CGMP Considerations for Cell Therapy Products Under IND

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Overview:

- CGMP & Product Development
- Regulatory Considerations
- Draft Guidance: Recommendations for CGMP Compliance
- Aseptic Processing for cell therapy production
CGMP & Product Development

**SAFETY INFORMATION**
- Source characterization
- Raw materials qualification
- DS/DP Characterization
- Testing/Qualification/Clearance of impurities, contaminants
- Process control esp. for safety processes (e.g., sterilization, virus clearance)

**DEVELOPMENT ACTIVITIES**
- DS & DP Characterization
- Formulation Development
- Raw Material/Component characterization
- Assay Development/Validation
- Specification Development
- Stability
- Manufacturing Process Control & Validation

**CGMP**
- Personnel
- Quality Control
- Facilities & Equipment
- Laboratory Control
- Component Control
- Production Control
- Distribution & Records
- Labeling

**Phase III**
- Pre-clinical
- Discovery
- NDA
- BLA
Regulatory Considerations

- Drugs and biologics including investigational new drugs are required to be manufactured in accordance with CGMPs [501(a)(2)(B)] FD&C Act
- IND regulations (21 CFR 312) (patient safety and clinical trial)
- Biologics regulations (21 CFR 600s) – licensing requirements
- CGMPs (21 CFR 210 & 211) – good manufacturing practices for drug/biologics products
- Combination products (21 CFR 800s, in addition to 21 CFR 600’s and 210 & 211)
FDA CGMP Guidance

**Draft guidance for Phase 1 INDs:**

- recognizes that some controls and the extent of controls differ between investigational and commercial manufacturing, as well as phases of clinical studies
- articulates the expectation that there will be greater control over the process through the various IND phases
Draft Guidance: Scope

Applies to:

- investigational new drug and biological drug products used during phase 1 development
- investigational recombinant and non-recombinant therapeutic products, vaccine, gene therapy, allergenic, plasma derived, and somatic cellular therapy products as well as in vivo diagnostics
Draft Guidance: Scope

Does not apply to:

- human cell or tissue products regulated solely under Section 361 of the PHS Act
- blood and blood components
- products regulated as devices
- already approved products/and or in phase 2/3 used in other phase 1 studies
- PET products
Draft Guidance: Recommendations for CGMP Compliance

- Effective quality control standards for Phase 1
  - Well defined written procedures
  - Adequately controlled equipment
  - Accurate and consistent recording of data (manufacturing and testing)

- Implement CGMP consistent with good scientific methodology, product development and quality principles
Draft IND-Phase 1 GD
General CGMP
Recommendations

- Personnel
- Quality Control
- Facilities
- Equipment
- Control of Components
- Production and Documentation
- Laboratory Controls
- Container Closure and Labeling
- Distribution
- Record keeping
Personnel

- Education, experience, training (or any combination) to perform assigned function(s)
- Training should include CGMP as outlined in this Guidance
  - Especially Quality Control principles
Quality Control

- **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

- **Responsibilities are performed independently from production**

- ** Appropriately trained individual(s) – sufficient to perform QC function**
The Importance of a Good Facility Design
Facilities

- Adequate and appropriate - HVAC, lighting, water, plumbing, space etc.
  - Maybe dependent upon product and process
- Adequate air handling to prevent contamination and cross-contamination
- Water of appropriate source and quality
- Adequate work areas for intended tasks
- Procedural controls to avoid contamination and mix-ups
Production and Documentation

- Production follows written procedures
  - Records of manufacturing and testing data – components, equipment and procedures used,
  - Records of changes in procedures and processes
  - Records of microbiological control for sterile processed drugs
Risk Assessment (RA)/Risk Management (RM)
How are you going about it?
Quality Risk Management as Part of Development

- Some focus areas related to risk management and risk mitigation a company should understand for their products are:
  - Raw Materials / Component – What risk do they pose?
  - Process and Equipment – What can go wrong?
  - Bioburden Control and Manufacturing Environment – Evaluate and control.
  - Testing and Validation/Qualification Programs – CAN THEY DETECT EARLY SIGNS OF PROBLEMS?
  - Risk areas not necessarily identified via process mapping (e.g., quality oversight, legacy systems, contract partners, etc.)

- Quality risk management should be implemented as early as possible in drug development
Multi-product/ Risk Management

- Multi-product aspects – potential impact on other products
  - Have you considered potential cross contamination issues?
  - Have considered the unknowns?
  - Are you placing existing systems, process and facilities at risk

- Common attribute of contract manufacturers
Multi-product Manufacturing Area

**Multi-product**

- Generally, only one product manufactured in an area/room at a time
- Same area/room may be used for multiple purposes, if:
  - Appropriate design & procedural controls allow for orderly handling of materials & equipment – prevent contamination/cross contamination, mix-ups
  - Effective Cleaning and change over procedures
Appropriate equipment qualification and controls in production are needed to assure safety related function (e.g., viral clearance, viral toxin inactivation, pasteurization)

- Will these manufacturing steps perform as intended?
- Do you have accompanying testing for safety related functions?
Sterile/ Aseptic Processing

- Remember for Phase I investigational products – “Safety and rights of subject” 21 CFR 312.22(a)
- Take special precautions
- Appropriate training
- Aseptic manipulation conducted under appropriate conditions (e.g., Class 100 conditions - laminar flow hood)
- Document and follow all procedures intended to maintain the sterility of the components, in-process materials, API and final product
Ideal Conditions for Aseptic Processing (1 of 2)

- **Personnel performance**
  - gowning and technique
  - Minimal excursions in the aseptic path

- **Validated, controlled sterilization of all**
  - product and added ingredients
  - containers and closures
  - equipment and utensils
  - product-contact surfaces

- **Facility Design**
  - containment/protection – protective buffer zone
  - enough space – hood near door (not a good idea)
Ideal Conditions for Aseptic Processing (2 of 2)

- **Environmental quality and control: Appropriate air quality for aseptic processing**
  - Biosafety cabinet (Class 100)
    - Qualified (twice year filter test)
    - Monitored when in use
  - Surrounding Class 100 rooms should also be appropriately qualified (Class 10,000 or 100,000) to help maintain the Class 100 cabinet

- **Appropriate pressure differentials for specified processing steps**

- **Closed processing systems where possible**
  - Use of tube welding devices or other aseptic connection devices for transfer of product from one step to the next
What EM Should be Considered in Early Phase Studies?

Routine dynamic monitoring of the "clean" environment and operators is important to insure that modes of bioburden introduction are under control.

The recommendation is to:

- at least monitor viable particulates during aseptic processing
- understand the airflow in the hood and pressure differentials in areas of operations as the pressure differentials may provide an indication that the area is suitable for use.
Example for media challenge for aseptic processing

- Simulate all steps as best as possible, following an approved procedure.
- Use sterile media to simulate cell suspension.
- Sterilization method for all utensils and product contact surfaces should be performed the way for the process as well as the media simulation.
- Simulate the addition of any antigens/viruses/reagents, by adding the sterile media as you would in the process.
- Simulate mincing or cutting of tissue with sterile agar and utensils.
- Represent worse case conditions (all interventions into the hood as well as operators moving in and out of the lab).
How Soon in Development Should You Validate Aseptic Processing?

- Should be working towards demonstration of aseptic manipulation in the form of process simulations (such as media challenges)
- Should have qualified Biosafety Cabinets of appropriate air classification and on a maintenance plan for filter testing
- Should routinely monitor (if even settling plates) during processing of a patients cells or tissues
- Should have procedures in place
Conclusion

- Compliance with CGMP **is** necessary from phase 1 onward
  - adequate documentation (traceability) and facilities
  - sterility assurance
  - QC/QA oversight
- Certain cGMPs develop with product
  - defined in-process controls
  - full process and assay validation
Careful Control of the Process at All Stages can make a Difference!
Special Thanks To:

- Kim Benton
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We Are Here to Help You!!

- For facility and aseptic processing issues, please call CBER/Office of Compliance and Biologics Quality/Division of Manufacturing Product Quality, 301-827-3031
- For product and clinical issues please call CBER/Office of Cellular Tissue and Gene Therapy, 301-827-5102