Overcoming Challenges in Technology Transfer of Cell Therapy Products

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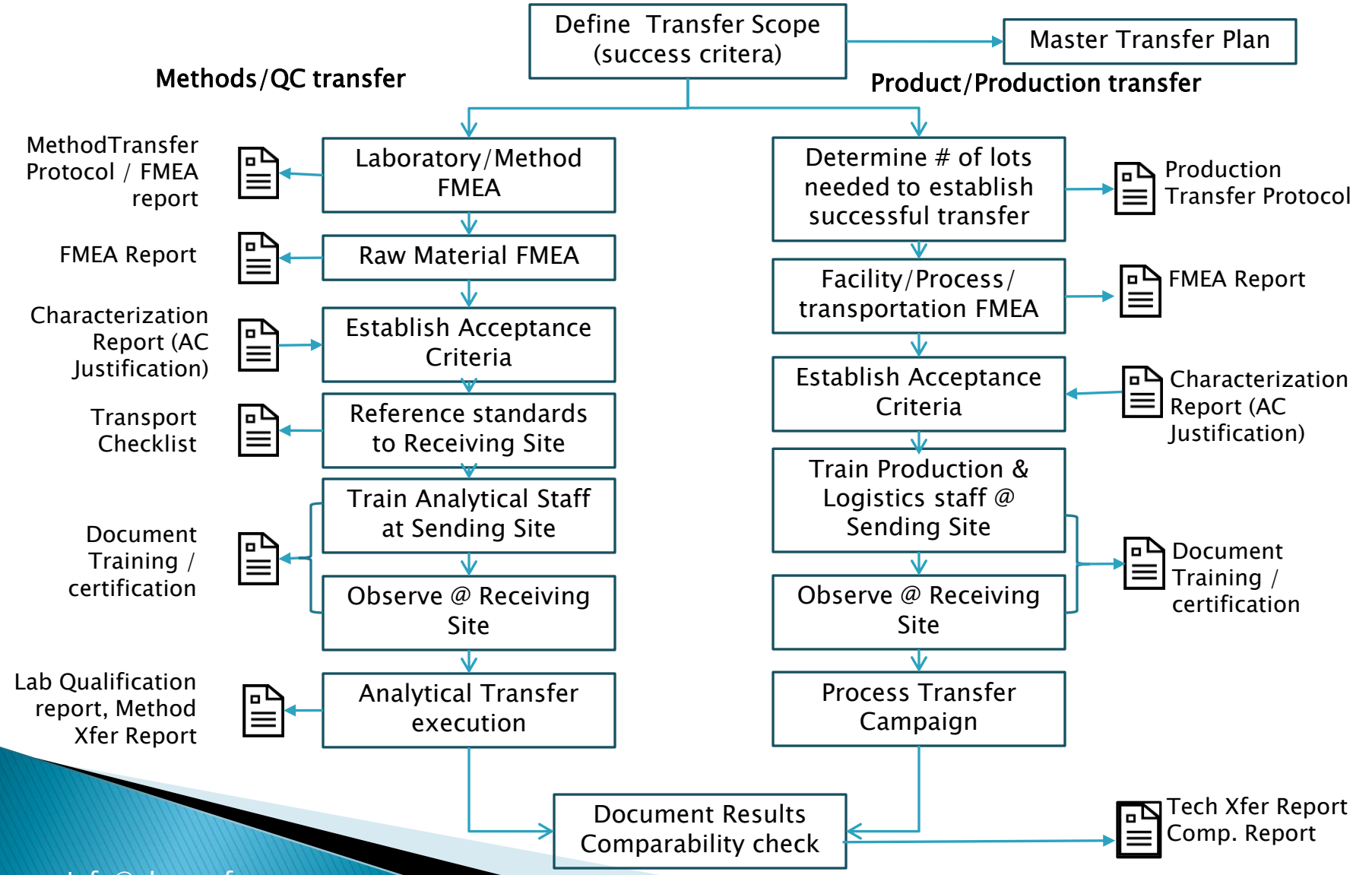
Background

- Cell therapy products quickly advancing from idea to commercialization, small number already commercial
  - 5 – Cord blood derived allogeneic products
  - 3 – Allogeneic cells for wound healing
  - 3 – Autologous (Laviv, Carticel, Provenge)
- Currently less involvement larger pharma companies, but slowly ramping up
- Most activity in small & mid sized companies

Some Common Characteristics (company)

- Resource constraints
- Smaller (sometimes non-existent) internal development capabilities
- Reliance on CMOs
  - Must transfer technology
  - Original work often done at a different lab
- Heavy reliance on key suppliers (often single sourced)
- Very aggressive timelines (competition or financial pressures)

Typical Technology Transfer Flow



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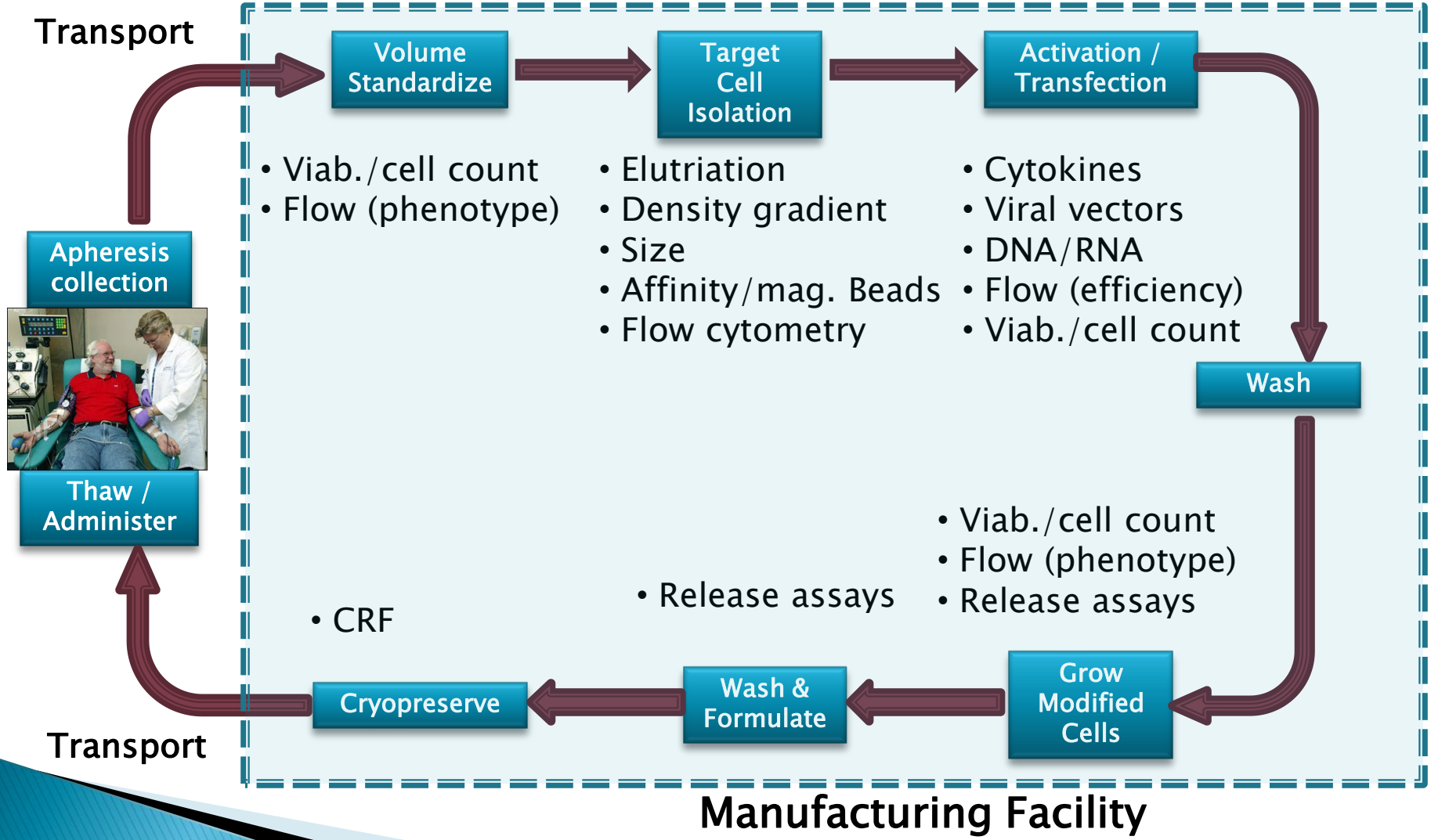
Simplified Autologus Cell Therapy Production Process



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Are Cell Therapy Transfers More Challenging Than Recombinant Proteins?

1. Process often ill-characterized – research or academia -> CMO
2. High degree of variability
    1. Manual operations – includes methods
    2. High variation of materials – (e.g. patient)
    3. # of experiments possible < needed
    4. Large # of runs to establish comparability
3. High contamination Risk – open operations
4. Disposables too often don't easily work with each other

Numerous Non-Technical Issues Add To The Challenge

- Quality of Documentation
- Unsupported changes
- Quality of Communication
- Expectation Management – particularly senior management
- Quality of Planning & Execution

Words to live by

"failing to plan is planning to fail" – Benjamin Franklin

"Common sense is the least common of the senses" – Voltaire

Common Transfer Failure Root Causes – The 7 Deadly Sins

Wrath
Poor Communication

Pride
Inadequate Characterization

Sloth
Poor Documentation

Envy
Untested Changes

Gluttony
Poor Execution

Greed
Optimistic Plans

Extravagance
Poor Risk Management

Case Study Examples

Process Examples:

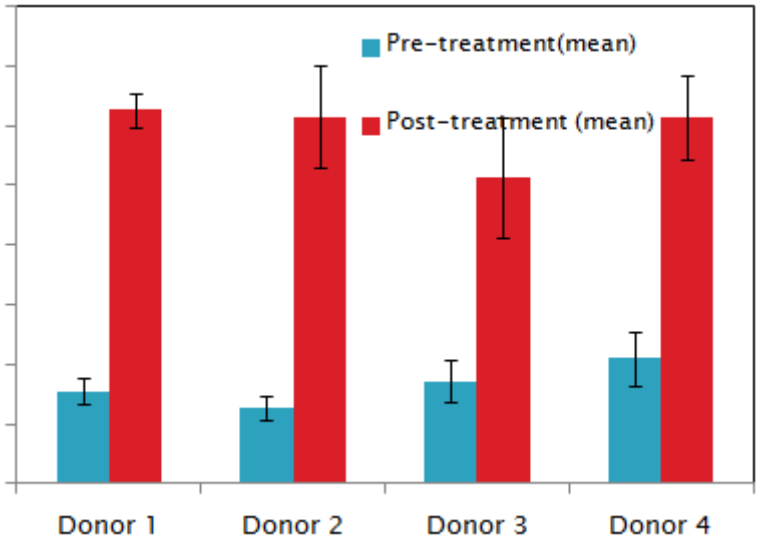
- 4 Autologus products at different stages
- Small – mid sized companies
- All products in CMOs/CROs at some stage

Method Examples:

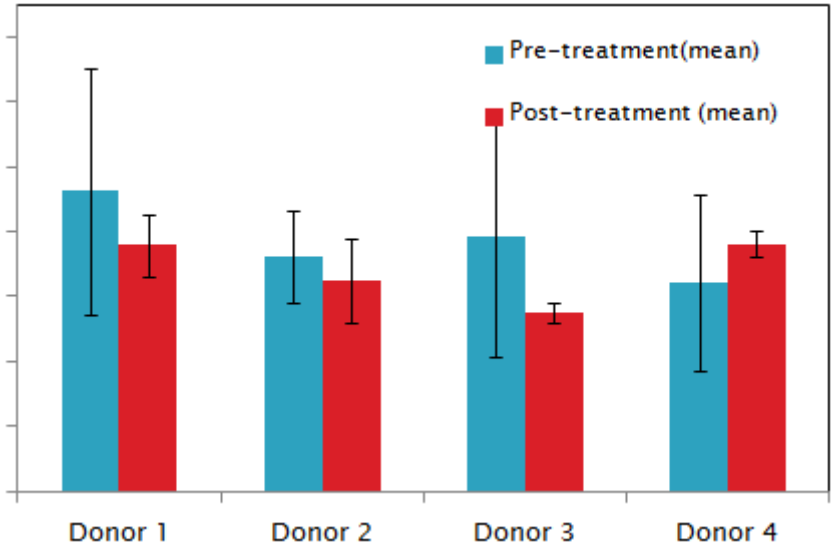
- From products above + Other immunology lab method transfers

Case Study #1

Description: Non-comparable results following transfer of product assay (Flow Based) from Company to CMO lab



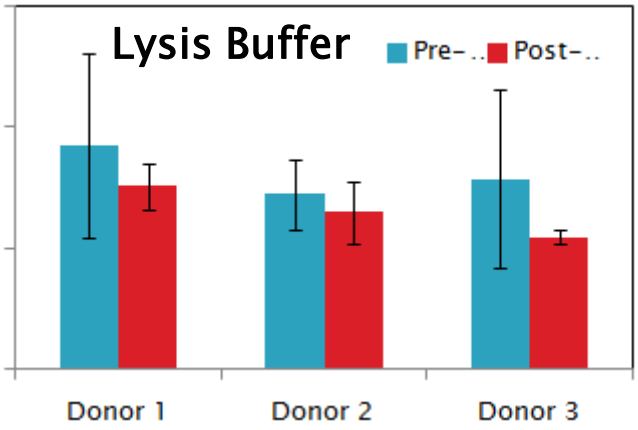
Assay results in sending lab

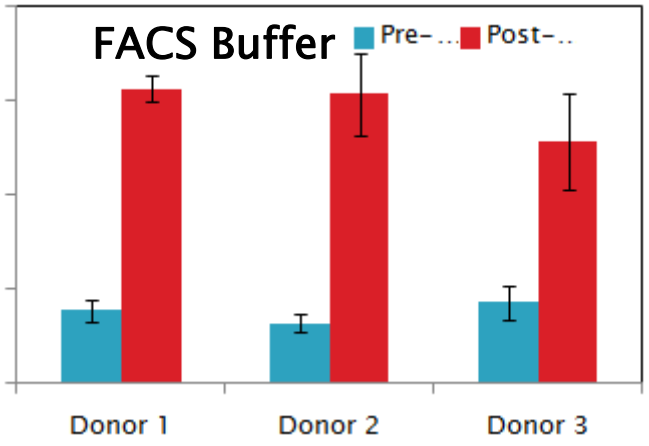


Assay results in receiving lab

Case Study #1– Root Cause

- Method called for RBC lysis followed by 2X wash using FACS buffer
- CMO “simplified” procedure and used 2X wash with Lysis buffer instead
- Lysis buffer contained alcohol based fixative
- Alcohol likely modified cell surface epitopes, affecting antibody binding





Case Study #2

Description: Critical reagent used in production of final product did not pass specification for use in process

- Reagent produced at CMO #1, shipped to CMO #2
- Filled in custom config., shipped to CMO#3
- Stored frozen until needed, then thawed and used in production
- Passed spec. after production at CMO #1; failed prior to use at CMO #3, all shipment performed per procedure, no red flags on TempTales
- Stability data available for up to 2 years −20 ± 5°C (specified storage conditions)
- Reagent was <2 years old at time of failure
- There were no notifications from any of the CMOs

Case Study #2 – Root Cause

- Records at CMO#3 revealed a “product movement form” – due to freezer failure
- Secondary freezer was a validated -30°C, CMO assumed “colder is better”, no notification to client
- Product formulation – Tris/NaCl based, with a crystalization temperature -24°C & T_g = -42°C
- Stability data available clearly showed product not stable at -30°C

Case Study #3

Description: Product produced at receiving site failed potency specification

- Flow based assay, used ratio of fluorescence intensity of cell surface marker before & after modification step
- Same process and analytical equipment used at both sites
- Client indicated that batch records and SOPs were “copied” exactly

Case Study #3 – Root Cause

- Apheresis received at both sites had similar characteristics – no red flags
- Batch records and SOP's – found to be comparable
- Raw materials and reagents sourced from same vendors
- Actual lots of raw materials and reagents shipped from each site to the other, then used to repeat runs – Same results

- Technicians and analysts sent to receiving site for "walk through"
- A small difference in a setting on flow cytometer discovered
- Analysis parameter for Fluoresence Intensity set to Log-Log (Geometric mean) at one lab, Log-Lin (Arithmetic mean) at other
- Report from instrument – "Y-mean" no indication of change
- Transfer protocol did not specify this setting!

Case Study #4

Description: Significant difference observed in modification efficiency during transfer from development to GMP manufacturing

- Difference measured at cell modification step
- Activation / modification conditions at sending and receiving site within acceptable process limits using same equipment
- All equipment and operating conditions verified to be same
- All reagents and material contact surfaces verified to be same or comparable

Case Study #4- Root Cause

- Statistical analysis revealed correlation between “sample hold time” & poor performing lots
- Hold times ranged from 2-7 hours at CMO due to operational constraints
- Process performance in development always measured using assay run in adjacent lab within 2-3 hours
- Controlled experiments revealed a 30% decrease in efficiency with 6 hour hold (ambient)
- Procedures modified to expedite analysis – long term assay may be moved to manufacturing to further expedite

Additional considerations for Improving Transfer Success to CMOs

- Knowledge/visibility to facility & procedures (e.g.)
  - Processing conditions vs. development lab
  - Peripheral procedures (e.g. material sanitization prior to entry into suite, how materials received, where stored)
  - Distance between processing suite & testing labs & movement procedures – hold time
- Detailed visibility to personnel (e.g.)
  - Turnover rate
  - Training of key staff
  - Number of personnel trained on your process/methods
  - How often do they perform those operations

Summary Of Lessons Learned

Change (intended or not) most common source of failure!

- No substitute for characterization, avoid change whenever possible

How the changes typically get in

- Change in supplier or grade of RMs (research vs. GMP)
- Changes in equipment or methods in order to “fit in”
- Significantly longer hold times (both process & analysis)
- Implementation of “improvements”

You may not be aware some things have changed!

Summary Of Lessons Learned

Documentation

- Good writing skills invaluable, no room for misinterpretation
- Opt for descriptive diagrams over text (use videos for training)

Planning /Execution/Communication

- Include reasonable contingencies in your plans (resist removing them to shrink your schedule)
- Document all decisions, especially the rationale

Risk Management

- Single points of failure – do you know them all?
- Do a complete "walk through" of your product in the facility
- Taking some risks is acceptable (often necessary) – Be sure they are clearly communicated!

Thank you for you time

Contact us with any questions:
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