CMC Challenges for cell therapy manufacturing

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The Premise

In the absence of absolute product characterization.....

Successful clinical trials demonstrate that:
• Consistent replication of process
• Reinforced by indicative quality attributes
• Delivers acceptably consistent and positive patient outcome

The product is the process

The manufacturing process used for clinical trials must match the commercial process.

Note: The focus of our experience has been creating process solutions enabling the commercial viability of patient-specific therapies.
Manufacturing a cell therapy product

The practical reality: Human derived cell source material exhibits substantial variations from patient to patient.

The products cannot be identical to each other

So what controls are available?

Monitoring quality attributes
• Phenotype, total number of cells, viability ……
  May influence the process
  • Decisions to proceed
  • Cell suspension management
Supports product release
• Correlation of this batch to clinical history

Assurance of process replication
• Are the cells experiencing the same journey?
• How can we know we did it the same way?
Did we say manufacture?

How can we be confident that every operator completes the process identically while:

• Hiring, training and retaining enough skilled staff?
• managing the quality across multiple sites?

We call it “Process Integrity”
You can create process integrity.
The cost of failure - Assigning a value to consistency

Process consistency failures:
- Manual errors requiring some changed procedure.
- Documentation errors resulting in follow up verification activities.

A review is required to assess whether the batch will be acceptable for clearance or must be failed.

Number of quality events per 100 doses processed
- 50 events per 100 doses has been observed regularly.
- Some observers suggest 100% of batches in clinical trials Let us say 50%
  - Cost of each minor event
    - Formal review by responsible persons labor time 10 hours say
    - Documentation, notification of the regulatory agency

The number of batch failures per 100 doses processed
- Less than 3% quoted, Estimate 1-2 doses per 100. Let us say 1.5%
- The cost of a batch failure
  - Formal review labor 20 hours say before decision to scrap batch and document
  - Reproduce the process and coordination with patient - duplicate cost of therapy

Contributes 5.3% CoGs

Contributes 1.7% CoGs
What are these failure events?

By observation – (and an in depth study may be warranted)

• Approximately 50% are clerical errors – eg equipment number transcribing
  • MES implementation and automated data capture that is estimated to reduce these errors by 70%

• And 50% are manual procedural errors.
  • Addressed through automation of process operations we call “Process integrity”

By the Way - These figures arise from clinical trial experience

• Highly skilled and motivated operations personnel

Manually expedited operations increasing the frequency of replication

• More different people who conduct them = more defects

1. Consistency is likely to be elusive in a volume production situation without actively controlling it.

2. What level of consistency should regulators expect?
Drilling deeper - Process vulnerability profiling

Vulnerability list

- On-line tube weld – where intermediate product is present
- Off line tube weld – where no primary material is present
- Tube seal and cut
- Spiking in
- Responsibility transfer – consider a QC sample and response process
- Operator prompt – the need to re-engage an operator in this particular process
- Manual process step – Where operator “skill” can alter the outcome – eg mixing
- Data input – transcribing information into equipment or the batch record – such as a weight from a scale
- Data output – Reading data from QC report or equipment that impacts the process
Reducing vulnerability using process integrity

Explore process implementations:
- Eliminating manual tasks where subjective skill affects outcome
- Eliminating or minimizing operational hazards
- Selecting and merging technologies that compliment each other.

<table>
<thead>
<tr>
<th>Process FMEA</th>
<th>“At risk” tube welds</th>
<th>Manual steps</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mature manual process</td>
<td>22</td>
<td>29</td>
<td>51</td>
</tr>
<tr>
<td>Incremental automation initiatives</td>
<td>10</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>Integrated automation</td>
<td>5</td>
<td>4</td>
<td>9</td>
</tr>
</tbody>
</table>
Process integrity justifies automation

Assembly of unit processes

- Cell selection
- Cell bank incubation
- Washing
- Formulate
- Fill and finish
- Sampling
- Sampling

Because the risks are between the unit operations
What are the benefits?

The likely frequency of batch defects is estimated by assessing the vulnerability profile.

Not only are minor events reduced, but batch failures are reduced.

There is a direct savings on the cost of goods to treat a patient.

The MES is justified at 500 patients per year.

The higher cost automated processing platform is justified at 5,000 patients per annum.

Combined savings represent a 23% reduction in the total cost of goods for every patient.

<table>
<thead>
<tr>
<th>Batch events</th>
<th>Batch failures</th>
</tr>
</thead>
<tbody>
<tr>
<td>% patients</td>
<td>% patients</td>
</tr>
<tr>
<td>Original process</td>
<td>50%</td>
</tr>
<tr>
<td>Incremental automation</td>
<td>36%</td>
</tr>
<tr>
<td>Integrated automation</td>
<td>31%</td>
</tr>
<tr>
<td>MES only</td>
<td>33%</td>
</tr>
<tr>
<td>Integrated auto with MES</td>
<td>13%</td>
</tr>
</tbody>
</table>

Therapy cost of goods savings

![Graph showing therapy cost of goods savings over patients treated per year]
Commercial process quality = CMC objectives

Robust quality independent of site or labor skills

Regulators have a preference for full implementation by mid phase 3
Practical implementation

Design directed by the requirements
Argos Therapeutics – A Closed and Automated Process

**Clinical Site**
- Small tumor/virus sample
- Leukapheresis

**Centralized Manufacturing Facility**
- RNA Extraction/Amplification
- Monocyte Isolation
- Cellular Processing, Formulation, & Fill
- Amplified RNA
- Intradermal Injection
Process Integrity through Tube Welding

- When assembling an operation, the process control calls for introduction of the reagent or in-process material.
- The operator scans the bar-code and when accepted, assembles it to the tube welder and fits the mating system tube with its key.
- The operator is prompted to weld the tubes when both correct keys have been fitted.

Integrated with the tube welder, the local control can ensure the correct tubes are loaded before enabling the weld to occur.

Indicator lights feed back to the operator that the installation is correct and the weld will occur when the start button is pressed.
Integrity of Reagents

• The label identifies: reagent type, lot number, use by date and volume in pack.

• A key is attached to the tube specific to the type of product in this tube.

• The process control calls for introduction of the reagent.

• The operator scans the pack bar-code.

• The control accepts the correct submission and monitors tube welding into the process set.

• The pack is loaded in position, the key is fitted to the station controlling the tube.

• The control observes the weight of the pack being loaded into the correct position and verifies the weight is within the expected range. The key is a fixed confirmation of the reagent at the station.

• We can proceed to the next step.
Removing QC samples from the correct location at the correct time:

Sensors at each of the sample points will be used to interlock the tube sealer/cutter so that it is only enabled if it is in the correct location at the correct time in the cycle.
Segregation in shared incubators

- Intermediate product in sealed packs
- Each pack labelled
- Packs for a common process retained in a tray with “bunding” to contain leaks.

Trays closed and labelled to mitigate risk of partial separation, or mixing of patient materials
Batch record capture does not necessitate an MES

- Islands of automation
- Batch Records printed in real time for review, verification and long term storage, and for process control (e.g. could be a barcode of cell count)
- No data storage within system boundary hence lower regulatory demands
- Enables progressive MES introduction
Thank You

A production system is like a set of false teeth

There may be many sets out there……

But only the one created for you will actually work