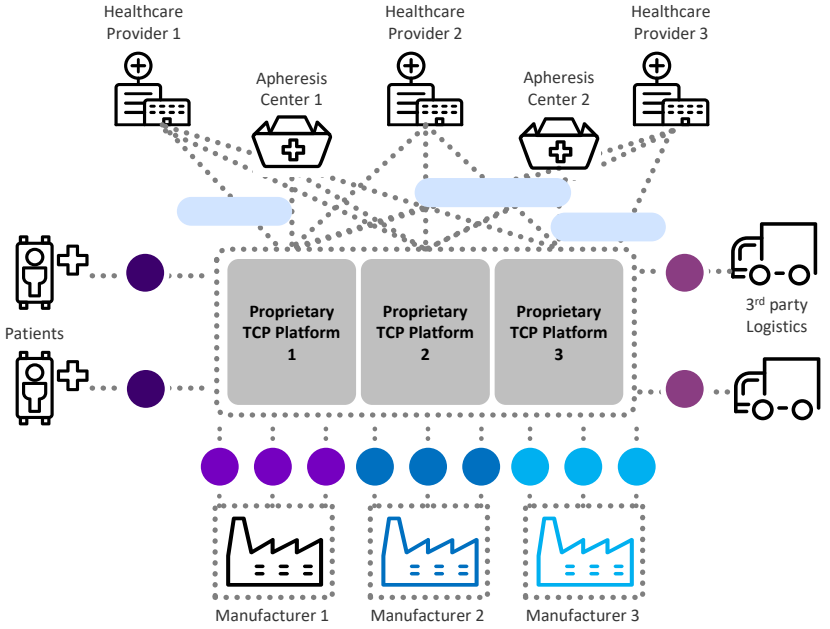
DRAFT

Orchestration Platform standardization vision

Health Care Providers envision a CGT Treatment Center Platform (TCP) that provides a "single front door" access to therapies

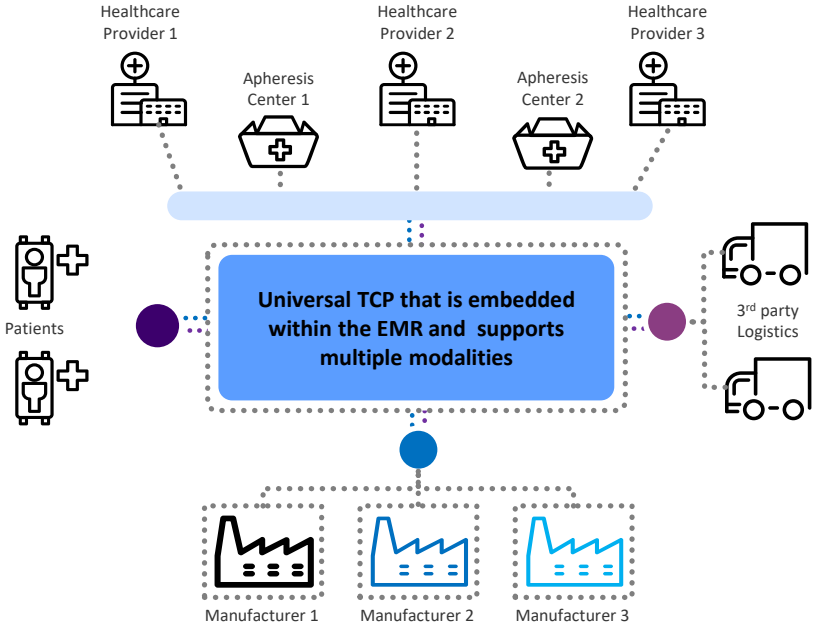
What it looks like for customers today:

Multiple portals, different processes, bespoke solutions



What the future will look like:

"single front door" with simplified experience



What are some lessons learned?
What are drivers of complexity to watch out for?

If systems are too rigid, unexpected events create added complexity

Out of Spec Product

- Convert from Commercial product to clinical (Single use IND)
- Shipment of a second dose in a single dose therapy.
- Ship as commercial product for issue credit memo for OOS.
- Ship expired product.

Apheresis Collections

- Split aph collection and hold for possible second manufacturing run.
- Cell lab change after order placed in system.
- Process second collection without cancelling initial order.

Financial Changes

- Commercial order reclassification (change to free of charge after order initiated).
- Ship drug product to different treatment center.
- Outcome Based Agreements – different milestones and payment scenarios by country.

Dosing and Subsequent Deliveries

- Combine available doses for dose optimization.
- Ship a second dose when first dose was in spec.
- Product damaged at treatment center after receipt – ship an available second dose.

Unplanned Supply Chain Events

- Change Ship-To after order entered and confirmed.
- Ship multiple doses in the same delivery.
- Ship drug product to different treatment center after order created (sometimes in a different country).

Other misc.

- Order cancellations – up to 50 different cancellation scenarios.
- Shipping prior to release.
- Second apheresis collection after first collection fails QA.

Are your systems designed to prevent these occurrences in the first place?

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Thank you

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