



# 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
- Mary Malarkey
- Carolyn Renshaw
- Chiang Syin