Production Assistance for Cellular Therapies

Educational Web Seminar

"Interpretation of the Final Rule: *cGMP and Investigational New Drugs Intended for Use in Phase 1 Clinical Trials*"

Thursday October 15, 2009

12:00 Noon - 1:00 PM ET

Today's Education Web Seminar

SPEAKERS

Laurie Norwood, MS
Deputy Director
Division of Manufacturing and Product Quality
Office of Compliance and Biologics Quality

Scott Burger, MD
Principal
Advanced Cell and Gene Therapy, LLC

The presentation slides for this web seminar are available publicly on the main page at:
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Web Seminar

Description

The web seminar will provide an overview of the Final Rule and its implementation in the manufacture of cellular therapy products. Regulatory requirements and approaches to compliance will be discussed.

Objectives

- Discuss the extent of GMP compliance required for the manufacture of products used for Phase 1 clinical trials.
- Assess the parameters that define early clinical supply manufacture.
- Discuss the regulatory requirements outlined the Final Rule regarding the proposed exemption of Phase 1 investigational drugs from part 211 compliance.

Faculty Disclosure

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Faculty Disclosure Information

Faculty	Disclosure	Nature of Relationship	Manufacturer/Provider
Scott Burger	None	non-PACT member	Advanced Cell & Gene Therapy, LLC
Laurie Norwood	None	non-PACT member	FDA/CBER
Lisa Davis	None	PACT member	The EMMES Corporation
Nathan Kassalow	None	PACT member	The EMMES Corporation
Karin Quinnan	None	PACT member	The EMMES Corporation
David Styers	None	PACT member	The EMMES Corporation
Debbie Wood	None	PACT member	The EMMES Corporation

CGMP for Phase 1 INDs

Laurie P. Norwood

Deputy Director
Division of Manufacturing and Product Quality
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

U.S. Department of Health and Human Services
Food and Drug Administration

Overview

- Regulatory Basis/Background
- Final Rule
- Regulatory Strategy
- Guidance
  - Principles
  - CGMP in Clinical Supply Manufacture
  - Guidance Goals

Regulatory Basis

- FD&C Act at 501(a)(2)(B): drugs, including investigational new drugs, are required to be manufactured in accordance with current good manufacturing practice (CGMP). This is often referred to as "statutory CGMP"
  - Statutory CGMP is applied to product intermediates, bulk drug substances and active pharmaceutical ingredients, as well as finished pharmaceuticals
- 21 CFR 210/211:- CGMP regulations for finished pharmaceuticals
- 21 CFR 600-680 : licensing and biological standards for biological products

Regulatory Basis (cont'd.)

- Preamble to 1978 CGMP regulations [Response to Comment #49]:
  - "The Commissioner finds that, as stated in 211.1, **these CGMP regulations** apply to the preparation of any drug product for administration to humans or animals, **including those still in investigational stages**."

Regulatory Basis (cont'd.)

- … the process by which a drug product is manufactured in the development phase **be well documented and controlled…"**
- "…The Commissioner is considering proposing additional CGMP regulations specifically designed to cover drugs in research stage..."

Final Rule

- On July 15, 2008, FDA published a final rule in the Federal Register amending the CGMP regulations for human drugs , including biological products, ***to exempt most investigational "Phase 1" drugs from complying with the CGMP regulations (21 CFR 210/211).***
- Effective date:- September 15, 2008
- FDA will continue to exercise oversight of the manufacture of these drugs under FDA's general statutory CGMP authority and review of INDs.

21 CFR 210.2(c)

- 210.2 Applicability of current good manufacturing practice regulations.

  (c) An investigational drug for use in a phase 1 study, as described in Sec. 312.21(a) of this chapter, is subject to the statutory requirements set forth in 21 U.S.C. 351(a)(2)(B). The production of such drug is exempt from compliance with the regulations in part 211 of this chapter.

21 CFR 210.2(c) (cont'd)

However, this exemption does not apply to an investigational drug for use in a phase 1 study once the investigational drug has been made available for use by or for the sponsor in a phase 2 or phase 3 study, as described in Sec. 312.21(b) and (c) of this chapter, or the drug has been lawfully marketed. If the investigational drug has been made available in a phase 2 or phase 3 study or the drug has been lawfully marketed, the drug for use in the phase 1 study must comply with part 211.

http://www.fda.gov/OHRMS/DOCKETS/98fr/E8-16011.htm

Regulatory Strategy

- Even though exempt from the requirements of Parts 210/ 211, ***Phase 1 investigational drugs remain subject to the statutory CGMP requirements* of** FD&C Act 501(a)(2)(B).
- Phase 2 and Phase 3 investigational drug products still subject to the requirements of Parts 210/211

Regulatory Strategy (cont'd.)

- Provisions of FD&C Act 501(a)(2)(B) allow the agency to retain the ability to take appropriate actions to address manufacturing issues
- Inspectional Activity
  - Manufacturing and testing sites are subject to inspection
  - No formal inspection prerequisite requirement for sites manufacturing clinical investigational drugs

Guidance- CGMP for Phase 1 INDs

- recognizes that some controls and the extent of controls differ between investigational and commercial manufacturing, as well as phases of investigational clinical studies
- articulates FDA's intent to implement an incremental approach to CGMP compliance for clinical investigational products

Guidance- CGMP for Phase 1 INDs

- compatible and complementary to IND regulations
- intended to serve as a companion to other guidance describing CMC information submitted and reviewed in IND applications
- intended to be a reference for CGMP for INDs - guidance focusing on approaches to attain compliance

CGMP in Clinical Supply Manufacture

- Assure
  - safety and quality of investigational products
  - ability to reproduce investigational product as needed
  - consistent quality of investigational product
    - within a trial
    - between trials
    - from development to commercial manufacture

General CGMP Requirements

- Personnel
- QC Function
- Facility and Equipment
- Control of Components, and Containers and Closures
- Manufacturing and Records
- Laboratory Controls
- Packaging, Labeling and Distributing
- Record Keeping

QC Function

- 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

Facility and Equipment

- Adequate and appropriate - HVAC, light, water, plumbing, space etc.
- Adequate air handling to prevent contamination and cross-contamination
- Sufficient space, clean environment, and appropriate construction

Facility and Equipment

- Properly maintained, calibrated, cleaned and sanitized following written procedures and at appropriate intervals
- Constructed with material that will not contaminate or be reactive, additive or absorptive with product
- Identified and documented in production records

Special Manufacturing Situations

- Multi-product Facilities
- Biological/ Biotechnological Products
- Sterile/ Aseptic Processing

Multi-product

- 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

Biological and Biotechnology Products

- Appropriate equipment qualification and controls in production needed to assure safety related function (e.g., viral clearance, virus/toxin attenuation, pasteurization) will perform as intended
  - Accompanying testing for safety related functions
- Need to consider possible need for containment considerations (highly toxic or infectious materials)
  - Recommend consulting the Center with FDA that is responsible for your product.

Sterile/ Aseptic Processing

- Remember for Phase I investigational products – "Safety and rights of subject" 21 CFR 312.22(a)
- Take special precautions –cleaning, equipment maintenance, monitoring
- Aseptic manipulation conducted under appropriate conditions (e.g., Class 100 conditions - laminar flow hood)
- Appropriate training for operation and release of sterile products
- Document and follow all procedures intended to maintain the sterility of the components, in-process materials, API and final product

Achieving CGMP Compliance

- Utilize effective quality control (QC) principles, i.e.:
  - well defined written procedures
  - adequately controlled equipment
  - accurate + consistent recording of all data
- Implement CGMP consistent with good scientific methodology, product development and quality principles

Considerations for Later IND Phases

- CGMP reflect and are consistent with good product development
  - quality perspective - continue to assure ***safe*** products
  - implement controls that reflect accumulated product and process knowledge and experience
  - provide greater assurance in linking product quality to commercial manufacture

Guidance Goals

- Provide some clarity on approach and expectations
- Help assure ***safe*** investigational products
- Facilitate product development

Special Thanks To:

- John Eltermann
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CGMP for Phase I INDs:
Manufacturing Cell Therapy Products

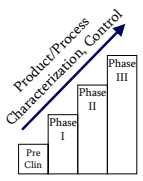
Scott R. Burger, MD
Advanced Cell & Gene Therapy

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

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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.

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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.

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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

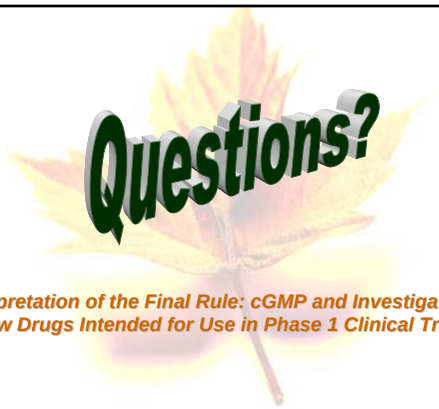
- Defined, written procedures - sample handling, assays
- Controlled analytical equipment and methods
- Assay validation not required at Phase I
- Accurate data records
  - Double sign-off?
- QC testing staff
  - Should be separate from manufacturing staff. If combined, then independent QA oversight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



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Speaker Contact E-mail

Scott Burger, MD
celltherapy@ac-gt.com

Laurie Norwood, MS
laurienorwood@fda.hhs.gov

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