FDA Perspective on Approaches for Complying with CGMPS During Phase I INDs: Draft Guidance for Industry

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March 29, 2006 PDA Chapter meeting

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

Overview:

- **Regulatory Basis/Approach**
- **FDA CGMP Guidance**
- **FDA Proposed and Direct Final Rule**
- **Draft Guidance: Developmental Principles**
- **Draft Guidance: Scope**
- **Draft Guidance: Recommendations for CGMP Compliance**

Regulatory Basis/Approach

- **Drugs and biologics <u>including investigational new drugs</u> are required to be manufactured in accordance with CGMPs**
  - if not, considered adulterated [501(a)(2)(B) Food, Drug and Cosmetic Act]
- **21 CFR 210, 211 Current Good Manufacturing Practices for Finished Pharmaceuticals Regulations [1978]**
- **No specific regulations for API production**
  - (Q7A GMP Guidance For Active Pharmaceutical Ingredients [Adopted by FDA, September 2001])

Regulatory Basis/Approach

- **CGMP regulations (i.e., 21 CFR 210, 211) are applicable for approved drugs and investigational new drugs for administration to humans or animals**
  - "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." [Response to comment #49, Preamble 1978 CGMP rule]

"… the process by which a drug product is manufactured in the development phase be well documented and controlled…" [Response to comment #49, Preamble 1978 CGMP rule]

Regulatory Basis/Approach

- **Some CGMP regulations are designed for repetitive, commercial manufacture of an approved product**
  - Defined product quality attributes; uses an established manufacturing process
- **Types and extent of some controls may differ – due to stage of development**
  - The Commissioner is considering proposing additional CGMP regulations specifically designed to cover drugs in research stage [Response to comment #49, Preamble 1978 CGMP rule]
- **CGMP principles are clearly applicable to manufacture of investigational new drug products**

FDA CGMP Guidance

- **FDA Guidance Documents are aimed at fostering compliance with CGMP, however, few directly address issues related to CGMP for clinical investigational products**
  - "FDA Guideline on the Preparation of Investigational New Drug Products (Human and Animal)" 1991
  - Section 19, Q7A GMP Guidance For Active Pharmaceutical Ingredients [FDA adopted September 2001]

FDA CGMP Guidance

- **The 1991 Guideline for preparation of investigational new drug products does not :**
  - adequately cover all manufacturing situations of investigational new drug products
  - fully address FDA's expectation that a specific stage approach to manufacturing controls is acceptable for investigational new drug products

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

Proposed and Direct Final Rule

- **On January 17, 2006, FDA published a proposed rule and a direct final rule in the Federal Register to amend current good manufacturing practice (CGMP) regulations for human drugs, including biological products, to exempt most investigational "Phase 1" drugs from complying with the CGMP regulation (21 CFR 210/211).**
  - Written comments are due April 3, 2006
  - http://www.fda.gov/ohrms/dockets/98fr/06-353.htm

Proposed and Direct Final Rule

- **“This action is intended to streamline and promote the drug development process while ensuring the safety and quality of the earliest stage investigational drug products, those intended for use in Phase 1 clinical trials.”**

Proposed and Direct Final Rule

- **"Even if exempted from the requirements of parts 210/211, investigational drugs remain subject to the statutory requirement the deems a drug adulterated, FD&C Act 351(a)(2)(B)."**
- **"Every IND must contain, among other things, a section on CMC that describes the composition, manufacture, and control of the IND 21 CFR 312.12(a)(7)."**
- **"Under IND authority, FDA had the option to place an IND on clinical hold if the study subjects would be exposed to an unreasonable and significant risk or if the IND does not contain sufficient information to assess the risks to subjects, 21 CFR 312.42."**

Proposed and Direct Final Rule

- **“Even though the FDA is exempting Phase 1 drug products from compliance with the specific requirements of the CGMP regulations, the agency retains the ability to take appropriate actions to address manufacturing issues.**

Proposed and Direct Final Rule

- **Proposal removes having to follow 211 designed for commercial production and not appropriate in some aspects with production of investigational products.**
- **We are not decreasing the standards but providing clarification**
- **Appropriate cGMPs still should be followed**

Companion Draft Guidance

- **At the same time, FDA published a draft guidance entitled *"INDs – Approaches to Complying with CGMP During Phase 1"* to provide guidance for "recommendations on approaches to statutory compliance" to manufacture Phase 1 material**
  - http://www.fda.gov/cber/gdlns/indcgmp.pdf

Draft Guidance: Developmental Principles

- **Developed by Agency workgroup (CDER, CBER, ORA) composed of compliance staff, CMC reviewers, and inspectors**
- **General CGMP**
- **Utilize risk-based approach**
  - available knowledge
  - **<u>emphasis on safety</u>**

Draft Guidance: Developmental Principles

- **Assure safe investigational products**
  - Assure quality of investigational product
- **Assure consistent quality of investigational product - ability to reproduce investigational product, as needed**
  - Within a trial
  - Between trials
  - Throughout development to commercial manufacture

Draft Guidance: Scope

- intended to serve as a companion to other guidance describing chemistry, manufacturing and control information submitted and reviewed in IND applications for Phase 1 studies

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

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 Guidance: Recommendations for CGMP Compliance

- **Utilize Technologies and Resources to:**
  - Facilitate
    - CGMP compliance
    - Product development (streamline)
- **For example, consider utilizing**
  - Disposable equipment and process aids
  - Prepackaged WFI & sterilized containers
  - Closed process equipment
  - Contract or shared production & testing facilities

Draft IND-Phase I GD
General CGMP Requirements

- 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 CGMPs 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**

Facilities

- **Adequate and appropriate - HVAC, light, 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**

Equipment

- Appropriate for intended function
- 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

Components

- Written procedures describing handling, and control of components
- Establish specified attributes & acceptance criteria (AC) (attributes & AC not always possible)
- Review of documentation (COA) to ensure conformance/ testing when documentation is incomplete
- Record relevant information – traceability

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

Laboratory

- **Production tests**
  - Specified quality attributes monitored – appropriate acceptance criteria applied (e.g., known safety-related and other tests as appropriate)
  - Scientifically sound analytical procedures (e.g., specificity, sensitivity, accuracy)
  - Tests conducted using written procedures under controlled conditions
  - Periodic calibration and maintenance of laboratory equipment
    - Consider systems suitability

Laboratory

- **Retain representative sample for additional release testing**
- **Initiate stability study to support use in clinical trials**

Container Closure and Labeling

- **Packaging to protect product from contamination, damage, etc., during handling, (including shipment) & storing**
- **Control labeling to prevent mix-ups**

Distribution

- **Describes the transport of the IND product from the point of production to the patient/subject for consumption**
- **Record should allow for traceability**

Record Keeping

- **Retain records related to quality and production process**
- **How long?**
- **Retention of records required by IND Part 312.** **[21 CFR 312.57]**
  - 2 yrs after approval of marketing application
  - 2 yrs after shipment and delivery of the investigational drug if discontinued and FDA notified

Special Production

- **Screening Studies/Microdose Producers**
- **Multi-product Facilities**
- **Biological/ Biotechnological Products**
- **Sterile/ Aseptic Processing**

Screening Studies/Microdose Producers

- **Studies often performed in small-scale lab or research lab**
- **When same area, study and research lab are used – special considerations'**
  - Orderly handling of materials and equipment
  - Avoid contamination of equipment and product
  - Prevent mix-ups
  - Equipment be used or single purpose (research only or production only) at any given time

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

Multi-product

- **Multi-product aspects – potential impact on other product**
  - Have considered unknowns
  - Don’t place existing systems, process and facilities at risk
- **Common attribute of contract manufacturers**

Biological and Biotechnology Products

- **Appropriate equipment qualification and controls in production needed to assure safety related function (e.g., viral clearance, viral toxin inactivation, pasteurization) will perform as intended**
  - Accompanying testing for safety related functions
- **Difficulty distinguishing changes in quality attributes or predicting impact of observed changes on safety**

Multiple Batches

- **Producers of multiple batches (e.g., therapeutic vaccines, cell therapies)**
  - Consistency among batches is important
  - Accelerated accumulation of data rather than typical manufacture
  - Periodic review and modification to control procedures and production operations
- **If not possible to follow/comply with CGMP**
  - Include rationale for approaches followed in records for investigational product
  - Include reasons

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**

What Does FDA Hope to Achieve By This Guidance?

- **Provide some clarity on approach and expectations**
- **Help assure safe investigational products**
  - Avoid cross contamination
  - Prevent microbial contamination
  - Assure purity of IND material
- **Facilitate product development/ Critical Path**

CGMP & Product Development

SAFETY INFORMATION

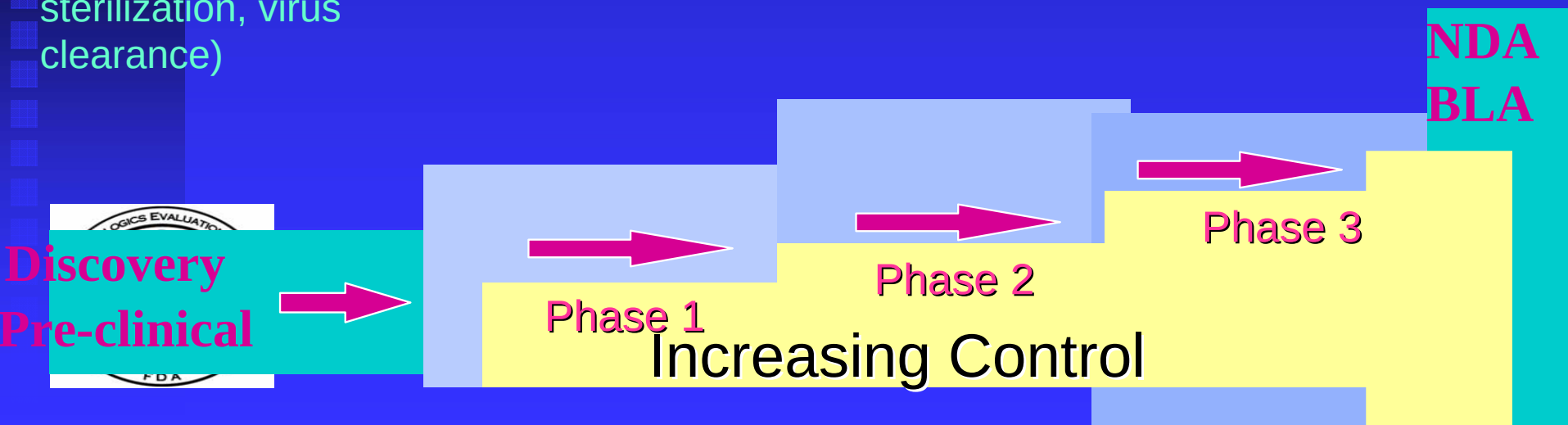
- Source characterization
- Raw materials qualification
- DS/DP Characterization
- Testing/Qualification/ Clearance of impurities, contaminants
- Process control esp. for safety processes (e.g., sterilization, virus clearance)

DEVELOPMENT ACTIVITIES

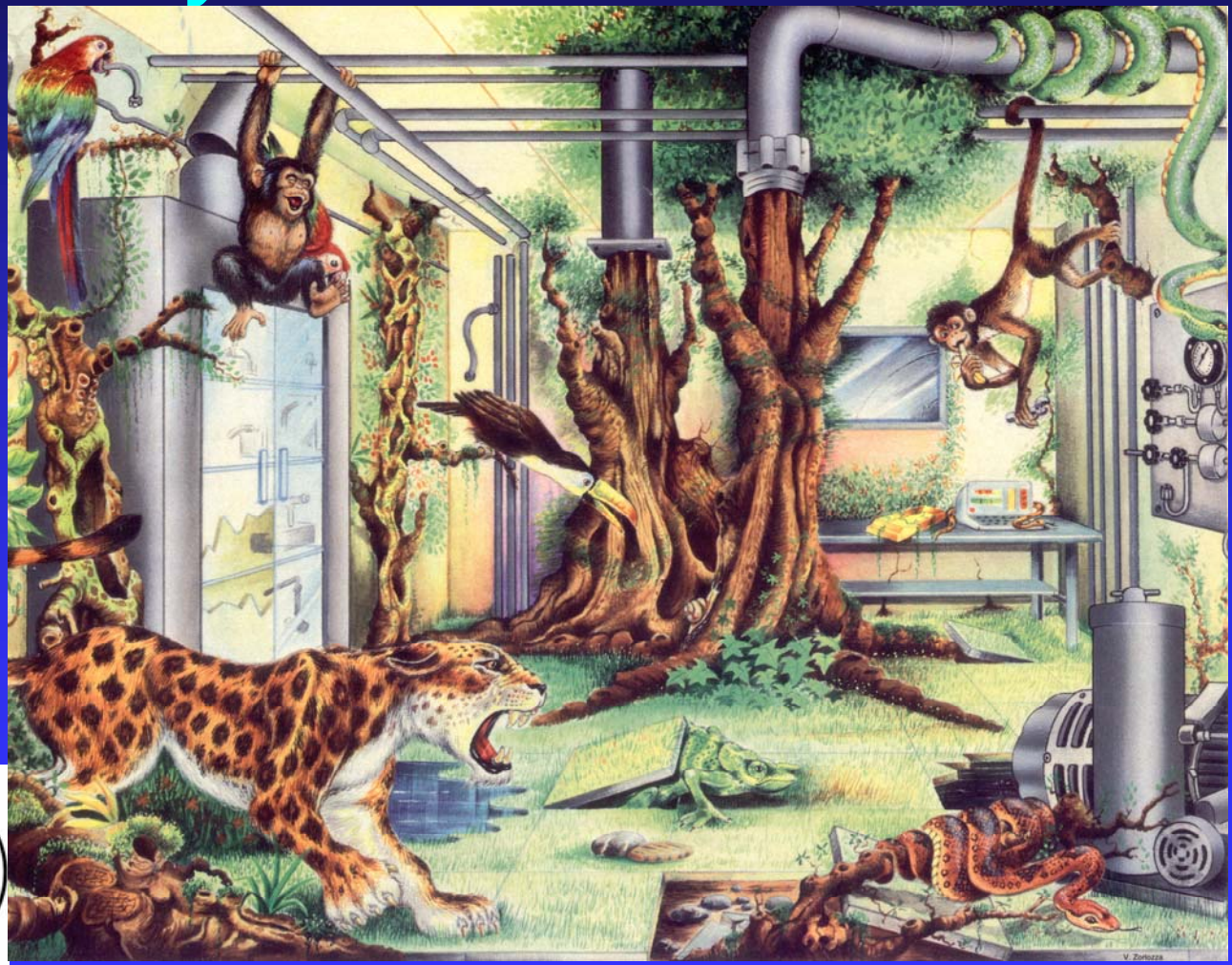
- DS & DP Characterization
- Formulation Development
- Raw Material/ Component characterization
- Assay Development/ Validation
- Specification Development
- Stability
- Manufacturing Process Control & Validation

CGMP

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



Are you in control of your process and systems?



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To Provide Comment to the Proposed and Direct Final Rule

- **To comment on the** proposed or direct final rule **to exempt phase 1 material from CGMP regulation (these rules are identical; any comments received will be applied to both) or Docket 2005N-0285, send your comments by April 3, 2006.**
- **You may send them electronically to: http://www.accessdata.fda.gov/scripts/oc/dockets/comments/SEARCHRESULTS.CFM**
- **Or send two copies of your written comments to:**
- **Docket 2005N-0285**
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