Addressing Variability in Cell and Gene Therapy Manufacturing

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Exploring Sources of Variability Related to the Clinical Translation of Regenerative Engineering Products – A Workshop
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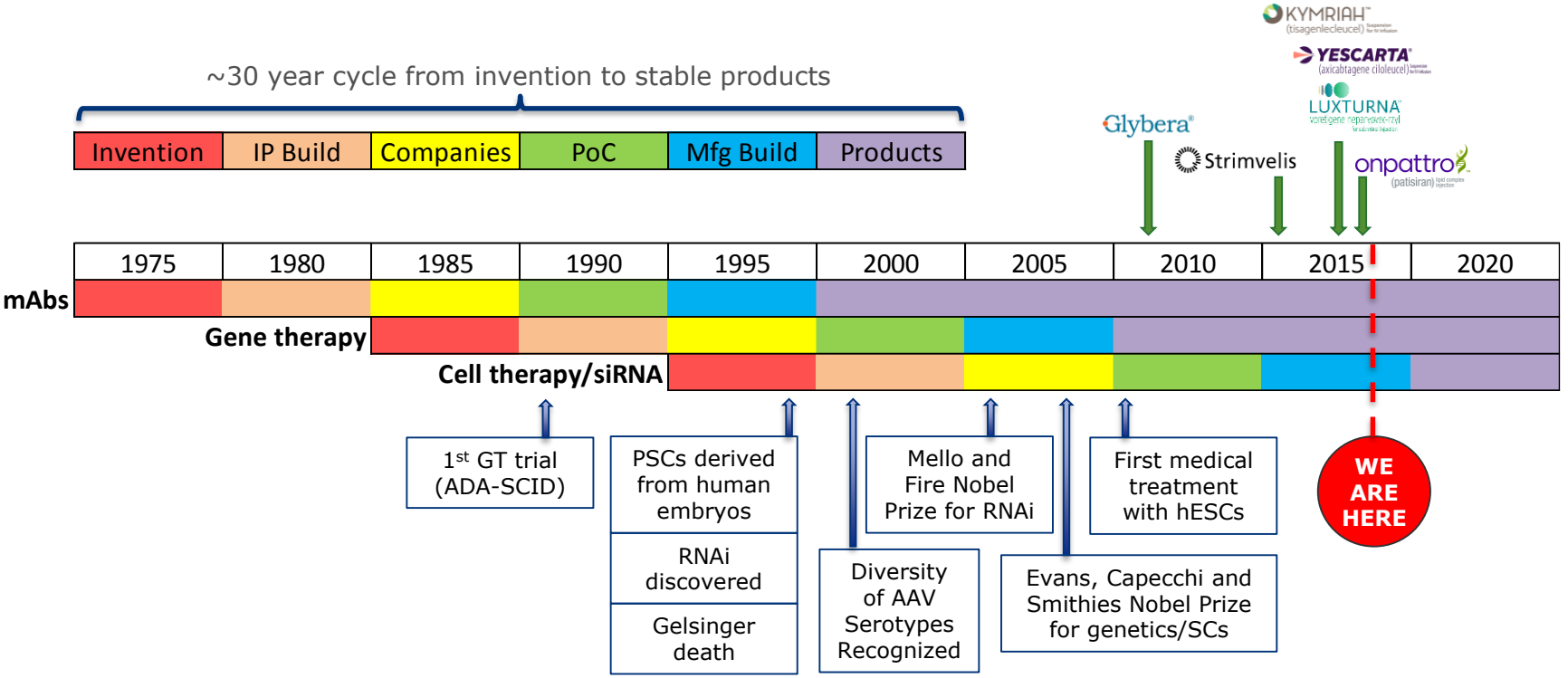
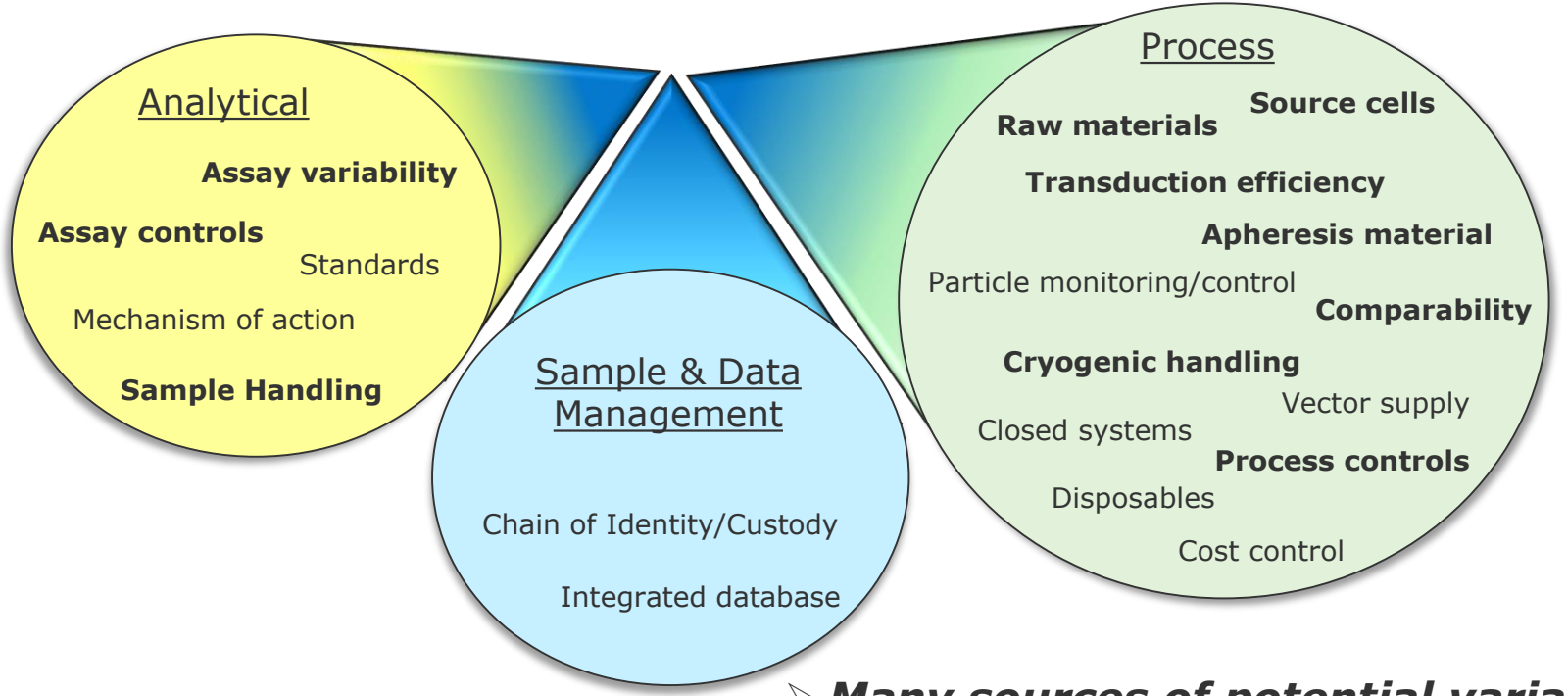
Transformative Drug Discovery Technologies



http://www.ddw-online.com/business/p97055-the-timetable-of-inventionsummer-06.html

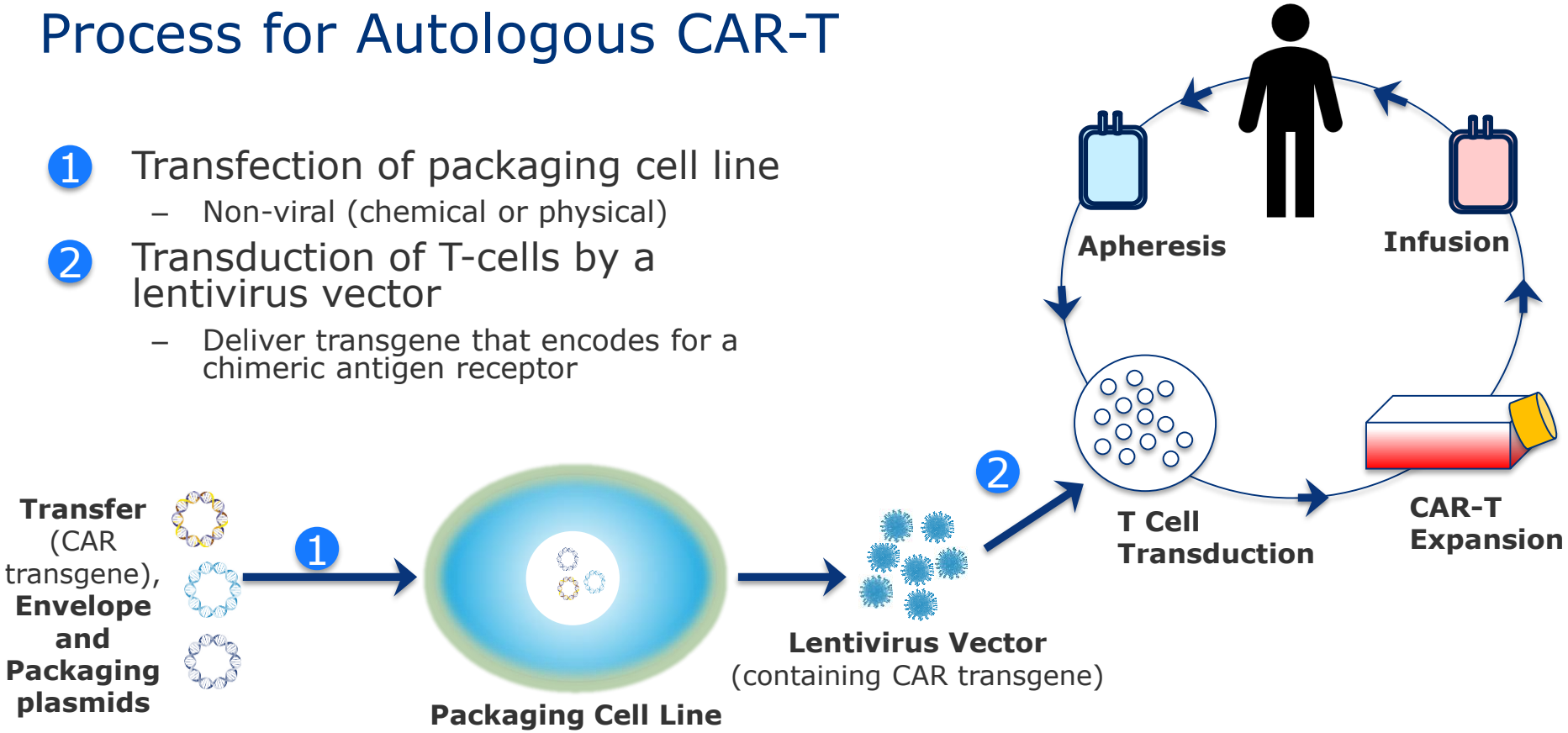
Challenges for Cell and Gene Therapy as a Developing Technology



➢ ***Many sources of potential variability***

Process for Autologous CAR-T

1. Transfection of packaging cell line
   - Non-viral (chemical or physical)
2. Transduction of T-cells by a lentivirus vector
   - Deliver transgene that encodes for a chimeric antigen receptor



The Process is the Product, or is it?

- With high complexity, standardization of the process can help to control variability early in development with limited process and characterization experience
- A tightly controlled process will benefit allogeneic cell production using the same input materials (e.g., cell bank)
- Variability of autologous input material may necessitate adjustments (within the defined process envelope) to achieve the appropriate cell expansion and cell populations

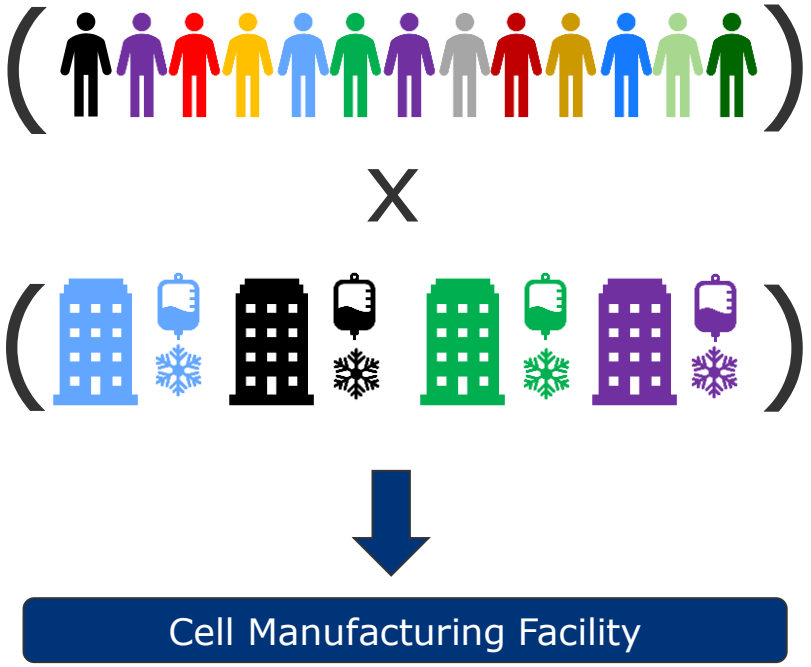
➢ *Process control, knowledge of CQAs & CPPs are critical*

Assessment of Variability is Complicated by …

- Limited quantities of different lots to compare
  - Sample size and number of variables affect statistical certainty
- Absence of a platform and standards
- Repeated process changes in early development
  - Including equipment and materials
- Different sources of input materials

Apheresis Variability - Autologous Cell Therapy

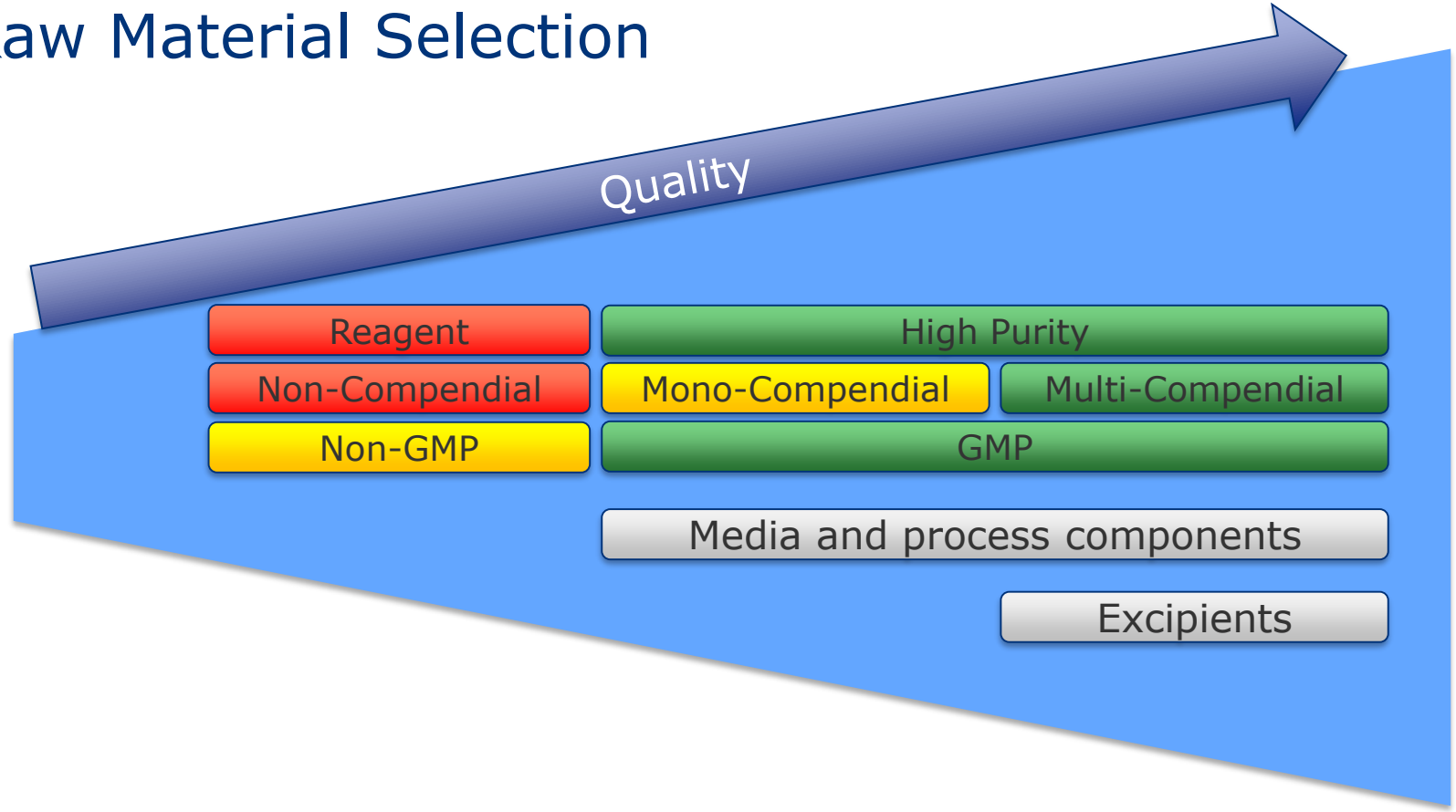
- Limited quantity
  - Affect final product yield
- Differences in patients
  - Individual uniqueness
  - Health state
  - Treatment history
- Different facilities
  - Equipment
  - Collection processes
  - Freezing techniques



Reasons for Variability in Raw Materials

- Many new materials are needed for a new technology
- Limited experience with manufacture
- Changes during process scale up for RMs
  - High demand industry-wide
- Inconsistency from different sources
  - More vendors entering the marketplace
- Transition from research grade to GMP
  - Not always smooth – avoid, if possible

Raw Material Selection



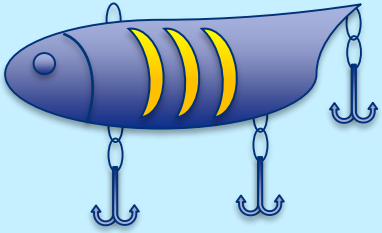
Raw Materials – Grades and Attributes

R&D
ACS
NF
USP
GMP
JP
EP
ChP

The Lure of Non-GMP Excipients

Readily Available

Lower Cost



Inadequate Documentation

Insufficient Change Control

Batch-to-Batch Variability

Investigations & CAPAs

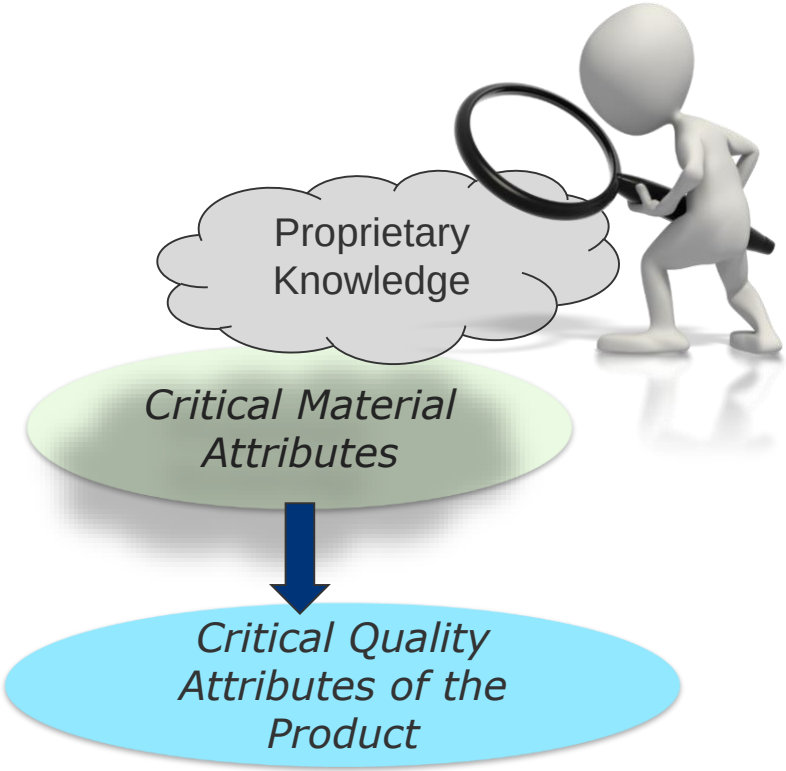
GMP Materials

- Controlled equipment and manufacturing process
- Defined and consistent procedures
- Documentation of process and testing
- Not necessarily compendial

Enables understanding of the impact of CMAs on the product CQAs, especially when issues arise

Raw Materials - Knowledge

- Novelty (both supplier and developer)
  - Limited experience with custom items (e.g., custom tubing sets and media)
  - Quality and manufacturing consistency
- Proprietary knowledge of components and processing
  - Unknown RM attributes may hamper development and correlation to the cell process and analytical performance
  - Unable to provide input into control of the RM process or attributes
  - Impacts ability to assess process removal or associated risks of residuals
  - May hamper process investigations



Control of Variability in Raw Materials

- Vendor partnership
  - In-coming source material screening at vendor
  - Process control
  - Notification of process changes
  - Release testing (avoid selection of particular lots)
- In-coming testing requirements
- May remediate certain components in the product process, if needed (e.g., supplementation)

➢ *Focus of implementation of GMP*

Raw Materials – Critical Components for Cell Therapy

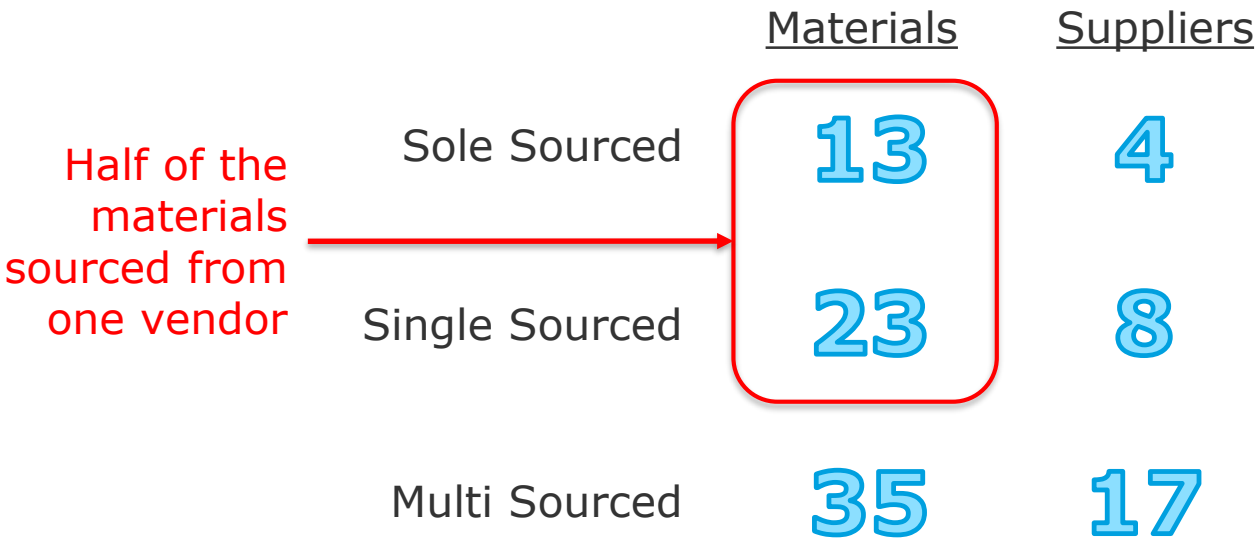
- Cell and cryopreservation media
- Transduction (esp. plasmids)
- Activation materials (e.g., CD3/CD28 beads)
- Isolation materials (e.g., CD4/CD8 beads)
- Consumables
  - Flasks and single-use kits
  - Sole supplier or customized sets limit sourcing options

- ➢ Limited access to pharmacy grade materials outside of hospital settings
  - Restricted use for research compared to commercial development
- ➢ Strategic collaborations with suppliers needed for unique components
  - Sourcing and quality agreements

Raw Materials - Sourcing

- Sole source
  - Only one supplier available (e.g., media)
  - Availability may be limited
- Single source
  - More than one supplier available but others not qualified or suitable
  - May not be different from sole sourcing if knowledge is low to compare vendors
- Cost of goods
  - Order volumes may be low and need to be priced accordingly
  - Sole sourcing and proprietary compositions may limit cost competitiveness

Phase 3 Raw Material Sourcing for an Allogeneic Cell Therapy



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Thank you

Questions?

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