A Response to “FDA Perspective for Approaches for Complying with cGMPs During Phase I INDs: Draft Guidance for Industry”

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BACKGROUND

- Phase I Guidelines - 1991
- Revised Phase I Guidelines - 2006
- European Guidelines - Annex 13 Manufacturing of Investigational Medicinal Products
- Q7A GMP Guidance For Active Pharmaceutical Ingredients - 2001

BACKGROUND

- FDA Perspective on Approaches for Complying with CGMPS During Phase I INDs: Draft Guidance for Industry
- Drugs and biologics including investigational new drugs are required to be manufactured in accordance with CGMPs

BACKGROUND

- Preclinical
- Phase I, II, III
- Commercial
- GMP Requirements continually increase

BACKGROUND
Revised Phase I Guidelines

- 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 I clinical trials.”

HISTORIC PERSPECTIVE

- “FDA Guideline on the Preparation of Investigational New Drug Products (Human and Animal)” 1991
- No specific regulations for API production
  - (Q7A GMP Guidance For Active Pharmaceutical Ingredients [Adopted by FDA, September 2001])

HISTORIC PERSPECTIVE

- The current 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

RATIONALE FOR NEW DOCUMENT

- Draft guidance for Phase I INDs: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

DESIRABLE FEATURES

- Utilize Technologies and Resources to:
  - Facilitate
    - cGMP compliance
    - Product development (streamline)
- For example, consider utilizing
  - Disposable equipment and process aids to reduce cleaning bioburden
  - Prepackaged WFI & sterilized containers to eliminate qualifying existing equipment

DESIRABLE FEATURES

- Use of closed process equipment to eliminate stricter room classification for air quality
- Use of contract or shared production & testing facilities for production and testing of investigational product.

Draft IND-Phase I
General CGMP Requirements

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

Screening Studies/Microdose Producers

- Studies often performed in small-scale lab or research lab
- When same area, e.g., study and research lab are used – special considerations include
  - Orderly handling of materials and equipment
  - Avoiding contamination of equipment and product
  - Preventing mix-ups
  - Equipment is used for 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

UNDESIRABLE FEATURES

- Even though the FDA is exempting Phase I 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.

What Does FDA Hope to Achieve By This Guidance?

- Provide 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

Guideline Comments - Industry

- Manufacturing processes are not locked in place during Clinical Trial material preparation
- Processes are often changed to:
  - Increase efficiencies
  - Increase yields
  - Meet requirements of larger numbers of clinical subjects

Guideline Comments - Industry

- Guidance may be misinterpreted as to the requirements for assuring sterility of injectable products
  - Need for environmental monitoring
  - Qualification of the aseptic processing by media fill trials

Guideline Comments - Industry

- Phase I proposed guidelines are supposed to reduce the quantity of documentation that is produced when a manufacturer develops a Phase I drug
- Because it is unknown if the proposed drug will enter Phase II Clinical Trials, the manufacturer may take a more conservative approach

Guideline Comments - Industry

- Material that remains following a Phase I study would most likely be used in a Phase II study
- Savings would, therefore, be questionable since the Phase II guidelines would follow commercial GMP requirements

Guideline Comments - Public

- FDA has understated the risk to patients
- FDA estimates that about 255 INDs would be impacted per year
- With a maximum of 80 volunteers per trial each year, upwards of 20,400 patients would be placed at risk

Guideline Comments - Public

- FDA typically inspects a product for the first time during the Pre-Approval Inspection at the end of the pivotal Phase III trial
- PAI inspections of facilities and operations are far different from those used for Phase I
- With these Phase I inspections, the individual investigators will have few inspection documents and fewer court cases for guidance purposes
- Industry will be left without clear rules

Guideline Comments - Public

- The guidance document is designed to replace CFR 211 for Phase I
- FDA does not always enforce these documents – thereby inviting misunderstandings and inconsistencies
- Medical Devices have experienced a more than 300% increase in the number of deadly recalls since 1998 – even with Design Controls in place

EU: GMPs for the Manufacture of Investigational Medicinal Products

- Specifications and Instructions
  - Specifications for raw materials, primary packaging materials, intermediate, bulk and finished products should be as comprehensive as possible given the current state of knowledge
  - Should be periodically re-assessed during development and updated as required to account for current technology, regulatory and pharmacopoeial requirements

EU: GMPs for the Manufacture of Investigational Medicinal Products

- Product Specification File should include:
  - Specifications and analytical methods for materials listed on previous slide
  - Manufacturing methods
  - In-process testing and methods
  - Approved label copy
  - Technical agreements with contract vendors
  - Stability data
  - Storage and shipment conditions

EU: GMPs for the Manufacture of Investigational Medicinal Products

- Qualified Person
  - Determines that equivalent standards of cGMP apply through knowledge of the Quality system employed at the manufacturer
  - Knowledge is normally acquired through participation in audit of the manufacturer's Quality systems (even during Phase I production)

EU: GMPs for the Manufacture of Investigational Medicinal Products

- Requirements for Batch Certification
  - Batch records, in-process test reports, any release reports, deviations
  - Production conditions
  - Validation status of facilities, processes and conditions
  - Examination of finished packs
  - Stability reports
  - Source and verification of conditions of storage and shipment

EU: GMPs for the Manufacture of Investigational Medicinal Products

- Requirements for Batch Certification (con't)
  - Audit reports concerning the manufacture's Quality systems
  - All other factors of which the QP is aware that are relevant to the Quality of the batch

EU: GMPs for the Manufacture of Investigational Medicinal Products

- Batch documentation held for five years after completion of the clinical study.
- Samples of each batch of bulk formulated product and packaging components should be retained for two years beyond the completion of the clinical trials.
- Reference: EU. Good Manufacturing Practices. Annex 13. Manufacture of Investigational Medicinal Products. July 2003

EU: GMPs for the Manufacture of Investigational Medicinal Products

- Immediate container and General case
  - Name, address and telephone # of sponsor
  - Dosage form, route of admin., quantity of dosage units
  - Batch number
  - Trial reference code
  - Trial subject ID # and treatment #

EU: GMPs for the Manufacture of Investigational Medicinal Products

- General case
  - Name of the investigator
  - Directions for use
  - “For clinical trial use only”
  - Storage conditions
  - Period of use (use by date)
  - “Keep out of reach of children”

CONCLUSIONS

- Phase I Guidelines (1991) offered a gradual cGMP progression
- Phase I Guidelines (2006, proposed) created a distinct difference – very loose for Phase I, full cGMPs for Phase II/III
- Proposed Phase I Guidelines created a chasm when compared to European GMPs for Investigational Medicinal Products

CONCLUSIONS

- European – How does one manage the Qualified person in the proposed Guideline environment
- Proposed Phase I Guidelines offer an orderly method, but need to gradually increase, not abruptly institute GMPs
- Citizens' Groups need to be assured that the FDA is safeguarding the public – even with Phase I Clinical Trial materials