Localization and Technology Transfer of CAR-T Cell Therapies

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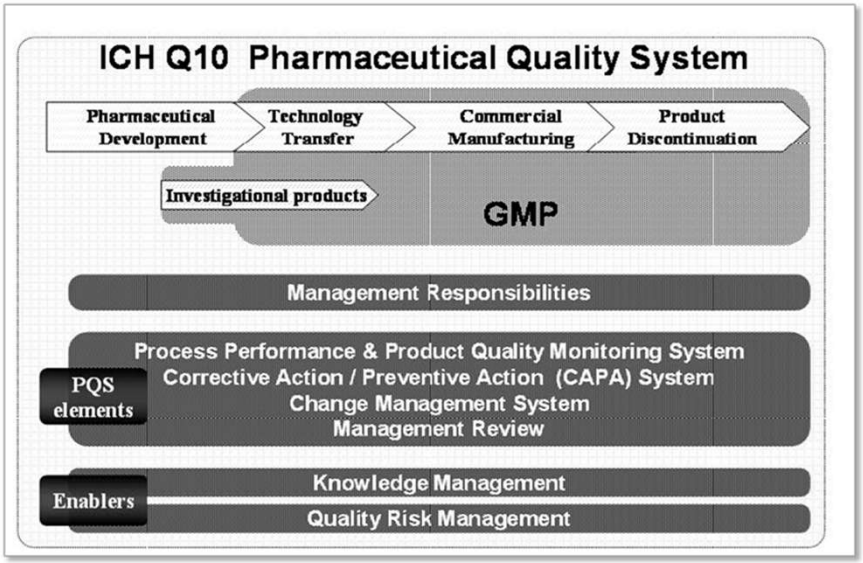
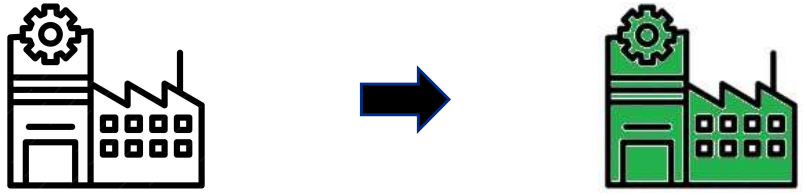
Technology Transfer

- "...transfer product and process knowledge between development and manufacturing, and within or between manufacturing sites to achieve product realisation."

  ICH Q10 - Pharmaceutical Quality System





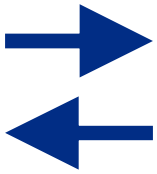
Sending Unit (SU) **Receiving Unit (RU)**

Establishing manufacturing and analytical capabilities in a second setting, to allow production of equivalent products at each site.

Conventional Technology Transfer Steps (I)

Sending Unit (SU)

- Process flow diagrams
- Batch records, SOPs
- Process qualification reports
- Analytical methods, specifications
- Analytical method qualification reports
- Bill of materials, suppliers
- Process development reports
- Regulatory documents
- Training records
- Change control
- Deviation reports



Receiving Unit (RU)

- Questions for SU, for example:
  - Total n of development and mfg runs? Process failure rate and root causes of failure?
  - How many variant manufacturing pathways have been defined?
  - What triggers a variant pathway, and how is this decided?
  - How often is a variant pathway needed? How many products made using each variant pathway?

Conventional Technology Transfer Steps (II)

- Risk assessment. Risk-based priorities for manufacturing and analytical development.
- Technology transfer and development plan
- Draft and review SOPs, template batch record(s), and other documents needed
- Materials sourcing and qualification, supplier qualification. Acquire and qualify any needed equipment.
- Development run(s). Sampling plan. Training run(s). Analytical method development (especially potency).
- Engineering run. Debrief, engineering run report. Additional development/engineering runs as needed
- Analytical method qualification. Process set. APS runs.
- Document review, sign-off MBR and other GMP documents, other prep for PQ runs and GMP operations.
- PQ runs
- Technology transfer report

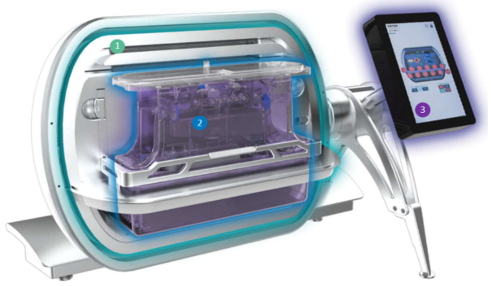
Challenges in Technology Transfer of Cell and Gene Therapy (CGT) Products

- Complex manufacturing processes and analytical methods, limited standardization
- Variability in cellular starting material
  - Especially for autologous products
- Incomplete understanding of product and process (i.e., Critical Quality Attributes and Critical Process Parameters)
  - Particularly at early stages of development and when transferring from academic institutions

Technology Transfer in Decentralized Manufacturing of CGT Products

- Decentralized manufacturing requires significantly automated manufacturing
- Details of technology transfer will depend on extent and robustness of automation

Miltenyi Prodigy



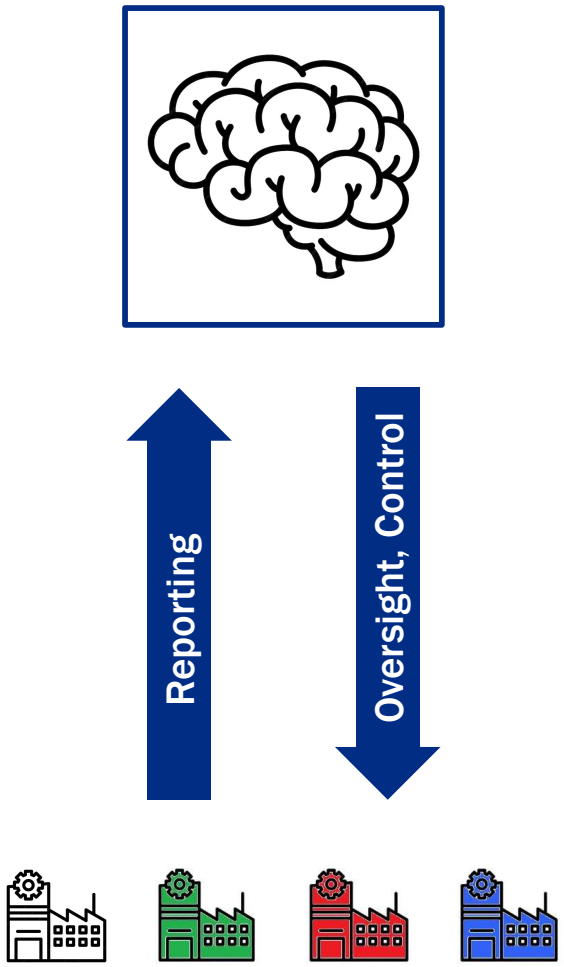
Lonza Cocoon

Cellares Cell Shuttle

Comparability as Part of Technology Transfer

- Comparability will be crucial for decentralized manufacturing
  - Mitigate risk of multiple manufacturing sites by including comparability when completing technology transfer and then at regular intervals for all sites
  - Reference standard (or standards) will be essential.
    - Establish in-house standard as soon as possible. Retains will be more important than ever.
  - Central reference site to serve as the comparability baseline, rather than comparing an existing manufacturing site with the new site.
  - Single reference lab likely preferable for QC testing, but shipping conditions and durations must be rigorously controlled.

Proposed Approach to Decentralized Manufacturing Tech Transfer and Control



Reference/Control Site

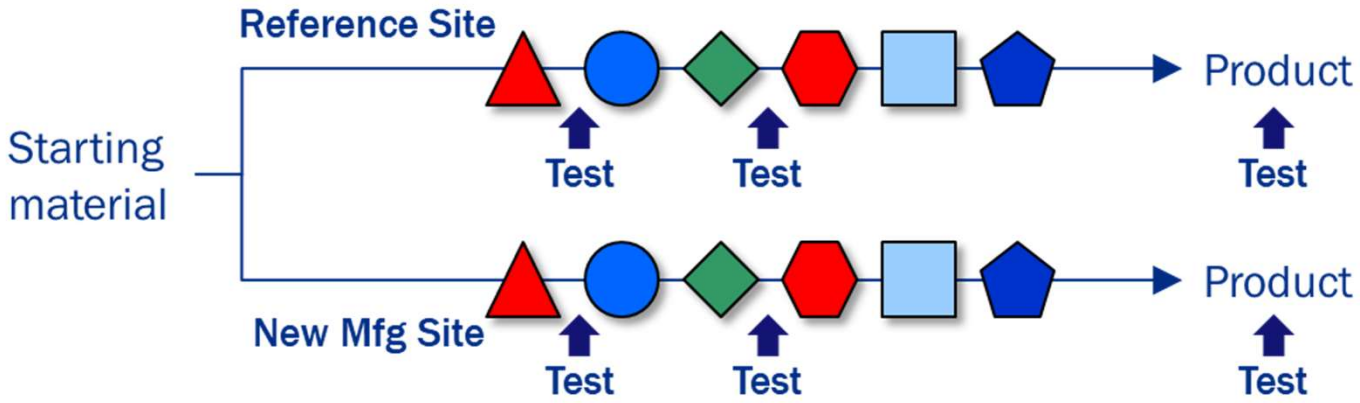
- Set up new sites, oversee tech transfer, PQs, training, materials/vendor qualification
- Comparability oversight and reference site
- Repository for reference standard(s), retains, reports
- Audits, oversee deviation investigations
- Informatics system
- Regulatory submissions
- Master File

Manufacturing Sites

- GMP manufacturing
- QC testing for release (alternatively, central/several QC testing lab(s), depending on distance)
- Deviation reporting to reference/control site

Comparability Study Design

- Split-source study design to address variability of cellular starting material



  - Paired difference analysis of data
  - Potential for artifact due to reduced number of cells

- Ideally, cellular source material should be the same as normally used in manufacturing, but supply of patient cells may be limited
  - May use cells from healthy donors or, if necessary, perform small-scale manufacturing runs. Include justification in study protocol and report.

Analytical Methods

- Release testing and in-process controls are *not* sufficient for comparability
  - Test quality attributes not routinely measured, *in addition to* lot release testing and in-process controls
  - Use additional well-controlled analytical methods
  - Orthogonal methods increase certainty, especially orthogonal potency measures
- Perform testing consistently
  - Side-by-side testing (testing pre- and post-change samples in the same experiment)

    OR
  - Analyze all samples using same analytical method performed at the same testing facility
- Use reference material -- in-house standards

Summary

- Technology transfer of CGT products presents unique challenges. CGT tech transfer in the setting of decentralized manufacturing requires further adaptation of tech transfer strategies and an especially rigorous approach.
- Using a single control/reference site for all tech transfers provides a consistent baseline and reduces risks associated with tech transfers between multiple decentralized manufacturing sites.
- Performing comparability as the final step in tech transfer mitigates risk by providing greater assurance of successful tech transfer than PQ runs alone.
- A split-sample study design, between the control/reference site and the new manufacturing site, is an effective way to perform comparability in decentralized manufacturing.

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