Multidimensionality of Commercial Readiness

ISCT North American Meeting
Philadelphia, September 10, 2013
A Paradigm Shift

Managing Change

From Science to Product

From Product to Therapeutic
What problem(s) are we trying to solve?

Deliverability
- Cost of Goods
  - Barrier to entry, stalling medical innovation
  - Sticker shock
  - Reimbursement / Reimburseability
- Robustness
  - For products that rely so heavily on ‘Process’, can humans cut it?
- Scalability
  - “It’s not just a bigger pot”, Chris Hewitt, Loughsborough
How has the approach to cost of goods and delivery changed over the past 2-3 years as these therapies move into commercial production? How do we expect it to change in the next 5-10 years? Is a change required?
When promising therapies proceed into later stage clinical trials and require scale-up or -out to meet the clinical needs, what types of process issues are often encountered and how best to address them?
Cell-based Product Development

General Challenges

- Developing therapeutics in a developing industry
- Extracting technical feasibility from great science
- Controlling costs in development and manufacturing

- Many questions remain unanswered

- Solutions are forming around the specific challenges that are presenting
Develop from the early stages with commercialization in mind

What does this mean?

• At Phase I
  • Build commercial capacity?
  • Validate assays, including potency?

• When to automate?
  • Is Phase I too early? Worse, is Phase III too late?

Even if the money is available?
DEVELOPMENT AND COMMERCIALIZATION PATH

- R&D
- Pre-Clinical Studies
- GMP Process Development
- IND-Enabling Studies
- IND Approval
- GMP Process Qualification
- GMP Clinical Manufacturing
- Clinical Trials
- GMP Commercial Manufacturing
- Reimbursed Clinical Use
RESOURCES DISTRIBUTION DURING COMMERCIALIZATION

- R&D
  - Pre-Clinical Studies
- IND-Enabling Studies
- GMP Process Development
- IND Approval
- GMP Process Qualification
- Clinical Trials
- GMP Clinical Manufacturing
- Clinical Use
- GMP Commercial Manufacturing

Facilities, Infrastructure & Logistics

R&D, Clinical Development
Unique Manufacturing Context

The comparability challenge – “flying blind’

From FDA Potency Test Guidance:

- Inherent variability of starting materials
- Limited lot size and limited material for testing
- Limited stability
- Lack of appropriate reference standards
- Multiple active ingredients
- Potential for interference or synergy between active ingredients
- Complex mechanisms of action(s)
- In vivo fate of product
Unique Manufacturing Context

Majority of standards and guidance have evolved out of pharmaceuticals and devices.

→ Need to innovatively apply and converge for CT

ICH Q8: Guidance, Pharmaceutical Development
ICH Q9: Guidance, Quality Risk Management
ICH Q10: Guidance, Pharmaceutical Quality System
ISO 14971: Application of risk management to medical devices
FDA Report: Pharmaceutical cGMPs for the 21st Century – A Risk-Based Approach
21CFR 210, 211: Drug/Biologics GMP regulations
21CFR 820: Quality System Regulation for Medical Devices
21CFR 1271: Good Tissue Practices (elevates to biologic for “manipulated” cells)
FDA Guidance: Potency Tests for Cell & Gene Therapy Products
FDA Guidance: CMC for Human Somatic Cell Therapy
Unique Manufacturing Context for Cell Therapy (CT)

Opportunity to apply medical device principles launched in mid-90s to CT manufacturing development.

<table>
<thead>
<tr>
<th>Medical Device</th>
<th>PSCT Manufacturing</th>
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<tbody>
<tr>
<td>Device is patient equipment</td>
<td>Device is GMP equipment</td>
</tr>
<tr>
<td>Design Controls*</td>
<td>Quality by Design**</td>
</tr>
<tr>
<td>Risk to patient by device and its use</td>
<td>Risk to product quality by device and its use</td>
</tr>
<tr>
<td>Do no harm to patient</td>
<td>Do no harm to cells</td>
</tr>
</tbody>
</table>

*Design Controls: ....procedures to control the design of the device in order to ensure that specified design requirements are met. (21 CFR 820)

**Quality by Design (QbD): A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. (ICH Q8)
Risk Management – A way of life

Comprehensive scope
- Funding risks (e.g. cash flow)
- Regulatory risks (e.g. product comparability)
- Quality risks (e.g. operator error)
- Commercial risks (e.g. value proposition vs cogs)

Comprehensive approach
- In thinking (e.g. planning)
- In procedures (e.g. Quality by Design/Design Controls)
- In design (e.g. FMEA)

The mindset: Preparing for success
Quality Risk Management – Working definitions

Quality Risk: Potential for harm to critical quality attribute of product.

Critical Quality Attribute (CQA): Characteristic or property that should be within a limit, range, or distribution to ensure product quality.

- Function CQA (e.g. potency, identity)
- Safety CQA (e.g. sterility)
Quality Risk Mitigation tied to CQAs

Risk mitigation for safety CQAs
• Closed system design
• Single-use disposable process

Risk mitigation for function CQAs
• Simplify and eliminate where possible
• Integrate and automate
## Quality Risk Severity tied to CQAs

<table>
<thead>
<tr>
<th>Ranking</th>
<th>Level</th>
<th>Severity Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Very Low</td>
<td>Negligible impact to product</td>
</tr>
<tr>
<td>2</td>
<td>Low</td>
<td>Minor impact to reported or actual CQAs, but still meets specs</td>
</tr>
<tr>
<td>3</td>
<td>Medium</td>
<td>Significant risk of product rejection</td>
</tr>
<tr>
<td>4</td>
<td>High</td>
<td>Product released with significant risk to function CQAs</td>
</tr>
<tr>
<td>5</td>
<td>Very High</td>
<td>Product released with significant safety risk to safety CQAs</td>
</tr>
</tbody>
</table>
Scope of quality risk assessment

Man (Operator)
Machine (Equipment)
Method (Process Procedure, Method Procedure)
Materials
Milieu (Environment)
Anatomy of a Unit Operation

A defined activity or set of activities intended to accomplish a specific outcome based on use of specified materials, equipment, procedures, and personnel and performed within a surrounding environment.
Manufacturing System Design and Development


FIG. 1 The Specification, Design, and Verification Process
Overall Therapeutic Development Objective

• Define Target Product Profile (TPP)
  • Establishes a living commercial development plan
  • Provides a tool for effective communication between
    • Developer and Regulator
    • Internal stakeholders
    • Developer and solutions’ providers

• Establish Design Space
  • Define Critical Quality Attributes (CQA)
  • Create a ‘design space’
  • Documented development program (‘TRD’)

• Consider the continuum of development objectives
  • Phase-appropriate implementation of objectives

• Data collection
  • Comparability assessment and demonstration

• Cost of Goods reduction throughout
  • Reduction in idle capacity
  • Automation philosophy (true scale up)
  • Informatics (EBR, DMS, LIMS, EM & Materials, etc)