

FDA Perspective NJ PDA Meeting Risk Based Cleaning, Sanitization, and Sterilization

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Overview FDA Perspective

- Federal Food, Drug, and Cosmetic Act
- Regulations (21 CFR 210 & 211)
- ICH Q7 / Q9
- Issues and Concerns
- Sterile & Non-Sterile Products

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Federal Food, Drug, and Cosmetic Act

Sec 501 [21 USC 351] Adulterated Drugs and Devices

- A drug or device shall be deemed adulterated -(a)(1) If it consists in whole or part of any filthy, putrid or decomposed substance;
- or (2)(A) if it has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health...
- (B) if it is a drug and 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...
- (b) if it purports to be or is represented as a drug the name of which is recognized in an official compendium...

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21 CFR 210 and 211

Finished Product Human and Animals

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21 CFR Parts 210 and 211

- CGMP regulations (21 CFR 210 and 211) apply only to preparation of drug products
- 1978 Preamble “These CGMP regulations apply to finished dosage form drugs (under 210.3(b)(4) and 211.1) and are not binding requirements for chemical manufacturing.”

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21 CFR Parts 210 and 211

- **21 CFR 211.56 Sanitation**
 - Any building used in the manufacture, processing, packing, or holding of a drug product shall be maintained in a clean and sanitary condition
 - written procedures...describing...cleaning schedules, methods, equipment, and materials to be used in cleaning
- **21 CFR 211.63 Equipment design, size, and location**
 - Equipment of appropriate design, size, and suitably located to facilitate operations for its intended use, cleaning and maintenance

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21 CFR Parts 210 and 211

■ 21 CFR 211.67 Equipment cleaning and maintenance

- Cleaning activities to prevent contamination of a drug product
- Written procedures for cleaning and maintenance of equipment
- Records shall be kept for cleaning, sanitizing and inspection

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21 CFR Parts 210 and 211

■ 21 CFR 211.67(b) Written procedures shall include:

- Responsibility for equipment cleaning & maintenance
- Cleaning and sanitizing schedules
- Detailed description of cleaning
- Removal of previous batch identification
- Protection of clean equipment
- Inspection of equipment prior to use

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21 CFR Parts 210 and 211

- **21 CFR 211.113 Control of microbial contamination**

- Written procedures to prevent objectionable microorganisms in drug products

- **21 CFR 211.182 Equipment Cleaning and Use Log**

- Written record of major equipment cleaning and use included in individual equipment logs
- Date, time, product and lot number of each batch processed

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ICH Q7

- FDA uses the Q7 during inspections to evaluate firm's compliance with CGMP expectations

- Applies to:

- APIs that are manufactured by chemical synthesis, extraction, cell culture/fermentation, recovery from natural sources, or any combination of these processes.

- Sterile APIs, but only up to the point immediately before the API is rendered sterile

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ICH Q7

■ Excludes:

- All vaccines, whole cells, whole blood and plasma, blood and plasma derivatives (plasma fractionation) and gene therapy APIs
- Bulk packaged drug (medicinal) products
- Radiopharmaceuticals and medical gases

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ICH Q7

■ Design and Construction

- Buildings and facilities used in the manufacture of intermediates and APIs should be located, designed, and constructed to facilitate cleaning, maintenance, and operations as appropriate to the type and stage of manufacture.

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ICH Q7

■ Utilities

- Adequate ventilation, air filtration and exhaust systems:
 - To minimize risks of contamination and cross contamination
 - To include equipment for control of air pressure, microorganisms (if appropriate), dust, humidity, and temperature, as appropriate to the stage of manufacture.
 - Appropriate measures should be taken to control risks of contamination and cross-contamination.

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ICH Q7

■ Containment

- Dedicated production areas for highly sensitizing materials (e.g., penicillin, cephalosporin)
- Dedicated production areas considered for infectious, high pharmacological activity or toxicity is involved (e.g., certain steroids or cytotoxic anti-cancer agents) unless validated inactivation and/or cleaning procedures are established and maintained.

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ICH Q7

■ Sanitation and Maintenance

- Written procedures for cleaning equipment should include
- Removal or obliteration of previous batch ID
- Protection of clean equipment from contamination prior to use
- Inspection for cleanliness immediately before use, if practical
- Maximum time that may be elapsed between completion of processing and equipment cleaning, when appropriate

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ICH Q7

■ Establishment of Hold times

- Dirty Hold time: from end of manufacturing to start of cleaning
- Clean Hold time: from cleaning until next use of equipment

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ICH Q7

- Acceptance criteria for residues, choice of cleaning procedures, and cleaning agents should be defined and justified
- Cleaning procedures should be validated
- Cleaning procedures should be directed to steps where contamination or carryover of materials poses the greatest risk to API quality

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ICH Q7

- Selection of API or intermediate for cleaning validation should be based on
 - Solubility
 - Difficulty of cleaning
 - Calculation of residue limits based on potency, toxicity, and stability

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ICH Q7

- Cleaning validation protocol should include:
 - Description of equipment to be cleaned
 - Procedures
 - Materials
 - Acceptable cleaning levels
 - Parameters to be monitored and controlled
 - Analytical methods
 - Types of samples to be taken, method of collection, and labeling practices

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ICH Q7

- Sampling should include swabbing, rinsing, or alternative methods to detect both insoluble and soluble residues
- Sampling methods should be capable of quantitatively measuring levels of residues on equipment surfaces after cleaning
- Analytical methods should be validated and sufficiently sensitive to detect established acceptance levels of residues or contaminants

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ICH Q7

- Cleaning and sanitization studies should address microbiological and endotoxin contamination for those processes where:
 - There is a need to reduce the total microbial counts or endotoxins in the API
 - Where such Contamination could be of concern (non-sterile APIs destined for sterile products)

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ICH Q7

- Cleaning procedures should be monitored at appropriate intervals after validation to ensure these are effective when used during routine production

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ICH Q9

- "...the protection of the patient by managing the risk to quality should be considered of prime importance."

- Two primary principles of quality risk management are:
 - The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and
 - The level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk.

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FDA Perspective

- Patient Risk / Population
 - Patient Harm
 - Pediatric or Compromised Immune System

- Product (Dosage form) / Process
 - Tablets (Wet vs. Dry Granulation),
 - Parenterals (Aseptic vs. Terminal Sterilization)
 - Liquids
 - Inhalers

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- **Cleaning Validation:** Establishing documented evidence that the **equipment** is consistently cleaned from **product, microbial** and **cleaning agent** residues to **predetermined** acceptable levels

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- **Life Cycle**
 - Monitoring
 - Change Control
 - Deviations / Investigations
 - Training and Retraining
 - Continued Control

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Issues and Concerns

- Failure to establish procedures
- No sampling plans
- Cleaning procedures too vague
- Operator's performance, reproducibility, and training
- Unknown peaks in chromatograms
- Inadequate investigations and corrective actions for unknown peaks in cleaning validation samples

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Issues and Concerns

- Re-cleaning, re-sampling and retesting of equipment without investigating the root cause for the OOS results
- Failure to evaluate, improve cleaning procedures or operator performance
- Failure to properly disassemble equipment for cleaning

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Issues and Concerns

- Worst-case surfaces, e.g., gaskets, rubber seals, difficult to clean spots, not always sampled
- Reuse / Repurposing of containers
- Use of common equipment to manufacture potent and non-potent drugs with out adequate cleaning

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Issues and Concerns

- Failure to specify and validate dirty hold times, or equipment remains dirty for extended periods exceeding those validated
- Failure to follow established cleaning procedures
- Failure to validate and test Sanitizing Agents / Sterilizers

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Questions?

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