CGMP for Phase I INDs: Manufacturing Cell Therapy Products

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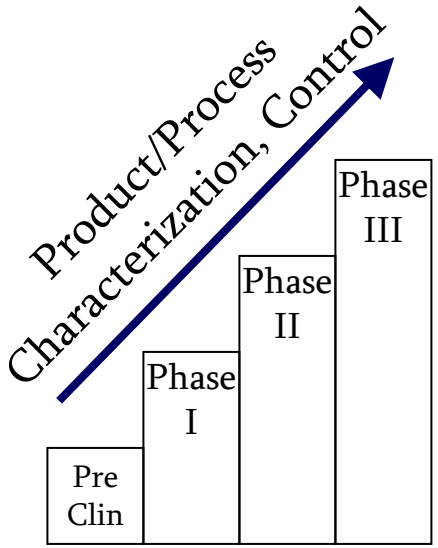
Introduction

- Not surprisingly, FDA is ***not*** telling us to abandon GMPs altogether at Phase I.
- How does the Phase I Final Rule relate to other regulatory requirements for cell therapy products, and how does it affect current cell therapy manufacturing operations?
- What are practical ways to comply with FDA's requirements and expectations for cell therapy product manufacturing at Phase I?

Risk-Based Approach to Regulation of Cell-Based Therapies (HCT/Ps)

- Products that present greater risk of adverse clinical outcome require more and better control, and hence more stringent regulation and oversight.
- Increasingly rigorous control as clinical development progresses



Current Good Tissue Practices (cGTPs)

- Methods, facilities for manufacture of human cellular and tissue-based products
  - Prevent introduction, transmission and spread of infectious disease
    - Donor screening and testing
  - Prevent mix-ups, cross-contamination
    - Product recovery, processing, storage, labeling, distribution

21 CFR Part 1271

- Quality Program
- Organization, Personnel
- Procedures
- Facilities
- Environmental Control, Monitoring
- Equipment
- Supplies and Reagents
- Process Controls, Changes
- Process Validation
- Labeling Controls
- Storage Requirements
- Receipt and Distribution
- Records
- Tracking
- Complaint File

What Does FDA Expect at Phase I?

- Controlled manufacturing, quality assurance, safety
  - "…the process by which a drug product is manufactured… well documented and controlled…"
  - "Assure safety and quality of investigational products"
  - "Ability to reproduce investigational product…"
  - "Consistent quality of investigational product"
- For HCT/P manufacturing, the Final Rule for Phase I products is not a major change. The existing risk-based regulatory structure, the progressive application of GMPs, and the GTP regulations have had much the same effect.

Quality Control Plan

- Regulatory Requirement
  - "Written quality control (QC) plan – responsibilities"
  - "Review and release components"
  - "Review and approval of production procedures, testing procedures & acceptance criteria"
  - "Release or reject each batch upon cumulative review"
  - "Investigate errors and initiate corrective actions"
- Compliance
  - These are Quality Assurance functions, specified in established regulations for HCT/Ps. Need QA staff and resources.

Quality Assurance Staffing

- Resources for staffing may be limited, especially for QA, yet independent oversight of manufacturing and testing, and other QA functions, are required even at Phase I.
- Explore leveraging QA resources and staff in other clinical areas - the routine cell therapy laboratory, blood bank/transfusion medicine, hospital QA/risk management.
  - Cover standard QA functions, such as document control, review of training documents, audits, deviation management, tracking and trending

HCT/P Manufacturing Facilities

- Multi-product facilities, aseptic processing are common in HCT/P manufacturing
- Regulatory Requirement
  - "Clean environment"
  - "Design and procedural controls … prevent contamination, cross-contamination, mix-ups"
- Compliance
  - These are fundamental aspects of GTPs. Procedures for segregation, change-over, tracking, cleaning should be in place in any tissue establishment.
  - Cleaning, sanitization, environmental monitoring

Equipment

- Regulatory Requirement
  - “Properly maintained, calibrated, cleaned and sanitized following written procedures and at appropriate intervals”
  - “Identified and documented in production records”
- Compliance
  - Equipment IQ/OQ/PQ, tracking, maintenance, calibration, sanitization program(s), SOPs
  - Batch records

Raw Materials

- Cells/tissues, ancillary materials, excipients, critical components
  - Sterile, pure, potent, high quality. Minimize risk of "introduction, transmission, or spread of communicable disease" (21 CFR 1271.210).
  - Select and qualify materials and suppliers. Tiered, risk-based approach to qualification. Materials should meet safety specifications, and should produce consistent results in your manufacturing process.
- Inventory control system - controlled handling, storage, tracking

Characterization Testing

- Safety
  - Sterility, endotoxin, mycoplasma, adventitious agents, tumorigenicity
- Purity, Identity
  - Cell viability, concentration, morphology, immunophenotype, gene activity/expression, etc.
- Potency
  - Relevant biological function may not be understood at Phase I, investigate potential functional assays.
- Stability
  - Demonstrate that product is within acceptable limits for planned duration of clinical use/proposed investigation

Characterization Testing - the QC Lab

- Defined, written procedures - sample handling, assays
- Controlled analytical equipment and methods
- Assay validation not required at Phase I
- Accurate data records
  - Double sign-off?
- QC testing staff
  - Should be separate from manufacturing staff. If combined, then independent QA oversight is essential.

Training

- Regulatory Requirement
  - Aseptic processing, for example, “…training for operation and release of sterile products”
  - Training for any of the tasks and skills required
- Compliance
  - Documented training program, proficiency testing, monitoring

Summary

- The Final Rule for Phase I products does ***not*** mean that GMPs can be omitted. Controlled manufacturing is required, to assure safety, quality and consistency. This entails the elements of GMPs and GTPs, applied in accordance with the risk-based, progressive approach for HCT/Ps.