Cell Therapy Technology Transfer Approach and Challenges

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Disrupting the cell and gene therapy (CGT) industry

Our Vision

ElevateBio was **founded** in late 2017 to enable the entire biopharma industry to maximize the potential of cell and gene therapies

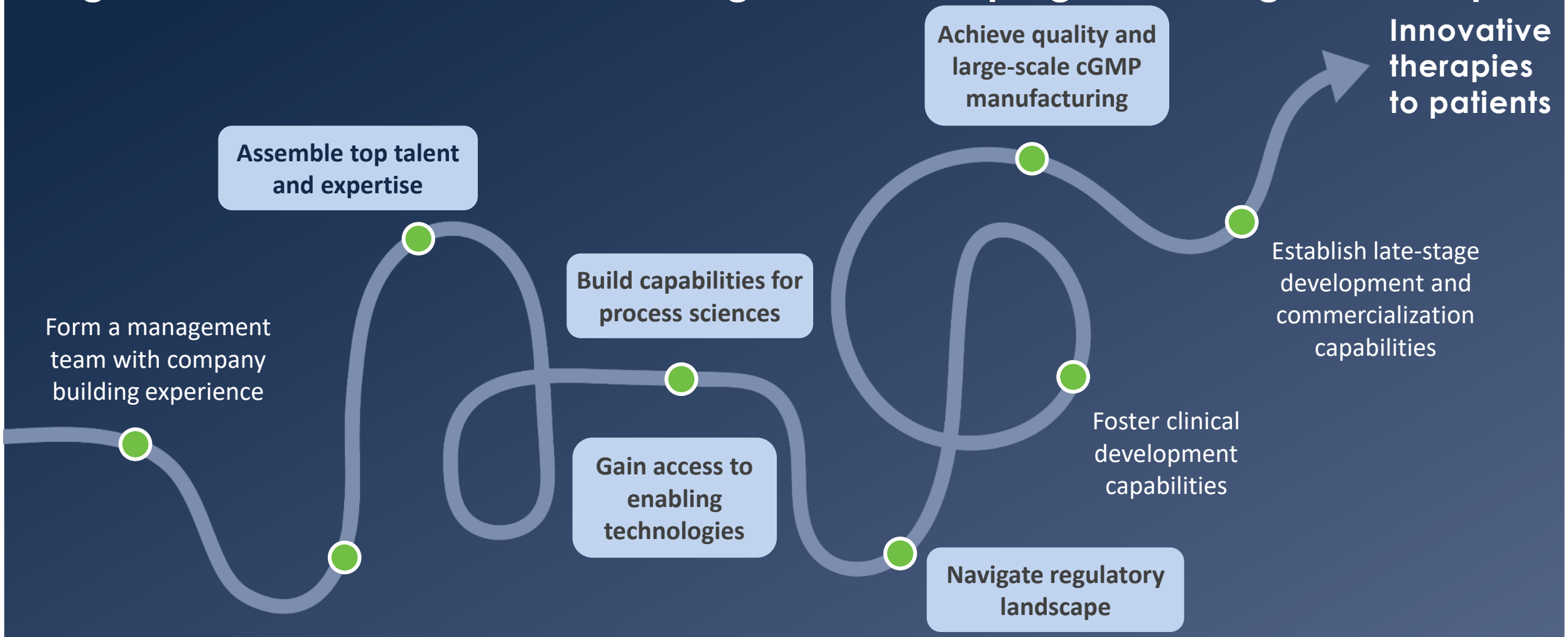
Our Mission

Our mission it to **power** cell and gene therapies forward by:

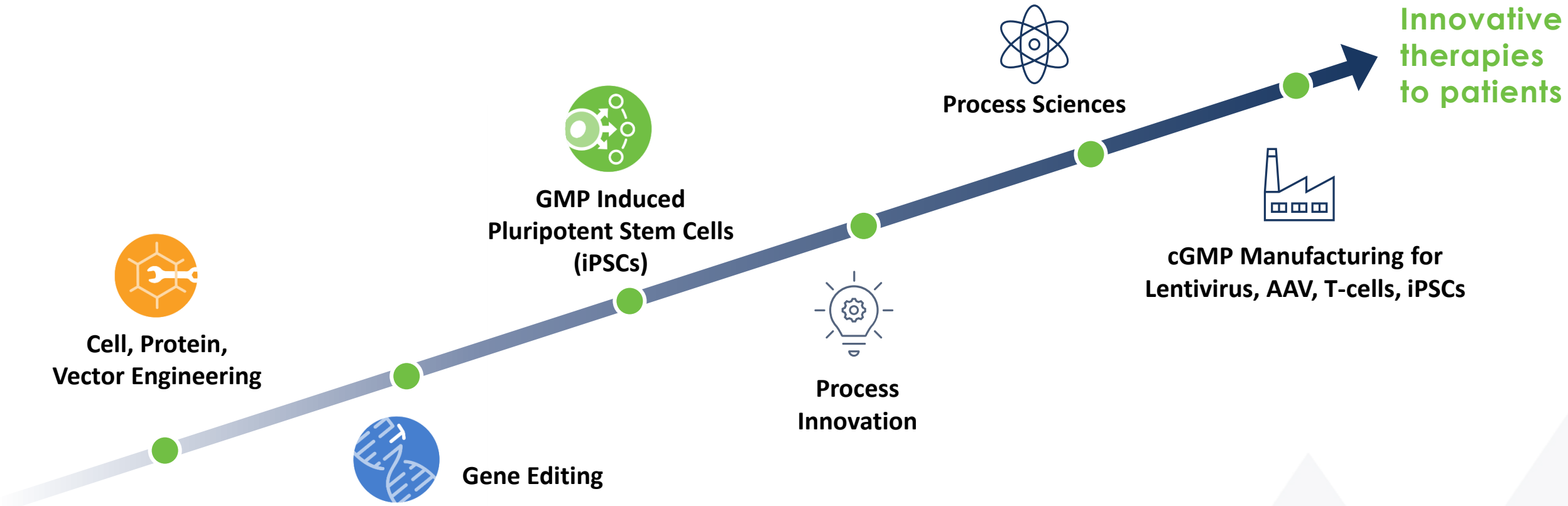
- Rewriting genes
- Regenerating cells
- Redefining manufacturing

RIGHT FROM THE START

Significant barriers to manufacturing and developing cell and gene therapies



ElevateBio's ecosystem is a disruptive solution to pave the path to accelerate the design, manufacturing and development of CGTs



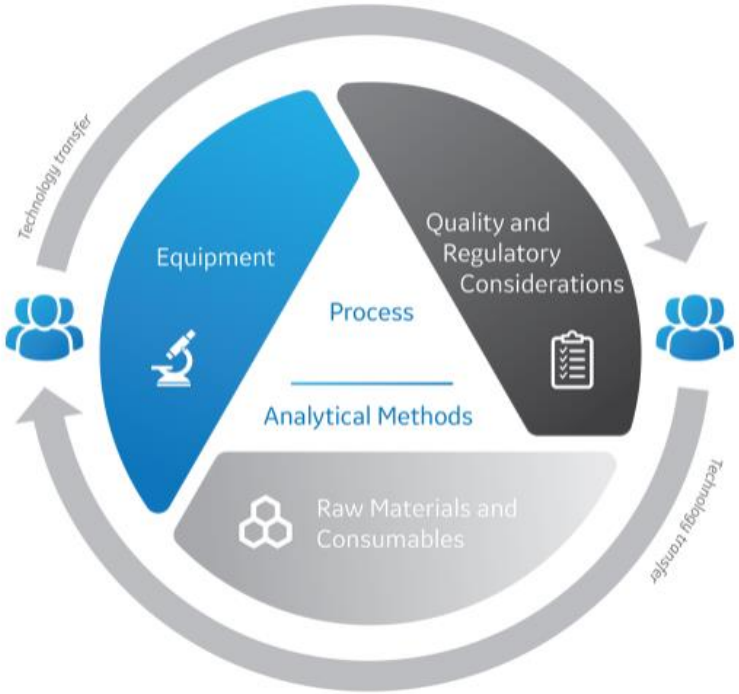
Talent › Next-Gen Enabling Technologies › PD/cGMP Manufacturing › Clinical and Regulatory Expertise

Technology Transfer Introduction

- ICH Q10 defines technology transfer as a stage of the product development life cycle:

  *"The goal of technology transfer activities is to **transfer product and process knowledge between development and manufacturing, and within or between manufacturing sites** to achieve product realization. This knowledge forms the basis for the manufacturing process, control strategy, process validation approach, and ongoing continual improvement."*

- We transfer more than just a cell therapy production process
- Tech transfer can take significant resources (time, cost, people, material) and if not done properly can lead to:
  - Delayed objectives (missed clinical cohorts, delayed IND, could set back by 1+ years)
  - Cost creep (> $1M)
  - Low quality results (e.g., dissimilar processes/analytics that do not support goals)



What is different for Cell Therapy

- Cell therapy product manufacturing processes are complex.
- There is a lack of standardized operations (i.e., different equipment, different methods, etc.).
- Each manufacturing process requires skilled manual operations. In some cases, it’s more of an art than a science. This applies equally to the analytical processes, too.
- Starting Material is usually from individual patient
- Unique Raw Materials
- Complex Analytical Methods

Before Tech Transfer Starts

Transferring Unit (TU)/ Sending Unit (SU)

Know your technology/process well

- What's unique or different about process/ tech?
- Need to demonstrate any hands-on complex steps?
- Are there unique raw materials and equipment that will need to be sourced?
- Will this transfer require any technology changes (e.g., Manual harvest vs Automated harvest)? Consider a risk assessment & comparability

Know your objectives, regulatory/ compliance needs

- Biosafety level
- Clinical phase
- Geography – which health authority are you going to?

Know the receiving organization well

- Are they industrial or academic? Academic orgs may not be as familiar with TTx procedures
- Have they done elements of this process before?
- Have they used any of the equipment before?
- Does the receiving org have a tech transfer process they like to follow?

Do you have hard deadlines?

- IND or CTA filings
- Clinical cohort start
- Corporate milestone
- Compact timeframes will need less conservative approach to risk, might need to consider doing studies with overlap or in parallel

Tech Transfer Start

- RFx (Request for…)
  - Start with RFI (information)>RFQ (Quotation)>RFP (Proposal)
- Start gathering documentation
  - Process Flow Diagram
  - SOPs and Method Description
  - Bill of Material (BOM)
- Agreements
  - Typically, can't start until you have a Master Service Agreement (MSA) and a Statement of Work (SOW) or a Letter of Intent (LOI)
  - Take the time to have a professional review these agreements and pay close attention to IP terms and their willingness to support you in a future TTx
  - **Know what the scope of the initial SOW and how to add more scope. Is RU willing to work at risk as you establish a new SOW?**
  - Quality Agreement can be worked on during the TTx

Document Sharing with Receiving Unit/Organization

- Share gathered documents with RU
- **This will help RU side team to understand the process, raw material need, equipment purchase, methods qualification, facility need etc**.

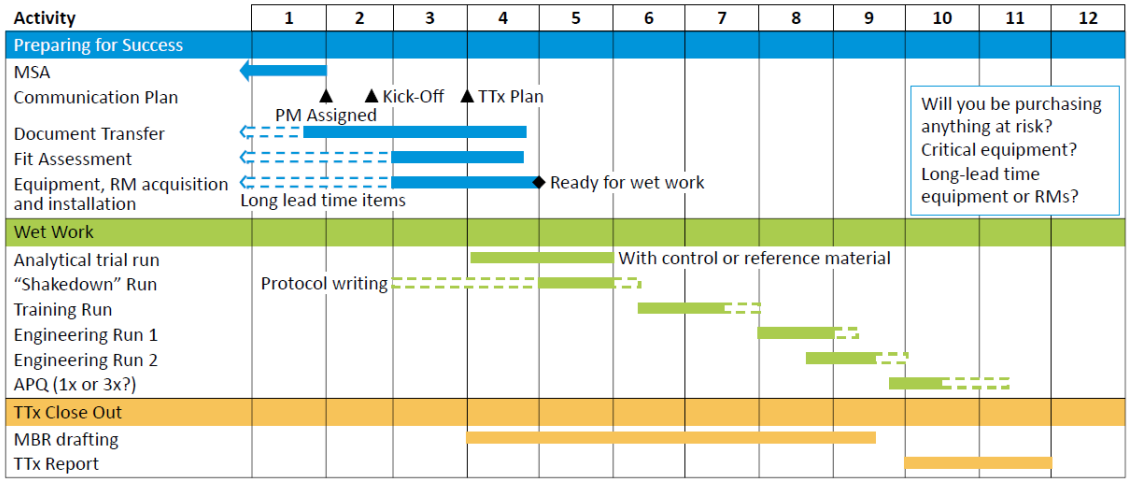
Kick-Off Meeting

- Kick-off meetings are not used by all organizations, but it is highly recommended and can be multiple meetings!
- RU and TU Team introduction (All cross-functional groups member present)
- Align on the communication approach:
  - Weekly meetings? Just for PMs or everyone? Where is data reviewed? Separate analytical meeting?
    - Who takes meeting minutes and action items?
  - Can each functional leader speak to their counterpart or does all communication funnel through the PM?
- Great time for the TU to introduce their product/concept to the RU.
- **Set clear goals (*e.g.,* IND by end of Q2 next year, successful engineering run complete by Dec 1 …)**
- Document sharing: Highly recommend a shared “Sharepoint-like” site over email
- Be clear on expectations:
  - Prepare to generate a detailed gantt of the tech transfer
  - What type of and number of Runs needed; Feasibility Run, Training Runs, Engineering Runs?
  - Starting in the cleanroom or development space?
    - What risks are you willing to take? Overlapping training runs? Overlapping ENG runs?
  - What needs a report
  - Who approves what documents, number of review cycles (often only 1 built in)
  - Do you have engineering targets?
  - **What is the definition of success?**

Create Timeline (Road Map)

- Based on kick-off meeting and alignment on expectation develop a timeline
  - IND filing goal
  - Type and number of runs (this is dependent on RU's capability and prior experience with similar process)
  - Equipment purchase and IOQ needs (complex vs simple)
  - RM qualification requirements
  - Analytical Methods qualification requirement (Qualified vs Validated)
- There will be lots of parallel activities

Sample TTx Gantt



Technology Transfer Stages

Stage 1 Initiation and Planning

- RFx (RFP/RFQ/RFI) and agreements (LOI/SOW)
- Document transfer (process description, BOM, SOPs, BRs etc.)
- Kick-off and program charter
- Assign resources

Stage 2 Knowledge Transfer

- Technology transfer plan & fit gap assessment
- Timeline creation
- Equipment and materials procurement
- Observation run at Transferring Unit (TU)
- Generate plan for equipment and method qualification

Stage 3 Execution

- Feasibility runs / training runs at Receiving Unit (RU)
- Engineering runs (can be stability run/ comparability run/ IND enabling runs)
- Lesson learned and process lock
- APS runs

Stage 4 Closure

- Lesson learned
- GMP run preparation activities (MBR, sample plan, method and raw material qualification completion, release & shipment readiness etc.,)
- Closure of technology transfer

Fit Gap Assessment and Tech Transfer Plan

Fit Gap Assessment (Facility, Utility, Equipment, Raw Material, and Assay)

- Determines the fitness (same or suitable equipment/method) and gaps of RU for successful start of the technology transfer
  - Equipment: same or suitable or purchase new
  - Raw Material: same or alternate source
    - In Cell Therapy, it is ideal to have same manufacturer raw material (e.g., HABS, HSA, Cytokines, final fill container etc.). It is okay to have alternate source for common consumables.
  - Analytical Method: In-house or CTO, Fit for Use vs qualified
- This can be living document and revise after Engineering or GMP Clinical Runs

Tech Transfer Plan (Roadmap)

- Define criteria for tech transfer success
- Define deliverables or activities to close tech transfer

Technology Transfer Runs

There are few type of runs associated with tech transfer. The terminology can differ between organizations

Observation Run at TU (SU)	Feasibility/ Development Run at RU	Training Run at RU	Engineering Run at RU
• RU gains experience • May provide hands on experience to RU MFG and Technical teams • Helps knowledge transfer	• This run is not always needed • Technical SME (PD) run the process at RU PD to ensure proposed process is feasible to transfer (executed with expected results) • MFG team can gain additional experience • Performed with PD BR and SOPs • Help development of MFG BRs and SOPs	• This run is key to successful transition to Engineering Runs • MFG team gets hand on training with SMEs guidance • Identify changes/edits in draft MFG batch records and sampling plan	• Test draft MFG Documents and support systems (testing, material management etc.) • Executed with set acceptance criteria • Can be used for Stability studies, IND enabling runs, and comparability study • Further training of MFG personal • Can generate material for method qualification/ validation • **Key milestone for Tech Transfer success**

Strategy for Success

- **Align on Tech Transfer Runs (training, engineering etc.), State of Equipment Qualification, Method Qualification, and Raw Material Qualification**
- **Having alignment at start is the key to success otherwise it can result in significant delays**

Starting material:

- Fresh vs frozen.
- Source (healthy vs patient).

Define critical engineering run targets:

- In-process targets (e.g., transduction time, viability, cell conc.).
- Drug product specification (release tests ranges).

Raw material:

- Ideal to have same source raw material (e.g., HABS, HSA, cytokines, final fill container etc.).
- Consumables can be source from alternate source.
- Define/align RM qualification strategy; test and release for clinical run vs release based on CoA for engineering run.

Analytical methods:

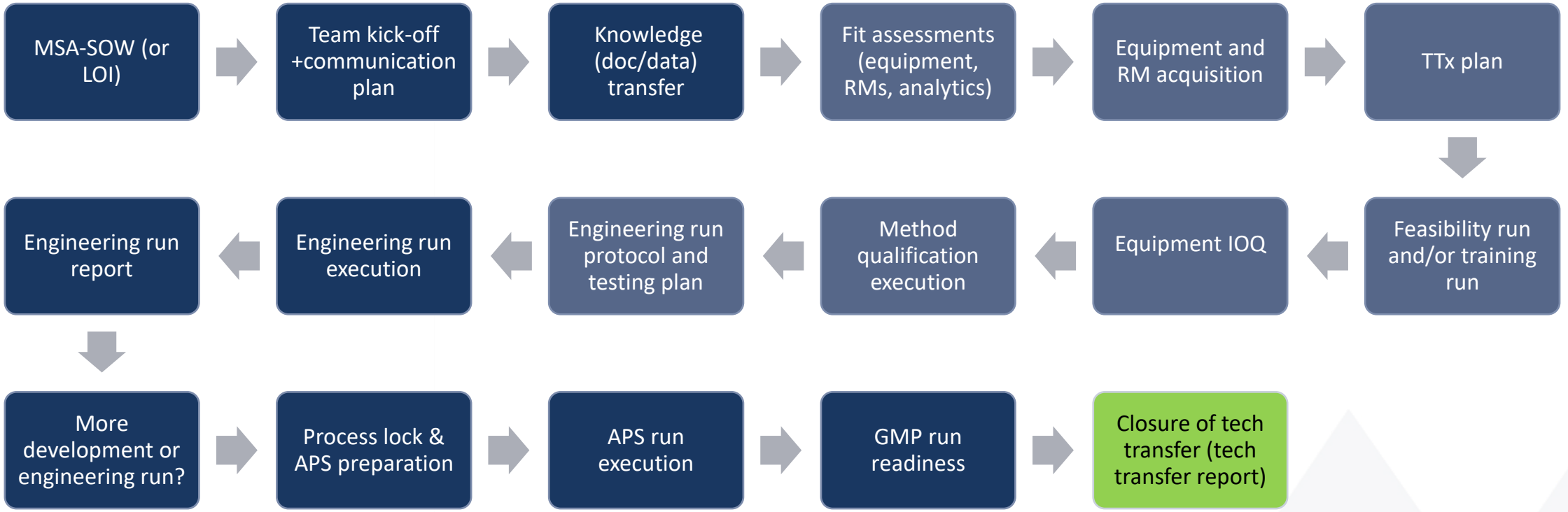
- Define state of methods (fit for use/qualified/validated) for Tech Transfer Runs.
- Well describe the analytical methods being transferred: can include (but are not limited to) tests performed on incoming product raw material (e.g., apheresis), in-process samples, and final product testing (e.g., identity, potency, viability & cell counts, phenotype, endotoxin, sterility, and mycoplasma testing).

Comparability

From Q5E: when changes are made to the manufacturing process, the manufacturer generally evaluates the **relevant quality attributes** of the product to demonstrate that modifications did not **adversely impact the safety and efficacy of the drug product**. Such an evaluation should indicate whether confirmatory nonclinical or clinical studies are appropriate.

- **Changing or having a new manufacturer is one such change**
- Need to assess differences between the process (environment, raw materials, manufacturing process, testing) at the new and previous facilities
- If not 'like for like' – require some comparability assessment
- Analytical comparability
    - Functional potency assay
- **Comparability is a big workstream**
    - Start early
    - Be organized
    - Establish the team – agree on who needs to be involved
    - Define the process differences:
        - what attribute could be impacted
        - measure it in a few lots
        - justify comparability

Overview of Tech Transfer Journey



Cell Therapy Tech Transfer and Challenges

Process

- Complex and manual process.
- Variability in raw materials.
- Inherited starting material variability impacts attributes.
- GMP vs PD Environments: Process can become unmanageable once a large number of time-dependent steps coupled with the real-time completion of documentation are required.

Process Development

- There may be a lack of basic GMP awareness in early-stage development, which can lead to the development of processes or methodologies that are not compatible with GMP requirements.

Raw Material

- Starting materials: usually obtained from individual patients and lack consistency in collection.
- Some reagents may not be available in either the quantity or quality required for advanced development or GMP manufacture, such as uncharacterized animal-derived materials (e.g., HABS).
- Establishment of RM Qualification program (long lead deliverables and sometime test method not available or feasible).
- Covid-19 and supply constrains (experienced delays in pipette tip, conical tube, vials, bags etc.).

Analytical Method

- For cell therapy process, method transfer is complex and requires more time to transfer.
- Development and transfer of potency assay is challenging and can be a bottle neck for submission.

Acknowledgement

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