CGMP Requirements for Outsourcing Facilities – Not Just About Sterility Assurance – Some Other Regulations

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Outline

- Background: Purpose and Scope of Regulatory CGMPs
- Ensuring Quality Attributes of Drug Products
- An Overview of Some Key Regulatory Requirements in Drug Product CGMPs

Drug quality attributes

- For injectables/implants
  - Sterility
  - Endotoxin
  - Identity
  - Strength (a.k.a. Potency)
  - Purity
    - Impurities include:
      - Drug substance and excipients degradants
      - Container-closure leachables
      - Others
  - Other, for example:
    - Content uniformity
    - Fill volume
    - Anti-microbial content/effectiveness (if multiple dose container)
    - Drug release
    - …

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Drug Quality Assurance

- Drug quality cannot be tested into the product.
  - Vast majority of all drug analytical tests are destructive.
  - Quality of non-tested units is inferred by test results, but not confirmed.
  - Out-of-specification results are more informative than passing results.
- Drug quality has to be intentional, predictable, consistent, and uniform.
- Drug quality is built into the drug by paying attention to and integrating facility and equipment design and maintenance, drug components, personnel behavior, and production processes.

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CGMP regulations: The Purpose

- 21 Code of Federal Regulations (C.F.R.) 210: "Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General"
  - 21 C.F.R. 210.1(a): "The regulations set forth in this…chapter contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug…has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess."

CGMP Regulations – Drug Products

- Preamble to 21 C.F.R. 211, from, FRN: , Vol. 43, No. 190 – Friday, September 29, 1978

  "…the scope of the CGMP regulations is to set forth the facilities, methods, and controls to be used for the manufacture, processing, packing, or holding of a drug product."

- 21 C.F.R. 211.1 "Scope"
  - (a) The regulations in this part contain the minimum current good manufacturing practice for the preparation of drug products…for administration to humans and animals.

Purpose of the 503B CGMP Draft Guidance

- “This guidance reflects FDA’s intent to recognize the differences between outsourcing facilities and conventional drug manufacturers, while maintaining the minimum standards necessary to protect patients from the risks of contaminated or otherwise substandard compounded drug products.”
- Describes FDA’s general intentions regarding the enforcement of regulatory CGMP requirements until separate regulations for outsourcing facilities (OFs) are finalized.

Sterility Assurance: Select 211 Regulations

- 211.25 – Staff appropriately trained.
- 211.28 – Staff appropriately clothed.
- 211.42(c)(10) – Aseptic processing facilities and equipment suitably design and maintained.
- 211.56 – Facilities maintained in a clean and sanitary condition, free of vermin.
- 211.67 – Equipment cleaned, maintained, and sanitized/sterilized, as needed.
- 211.113(b) – Written procedures in place and followed to prevent microbial contamination of drug products purporting to be sterile.

Process Validation

- Required under 211.100(a) – "*There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to process.*"
- One part of an integrated whole to ensure that the finished product can and will meet its pre-established quality attributes.
- From FDA's Guidance for Industry *Process Validation: General Principles and Practices*, process validation is defined as:
  - "The collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product."

Process Design/Development

- Process validation is preceded by process development and design
  - Goal of process development and design is to devise a process suitable for production of products with desired quality attributes.
  - Development and design includes selection and qualification of drug components (active ingredients and excipients or FDA-approved manufactured products), container-closure, personnel, equipment and parameters (e.g. mixing speed and time, hold times).

Qualification of Drug Components? (When using bulk substances)

- Why can't I use components that just meet *USP-NF* specifications?
  - *USP-NF* monographs:
    - Are a minimal set of standards, do not include specifications for all quality attributes that might impact process parameters or finished drug product quality attributes
  - For example, substance monographs rarely include specifications for:
    - Polymorphs
    - Particle size
- What about components in which there is no *USP-NF* monograph?
- See also: 211.84 *Testing and approval or rejection of components, drug product containers, and closures*.

Container-closure qualification?

- Need to ensure that the container-closure system:
  - Can maintain microbial quality of finished product during shelf life (container-closure integrity tests). For sterile product, container-closure system has to be demonstrated to maintain sterility.
  - In presence of drug product as formulated does not promote degradation or leach substances at toxic levels
    - www.fda.gov/drugs/drug-safety-and-availability/fda-notifies-health-care-professionals-becton-dickinson-replaced-problematic-rubber-stoppers-its
- See also: 211.94 *Drug product containers and closures*

Equipment Qualification?

- Design qualification (DQ)
- What do you need the equipment to do?
- What are its design specifications?
  - For example:
    - Power source needed
    - Materials of construction, especially anything that comes in contact with components, in-process material, finished product
  - See also: 211.63 *Equipment design, size, and location*; 211.65 *Equipment construction*; 211.67 *Equipment cleaning and maintenance.*

More equipment qualification

- Installation qualification (IQ) – does it meet its design specification after installation at facility? Review of equipment against its design specification.
- Operational qualification (OQ) – does it work, as specified, when you turn it on?
- Performance qualification (PQ) – does it work, as specified, under conditions of actual use?
  - PQ will have to be routinely performed throughout lifecycle of equipment to ensure it consistently performs as specified.

Process Performance Qualification (PPQ)

- Combines the actual facility, qualified components, qualified containers and closures, qualified equipment and trained personnel, in accordance to the master formulation record, to produce a commercial-size batch that meets all predetermined quality attributes/specifications.
- See also: 211.186 *Master production and control records* and 211.188 *Batch production and control records.*
- By the way:
  - During PPQ and later production of batches requires that in-process control, tests, and or examination be established and performed to demonstrate production remains under control.
  - See 211.110 *Sampling and testing of in-process materials and drug products*

Anything else?

- 211.137 – Requirement for a drug product to be labeled with an expiration date based upon a stability study.
- 211.166 – Requirements for performance of stability studies.
  - As per regulations, stability studies are to be performed in container-closure systems in which the drug product is to be marketed.

Release versus Shelf-Life Specifications

- 211.160 *Laboratory Controls – General Requirements* require the establishment of meaningful quality attributes specification for drug products.
- Release specification – quality attribute specifications, set by a drug producer, that must be met before a drug product is acceptable for release
  - See: 211.165: *Testing and release for distribution*
- Shelf-life specification – quality attribute specifications that drug product must meet throughout its shelf-life (expiration date or BUD).
  - Stability study establishes that the shelf-life specifications can be met. See 211.166

When Process Validation meets Release Testing – 503B Guidance

- 211.68 – *Automated, mechanical, and electronic equipment.*
  - (a): Allows for the use of such equipment; requires that they be routinely calibrated, inspected, or checked; records of calibration checks and inspections must be maintained.
  - (b): Appropriate controls must be exercised over computer systems to ensure data integrity.
  - (c): When automated equipment is used, reduces (but not eliminates) the need for personnel oversight over the operation.

Draft 503B CGMP Guidance

- If "Drug product is a multicomponent injectable drug product…compounded from APIs produced only by FDA-registered [drug product] manufacturers, the finished product is compounded using automated equipment with validated software, and the equipment is calibrated immediately before and after each personnel shift…FDA generally does not intend to take regulatory action…regarding…release testing for identity and strength…"
- Note: Other release tests are still required (i.e. sterility, endotoxin, etc.)

What Else?

- “Violations cited in this [warning] letter are not intended as an all-inclusive list. You are responsible for investigating these violations, for determining the causes, and for preventing their recurrence, and for preventing violations. It is your responsibility to assure that your firm complies with all requirements of federal law and FDA regulations.”

Quality Unit

- 211.22: *Responsibilities of quality control unit*
  - 211.22(a) – *There shall be a quality control unit that shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging materials, labeling, and drug products, and the authority to review production records…The quality control unit shall be responsible for approving or rejecting drug products….*
  - 211.22(c) – *The quality control unit shall have the responsibility for approving or rejecting all procedures or specifications impacting on the identity, strength, quality, and purity of the drug product.*

- Problems within QU exists when:
  - They have not been empowered to render final decision regarding quality issues.
  - Resources have not been adequately allocated to QU.
  - QU responsibilities have not been adequately defined, implemented, and/or sustained.
  - QU has not achieved functional maturity.

Contract Facilities

- FDA regulations for contract facilities:
  - Under 21 CFR 200.10(b), FDA regards extramural independent contract facilities, such as testing laboratories, as an extension of the manufacturer's own facility. This means that the drug manufacturer/503B facility bears ultimate responsibility for the contract facility's methods, results, and use of the results in making decisions.
  - Under 21 CFR 210.3(b)(12), FDA defines the manufacture of drug products as including quality control.
  - Under 21 CFR 210.2(b), an entity that engages in only some operations subject to CGMP regulations need only comply with those regulations applicable to the operations in which it is engaged.
- Contract facility oversight is the responsibility of the Quality Unit.

Contract Testing Laboratories

- Common inspectional observations:
  - Drug product certificates of analysis state, “Test not performed in accordance with CGMP requirements.”
  - Analytical methods used and their corresponding analytical validation studies are not disclosed by CTL and available to the firm’s QU (and FDA) for review to determine their suitability for intended use.
  - 21 C.F.R. 200.10(d) – “The Food and Drug Administration does not consider results of validation studies of analytical and assay methods and control procedures to be trade secrets that may be withheld from the drug manufacturer by the contracted extramural facility.”

Select References & Readings

- FDA Guidance for Industry: *Current Good Manufacturing Practice - Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act* (draft)
- FDA Guidance for Industry: *Process Validation: General Principles and Practices*
- FDA Guidance for Industry: *Container Closure Systems for Packaging Human Drugs and Biologics*
- FDA Guidance for Industry: *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production*
- FDA Guidance for Industry: *Contract Manufacturing Arrangements for Drugs: Quality Agreements*
- ICH Q3B: *Impurities in New Drug Products*
- ICH Q6A: *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*
- ICH Q9: *Quality Risk Management*
- ICH Q10: *Pharmaceutical Quality Systems*
- 21 C.F.R. 211 – *Current Good Manufacturing Practice for Finished Pharmaceuticals*


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