CGMPs for Early Phase Manufacturing

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• The views, positions, and opinions in this presentation are that of the presenter and not of the FDA
Foundation

• The investment in controls and development for early phase manufacturing is a balance between risk acceptance and risk mitigation

• But of what risk are we speaking?
  – To the patient?
  – To the manufacturing process?
  – To the study reliability?
  – To further product development / commercialization?

• What do we want:
  – Safe product
  – Meaningful results
  – Further development is built on data driven knowledge

• The objectives of trials should guide the objectives in manufacturing and development
Current FDA framework

• 501(a)(2)(B) of the FD&C Act
  – Phase I – 2008 GFI: CGMP
  – Phase II/III – 21 CFR 210 and 211
  – Commercial - 21 CFR 210 and 211
Does CGMP Apply to Clinical Trial Material?

49. One person proposed that the term "drug product" be replaced with the words "commercial dosage form" to exempt drugs undergoing development from the requirements of these regulations.

- 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. It is appropriate that the process by which a drug product is manufactured in the development phase be well documented and controlled in order to assure the reproducibility of the product for further testing and for ultimate commercial production. The Commissioner is considering proposing additional CGMP regulations specifically designed to cover drugs in research stages.
Does CGMP Apply to Clinical Trial Material?

62. A comment was received stating that the term "drug product" as defined in 210.3(b)(4) excludes placebos because the definition includes the phrase "active drug ingredient.

- The intended use of placebos in medical treatment is to bring about a therapeutic effect, without a pharmacologically active agent, because of the psychic effect in some patients that may produce symptomatic relief. In addition, it is often used as a control in clinical trials for new drugs. Even though the chemicals from which the placebos are made are not intended to cause a direct pharmacologic response, the maintenance of their quality is important because of their use in patients, particularly in controlled drug studies. By its use, a placebo meets the definition of a "drug" contained in section 201(g) of the act. Therefore, to eliminate any doubt whether these regulations apply to placebos, the Commissioner has revised the definition to include them specifically.
Foundation

• What is CGMP?
  – A proactive approach to ensure that a drug meets its quality requirements
  – A philosophy to ensure appropriate design, control and continuing development throughout the product lifecycle
  – A culture that accepts that mistakes and failures will happen, but that these must be used as learnings to improve the process, controls, and product

• What isn’t CGMP?
  – Checklist approach to meet quality requirements.
Phase I Guidance Overview

• Applies to phase 1 investigational drugs whether they are manufactured in small or large scale environments

• Does not apply to:
  – Human cell / tissue, Devices, Phase 2 / 3 products, Approved products, PET drugs

• Recommendations that provide flexibility to the manufacturers in implementing CGMP controls appropriate to their specific situation and application
Phase I Guidance Overview

• At its core, the CGMP guidance for phase I aims to ensure two major objectives

  – A comprehensive and systematic evaluation of the manufacturing setting to identify potential hazards

  – Appropriate actions to eliminate or mitigate potential hazards to safeguard quality of the drug
Phase I Guidance Overview

• This is achieved through:
  – Well-defined, written procedures
  – Adequately controlled equipment and manufacturing environment
  – Accurately and consistently recorded data from manufacturing (including testing)

• Benefits:
  – Phase 1 drug quality
  – Study integrity
  – Future process development integrity
Phase I Guidance: Focus Areas

A. Personnel
   - Adequately trained with proper education and experience to perform their duties
   - Familiar with QC principle in complying with CGMP

B. QC – roles and responsibilities
   - Ensure C/C/C are adequate for use
   - Review and approve manufacturing / testing procedures
   - Release / reject batch
   - Investigate unexpected results / errors / complaints
   - Corrective Action, if needed
Phase I Guidance: Focus Areas

C. Facilities and Equipment
   – Clean and of adequate size
   – Constructed to prevent contamination and obtain the correct product

D. Control of C/C/C
   – Handle and store in a manner to prevent mix up, contamination, degradation
   – Ensure only adequate materials are used (meets acceptance criteria for specified attributes)
   – Track and trace materials
E. Manufacturing and Records
- Record to document materials, equipment, procedures used, and any problems encountered during manufacturing
- Record and rationale for changes
- Record of microbiological controls

F. Laboratory Controls - Laboratory tests should
- Be sound, suitable, and reliable
- Demonstrate that product meets acceptance criteria (those known at the time)
- Be Conducted under controlled conditions
- Be Conducted with calibrated and maintained equipment
- Be Documented for conformance and changes
- Have samples retained for potential future investigations
- Include stability testing for the duration of the clinical trial to ensure quality during use
Phase I Guidance: Focus Areas

G. Pack Label and Distribution
   – Packaged to protect from alteration, contamination or damage during packing, storing, and distributing
   – Product segregation, label reconciliation, verify operations by a second person, confirmatory laboratory testing, QC review, temperature control (if needed)

H. Recordkeeping - Complete records for:
   – Equipment maintenance and calibration
   – Manufacturing records and related analytical test records
   – Distribution records
   – QC functions (as defined in section V.B)
   – Component records
   – Deviations and investigations, complaints
Common Themes

• Aims to ensure suitability of early stage CTM manufacturing operations in support of clinical trials.
  – Maximizes safety
  – Prevent contamination and mix-ups
  – Ensure facilities, equipment, materials, C/C/C are suitable for use (testing and oversight)

• Quality Systems to control operations as much as possible
  – Supports reproducibility
  – Provides platform for process evolution understanding (development of manufacturing operations to the proposed commercial process)
  – Build process knowledge
  – Manage deviations
Phase I Guidance: Additional Focus

- Quality systems: Unplanned deviations
  
  “Responsibility for investigating unexpected results or errors that occur during manufacturing or from complaints received and initiation of corrective action, if appropriate.”

- There should be oversight to document, evaluate and determine the impact of an unplanned deviation on:
  
  - Product quality
  - Patient safety
  - Need for corrective action
  - Batch release decision
  - Process understanding / evolution
Phase I Guidance: Additional Focus

• Equipment:
  – Sufficient space, clean environment, appropriate construction
  – Appropriate lighting, ventilation, and heating
  – Appropriate cooling, plumbing, washing, and sanitation
  – Appropriate equipment to maintain an air cleanliness classification suitable to the operation performed in the area
  – Appropriate equipment that will not contaminate the phase 1 investigational drug or otherwise react with, add to, or be absorbed by the phase 1 investigational drug; and that is properly maintained, calibrated, cleaned, and sanitized at appropriate intervals following written procedures

• Ensure equipment is suitable for its intended use and capable of delivering the intended quality of the product under the actual conditions of use.
Phase I Guidance: Additional Focus

- Batch Documentation and Execution should minimally include:
  - Materials
  - Equipment
  - Actual procedures utilized
  - Problems / deviations encountered during manufacturing
  - Record of changes in process / procedures and rationale for these changes
  - Record of microbiological controls
Phase I Guidance: Additional Focus

- Adequate documentation allows for quality and technical review to support:
  - Quality of material manufactured
  - Batch release decision
  - Process development
  - Conformance with clinical program needs
  - Replication of the process
Phase I guidance

• The driving concepts:
  – Patient safety
  – Product quality
  – Study reliability
  – Manufacturing evolution
Example

• Product:
  – Modified release tablet consisting of successive coating layers

• Indication:
  – Treatment of primary hypertension

• Design:
  – Inert tablet coated with IR drug layer, DR layer, IR drug layer, protecting coat

• Coating process employed pan coating operations

• Intended commercial site, equipment, process used for pivotal clinical trial material
Example

• Pre Inspection Assessment:
  – Drug product design had very small amounts of coating in the 1st DR layer and protective coat layer
  – Coating process controls were ambiguously described in the application

• Inspection:
  – PAI found that equipment was not qualified to coat to levels needed for product
  – PAI found that control methodology hid significant variability
Example

- Post Inspection Assessment:
  - Same facility, process, equipment and quality system was used for both CTM and demonstration batch manufacturing
  - Failures observed on PAI called the reliability of CTM product into question
  - Variability observed in the qualification study held that CTM drug layers could be anywhere from 0%-200% of the intended target
  - Control methods employed were not powered to detect this variability
  - As a result, there was no confidence that the clinical study was evaluating the product that the firm intended to manufacture
In Summary

• Keep the goals in mind:
  
  – Ensure product quality does not adversely impact patient safety
  
  – Provide confidence that product quality does not adversely impact the reliability of clinical studies; ‘variability cognizance’
  
  – Provide a foundation where the process / product evolution is clear and understandable so that decisions in support of a commercial manufacturing process can be justified
Intentions Drive Behavior, Behavior Drive Outcomes

• Care about the people you are treating

• Care about the integrity of your science

• Care about the quality of your product

• Seek ways to make your product / process better

• Failures will happen, however react, prevent, and design accordingly
Questions?

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• Backup
Phase 1 CGMP Guidance

• if an investigational drug has already been manufactured by an IND sponsor for use during phase 2 or phase 3 clinical trials or has been lawfully marketed, manufacture of such a drug must comply (21 CFR 211.1) with 21 CFR part 211 for the drug to be used in any subsequent phase 1 clinical trials, irrespective of the trial size or duration of dosing.