Phase appropriate cGMP for Investigational Drugs

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Presentation outline

Background

- Definition
- Regulatory framework- law, regulation and guidance

Phase Appropriate GMPs and CMC information

- Quality System, cGMP, and CMC

GMPS during development

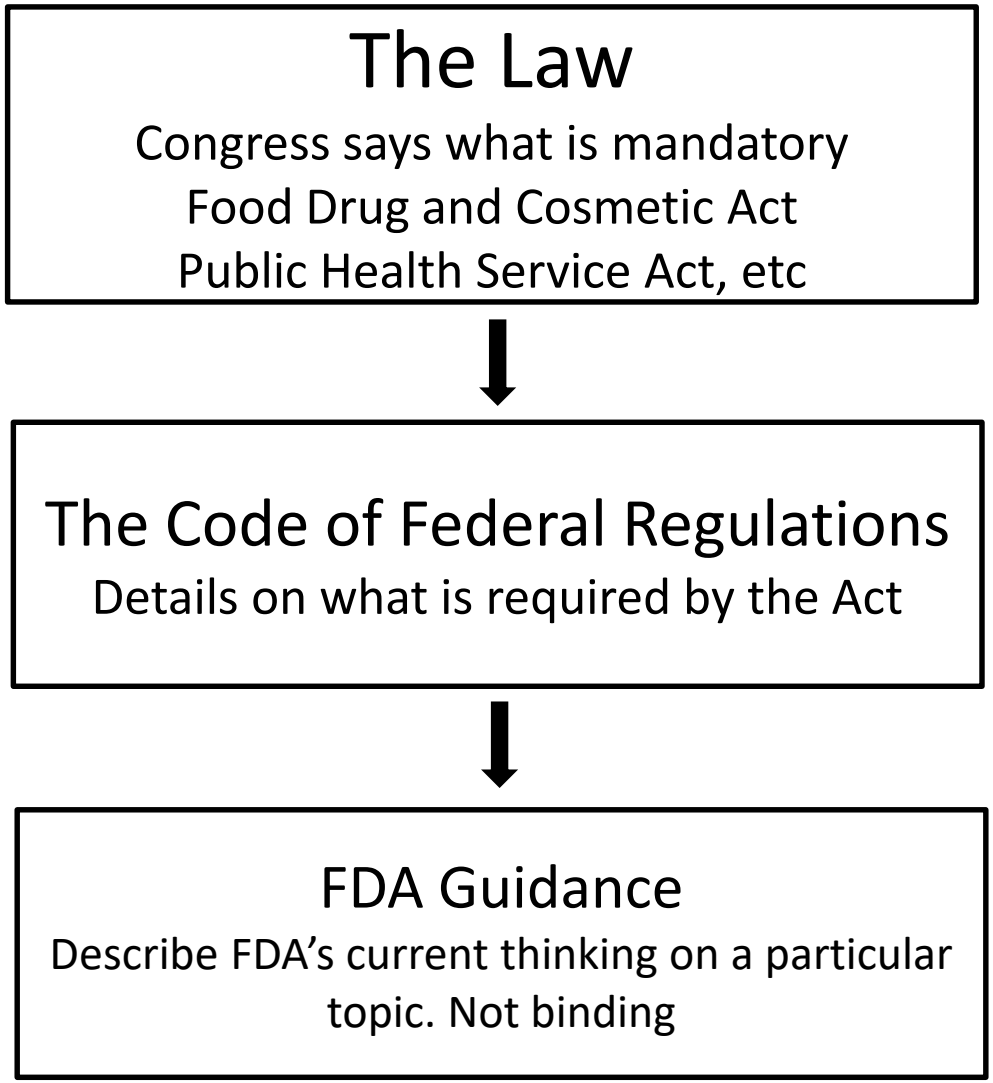
- R&D and pre-clinical
- Phase1
- Phase 2 and 3
- Inspections

What are CGMPs?

- Refer to Current Good Manufacturing Practices regulations enforced by FDA
- Provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities.
- Assure the identity, strength, quality, and purity of drug products by requiring that manufacturers adequately control manufacturing operations (quality management systems, quality of raw materials, detection/investigation of deviations, testing laboratories)
- Quality built into the design and manufacturing process and not on product testing alone

- Current GMP
  - Flexible, dynamic to allow innovation
  - Require use of up-to-date technologies and systems to comply with the regulations

Regulatory Framework



Legal bases for cGMP

Section 501(a)(2)(B) of the FD&C Act requires drugs to comply with current good manufacturing practice

"A drug...shall be deemed to be adulterated...if...the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess."

Legal bases for cGMP

FDASIA 2012 amendment to Section 501

"…'current good manufacturing practice' includes the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products.''

GMP Regulations

To implement the cGMP statutory requirement, FDA issued CGMP regulations for drugs and biological products:

- **Title 21 Code of federal regulation (CFR) part 210**: CGMPs in manufacturing, processing, packing, or holding of drugs; General
- **Title 21 Code of federal regulation (CFR) part 211**: CGMP for Finished Pharmaceuticals
- **Biological products** are subject to 21 CFR parts 210 and 211 and to 21 CFR parts 600-680, as relevant
- **GMPs apply to investigational New Drugs**

Phase appropriate cGMPs

Phase 1

- Must meet statutory GMPs
- Exempted from complying with 21 CFR part 211 under 21 CFR 210 (c)

"An investigational drug for use in a phase 1 study, as described in 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…"

- Exceptions to 21 CFR 210 (c):

- Investigational drug has been available in a phase 2 or 3 study
- Investigational drug used in a phase 1 clinical studies is marketed (e.g new indication)

Phase appropriate cGMPs

Phase 1 (cont'd)

Current GMP expectations for Phase 1 described in FDA guidance document: Current Good Manufacturing Practice for Phase 1 Investigational Drugs, July 2008
http://www.fda.gov/cder/guidance/GMP%20Phase1IND61608.pdf

– Facilitate initiation of investigational clinical studies
– Protect humans subjects

Phase 2 and 3

Subjected to 21 CFR parts 210 and 211

Graded CMC information

312.23(a)(7)(i) regulations emphasize the graded nature of manufacturing and controls information.

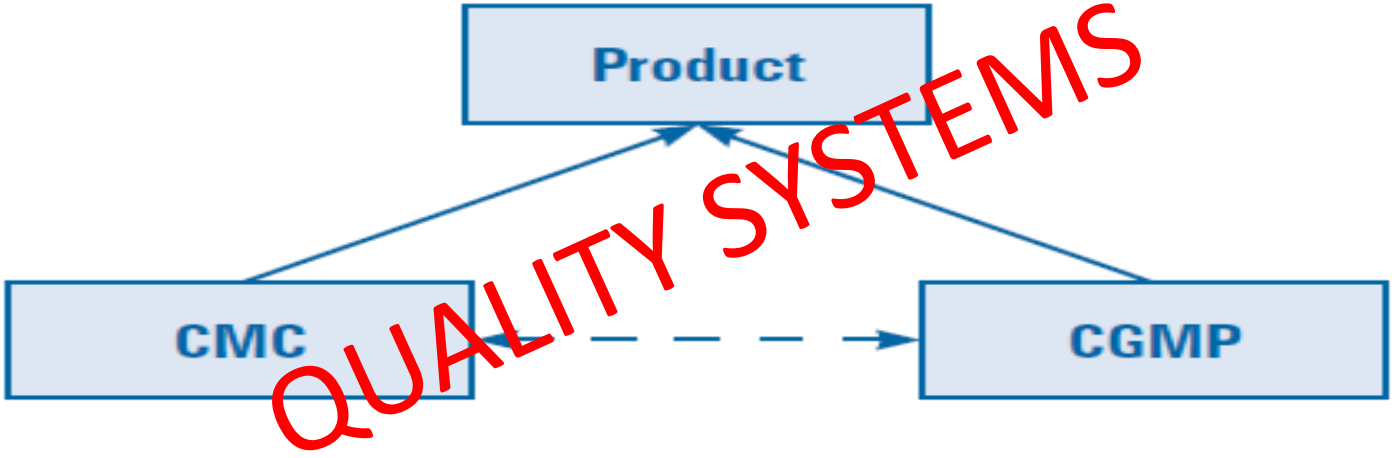
" Although in each phase of the investigation sufficient information should be submitted to assure the proper identification, quality, purity, and strength of the investigational drug, the amount of information needed to make that assurance will vary with the phase of the investigation, the proposed duration of the investigation, the dosage form, and the amount of information otherwise available."

Quality systems

- Support the development and manufacture of the investigational drug
- Assure the safety and quality of products intended for use in clinical trials
- Allow manufacture of equivalent/comparable IND product for future clinical trials[1]
- Graded implementation throughout development
- Evaluated during facility inspections

[1]Preamble to the CGMO 1978, comment 49…"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…"

cGMPs and CMC support product quality



- Information provided in the submission
- FDA Regs: IND, BLA, or NDA regulations, relevant FDA guidances and ICHQ1-6, ICH Q8

- Information collected at manufacturing/testing facility
- FDA Regs: 21 CFR parts 210 and 211, and 21 CFR parts 600-680 for BLA products.
- Relevant FDA guidances and ICH Q7, Q8-10

Figure modified from PDA Technical Report No. 56

GMPs during R&D and toxicity studies

GMPS do not apply in the strict sense

Knowledge development

Data and information are documented and traceable

- Production of R&D and toxicology batches
- Characterization and testing of the toxicology material
- Raw material records

Use the preclinical data to support the safety of the clinical materials

Ensure that the process is scalable and transferrable to a GMP facility without impact to CQAs

GMPs during development: Phase 1

Adherence to CGMP during manufacture of phase 1 investigational drugs occurs mostly through:

- Well-defined, written procedures
- Adequately controlled equipment and manufacturing environment
- Accurately and consistently recorded data from manufacturing (including testing)

GMPs during development: Phase 1

- Consider hazards and associated risks from the manufacturing environment on product quality (e.g. cross contamination)
- Take appropriate actions prior to and during manufacturing to eliminate or mitigate potential hazards and risks
- Must be in effect for the manufacture of each lot of investigational drug used in phase 1 clinical trials
- Both sponsor and contractor are responsible for assuring the Phase 1 material is manufactured under CGMP

GMPs during development: Phase 1

Manufacturing controls applicable to the manufacture of phase 1 investigational drugs

A. Personnel - appropriate training
B. Quality Control Function- independent of manufacturing responsibilities
C. Facility and Equipment –adequate work areas and equipment
D. Control of Components, and Containers and Closures - written procedures, acceptance criteria, identity testing
E. Manufacturing records- detailed to replicate the manufacturing process
F. Laboratory controls, suitable methods, equipment calibration, retain samples. Stability study.
G. Packaging, labeling and distribution- protect from contamination
H. Recordkeeping

Document control

- Data and information should be recorded
  - Release testing
  - In process testing
  - Raw material qualification
  - Manufacturing
  - Changes to procedures/processes, including rationale for change
- Fully traceable to primary or source data
- Not vulnerable to alteration
- Retention of complete and accurate data is a GMP requirement

Additional considerations

A. Multi-purpose facilities

- Only one Investigational drug at a time
- Appropriate cleaning and procedural controls to ensure no carry-over of materials or products, or mix-ups.
- Adequate design or layout of manufacturing area

B. Biological products

- Adventitious Agents

Risk of contamination or product and/or environment

In place cleaning and testing to prevent/detect AA contamination

C. Sterile products/aseptic process

- Aseptic manipulations in aseptic workstation
- Process simulation using bacterial growth media
- Environmental monitoring
- Release the IND product after acceptable sterility results

cGMP for Phase 2 and 3

- Risk based approach to cGMP during development
- Some GMP aspects start early and continue throughout development (training, instrument calibration, endotoxin and bioburden testing, etc.)
- Some GMP requirements vary by phase development (e.g. method validation)
- Some GPM aspects are implemented later in phase 2 and 3 (e.g., validation of the commercial process)
- Compliance with 21 CFR part 211

Phase appropriate cGMPs

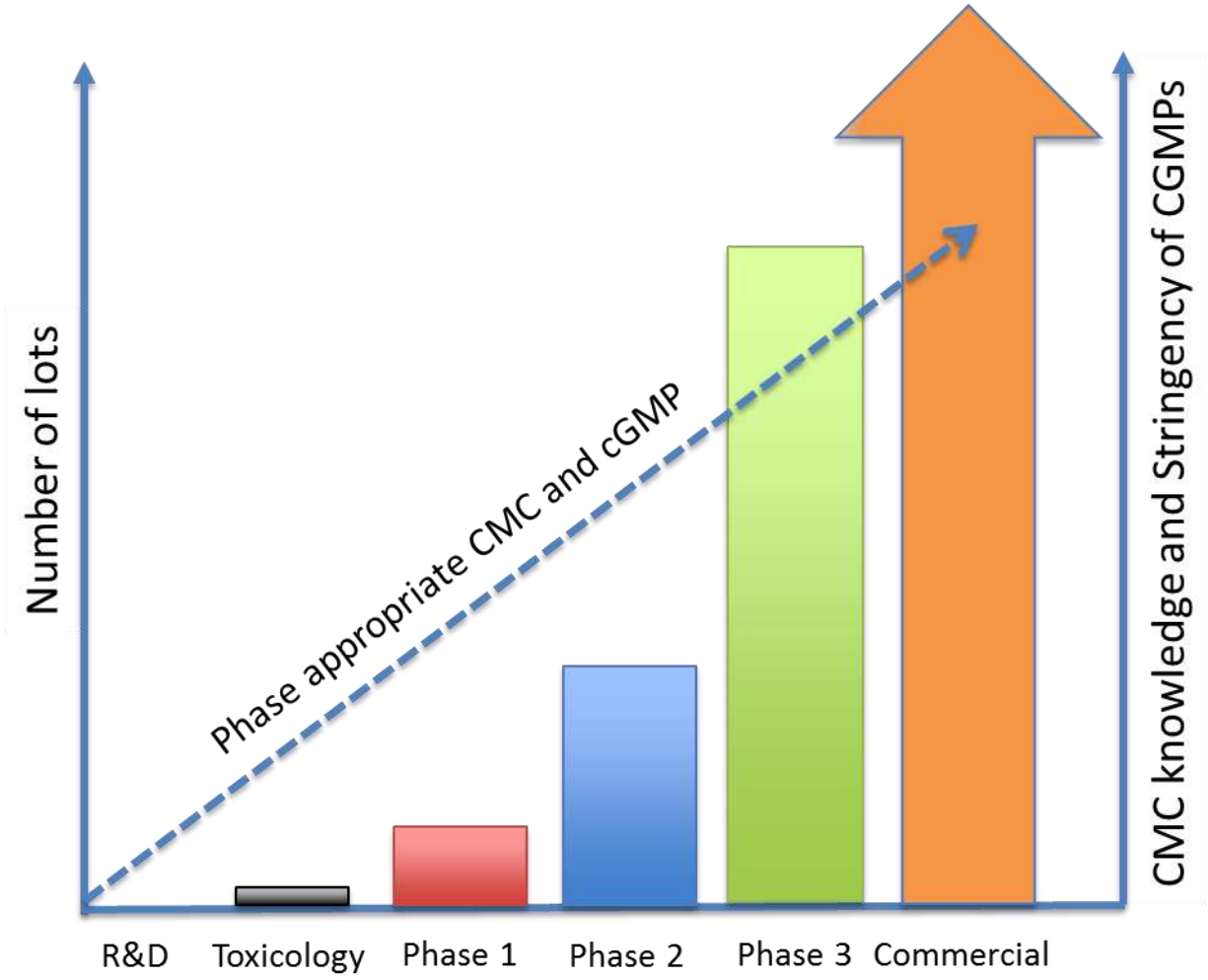


Figure modified from PDA Technical Report No. 56

Inspections

- No requirement for inspection of IND clinical materials manufacturers
- Facilities can be inspected at any time
- For cause inspections- FDA may decide to conduct an inspection
- May be triggered by Treatment IND
- Adherence to cGMP during development evaluated during PLI

Case study

- BLA submission of a new biologic
- Pre-license inspection of the DP facility
- DP facility had never been inspected by FDA
  Sponsor hired an external consultant to evaluate readiness for inspection
- Identification of gaps in the documentation control system
- Documentation system was vulnerable to manipulation
- Evidence of data manipulation and deficient data quality oversight

Case study (contd.)

- Question the accuracy of the data provided to support the BLA
- During the review cycle all data were re evaluated for, traceability, accuracy and impact on lots used to establish product safety and efficacy
- Appropriate CAPA needed to address the identified vulnerabilities to mitigate risk of future manufacturing

Summary

- Phase appropriate GMPs: GMP for clinical trial material consistent with the stage of development
- Process and test procedures are flexible to allow changes as knowledge of process and clinical testing progress
- Documentation is key- development and manufacturing, analytical methods for release of clinical material, production and control records
- Retain samples
- Regulations applicable to GMPS: 21 CFR 210 and 211
- 21 CFR 210 and 211 describe the minimum cGMP expectations
- Phase 1 clinical material must meet statutory GMPs but exempted from complying with 21 CFR part 211 under 21 CFR 210 (c)
- 21 CFR part 211 apply to phase 2/3 clinical material

Resources

- U.S. Code of Federal Regulations Title 21 Part 210: Current Good Manufacturing Practice in manufacturing processing, packing of holding of drugs; general
- U.S. Code of Federal Regulations Title 21 Part 211: Current Good Manufacturing Practice for Finished Pharmaceuticals
- U.S. Code of Federal Regulations Title 21 Part 312: Investigational New Drugs
- PDA Technical Report No. 56. Application of Phase-Appropriate: Quality System and cGMP to the Development of Therapeutic Protein Drug Substance (API or Biological Active Substance)
- FDA Guidance for Industry: CGMP for Phase 1 Investigational Drugs
- FDA Guidance for Industry: Quality Systems Approach to Pharmaceutical CGMP Regulations
- FDA Guidance for Industry: Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

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Questions?

Please evaluate this session:

surveymonkey.com/r/DRG-D2S04

Thank you for your attention!

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