Regulatory Education for Industry (REdI):
Focus on CGMPs & FDA Inspections

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Facilities & Equipment: CGMP Requirements

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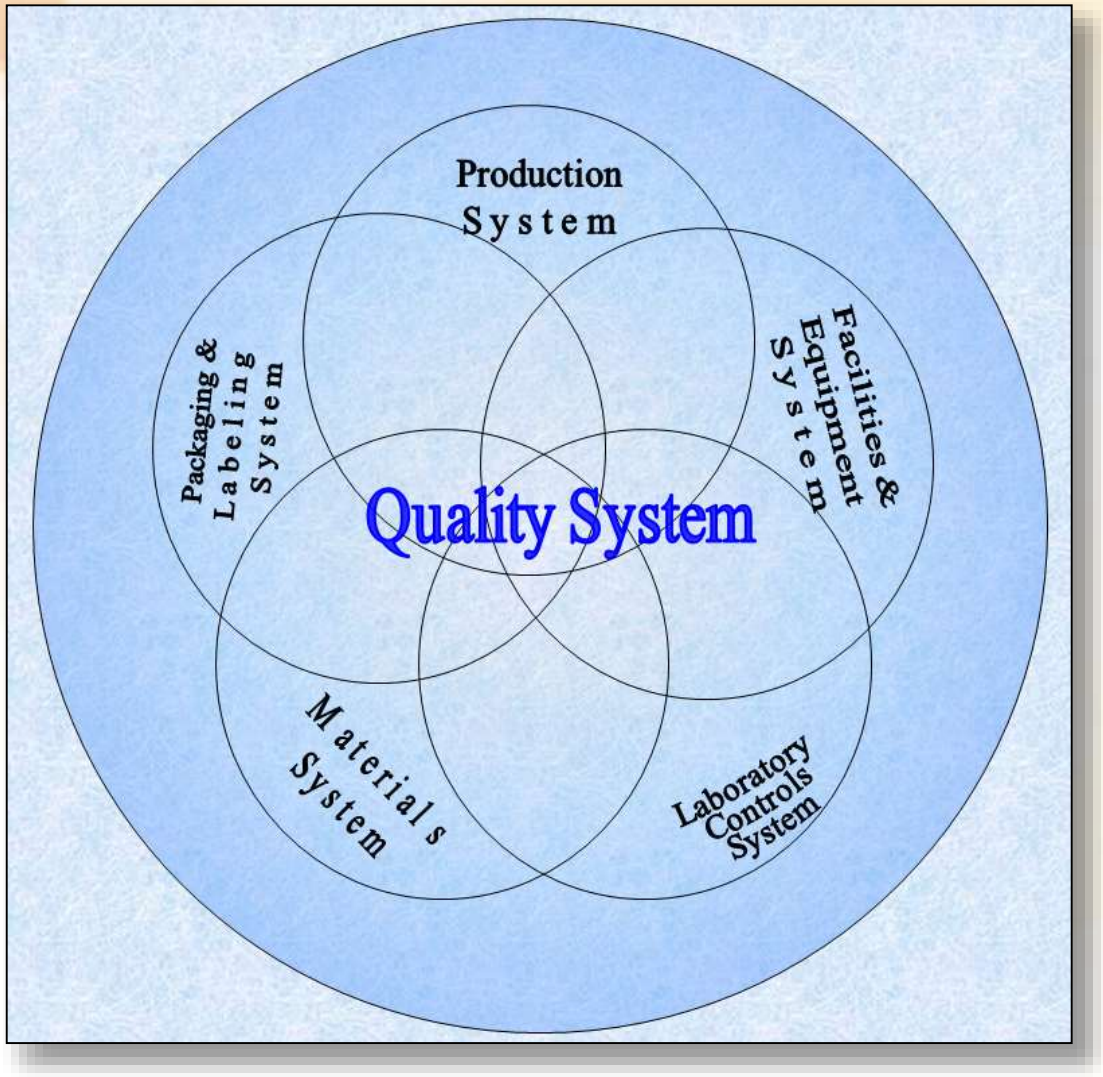
The Six Components

- Quality
- Production
- Laboratory
- Materials
- **Facilities & Equipment**
- Packaging & Labeling



Objectives

- **Facilities and Equipment CGMP Highlights**
- **Aseptic Manufacturing Facility**
- **Equipment Qualification**
- **Cleaning Validation**

Subpart C – Building and Facilities
Section 211.42
Design and Construction Features

- **Suitable size, construction, and location *to facilitate cleaning, maintenance, and proper operations***
- **Plan adequate space for orderly placement of equipment and materials *to prevent mix-ups and contamination***
- **Design the adequate flow of materials & persons *to prevent contamination***

Complies with 21 CFR 211.42?

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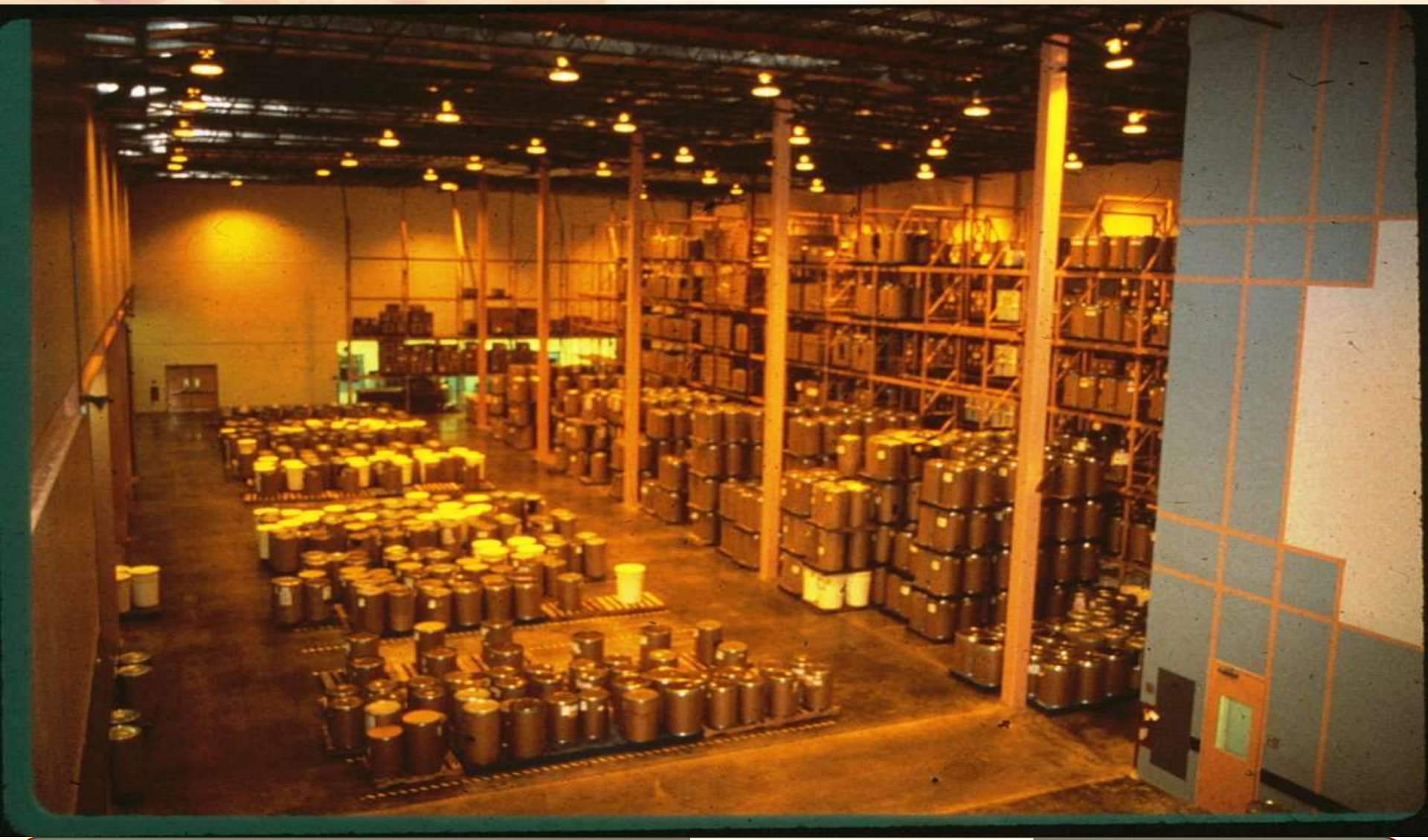

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Subpart C – Building and Facilities 211.42

Design and Construction Features

- **Operations performed within *separate or defined areas or such other control systems as are necessary to prevent contamination or mix-ups, including:***

    1. **Receipt, ID, storage and withholding from use of components, drug product containers, closures, and labeling pending QC sampling, testing, or examination**
    2. **Holding rejected components, drug product containers, closures and labeling before disposition**

Subpart C – Building and Facilities 211.42

Design and Construction Features

- **Including (Cont.):**

3. **Storage of released components, drug product containers, closures and labeling**
4. **Storage of in-process materials**
5. **Manufacturing and processing operations**
6. **Packaging and labeling operations**
7. **Quarantine storage before release of drug products**
8. **Storage of drug products after release**
9. **Control and laboratory operations**

Subpart C – Building and Facilities 211.42

Design and Construction Features

10. **Aseptic processing to include, *as appropriate*:**

    i. **Easily cleanable floors, wall, and ceilings of smooth, hard surfaces**

Subpart C – Building and Facilities 211.42

Design and Construction Features

10. **Aseptic processing to include, *as appropriate*:**

ii. **Temperature and humidity controls**

Subpart C – Building and Facilities 211.42

Design and Construction Features

10. Aseptic processing to include, *as appropriate*:

    iii. An air supply filtered through *high-efficiency particulate air filters* (HEPA) under *positive pressure*, regardless of whether flow is *laminar or nonlaminar*

Efficiency Testing of HEPA Filters

- **HEPA filters generally tested for efficiency at the filter manufacturing site using a thermally generated dioctylphalate (DOP) aerosol**
- **Challenge is a homogeneous, monodispersed aerosol with a particle size of 0.3 micrometers**
- **Penetration of DOP through filter should not exceed .03% (Note: 100% - .03% = 99.97% efficiency)**

Integrity Testing of HEPA Filters

- **A similar test used for the verification of filter integrity (leak testing or pinhole detection)**
- **Includes cold DOP, DEHS, Emery 3000 POA leak test**
- **Test differs from efficiency test in the complexity of the aerosol generator and portability of the photometer employed**

Integrity Testing of HEPA Filters - Cold DOP

- Aerosol generator used to produce an polydispersed aerosol containing a range of particles (0.1 - 3 micron) that is introduced upstream of the filter bank while in operation
- Downstream side of filter is scanned with optical measuring device, usually a light scattering photometer
- If pinhole leaks are present, particles pass through filter and are detected by optical device

Pressure Differential Control

- **Pressurization used to prevent cross contamination between environments and ingress of contaminants into production areas from adjacent areas**
- **Pressure gradients established to provide critical environments with higher pressures than less critical areas**
  - **Sweeps contaminants away from work surface area**
  - **Provides pressure cascade**

Pressure Differential Control

- **High pressure areas receive more air input and less air exhaust**
- **Difference in air pressure between areas should be adequate to maintain desired direction of air flow**
- **Pressure differentials should be measured with doors opened and closed**

Pressure Differential Control

- **Positive air pressure used to prevent the ingress of contaminants from less clean areas**
  - **Cleanroom man and materials entry from adjacent clean corridor or clean area**

- **Negative air pressure effective in containing or preventing dispersion of sensitive or highly toxic materials**

Clean Corridor Adjacent to Cleanroom

Air Shower

Unidirectional or Laminar Airflow

- **(FDA Guidance definition) An airflow moving in a single direction, in a robust and uniform manner, and at sufficient speed to reproducibly sweep particles away from the critical processing or testing area**

  9/2004 Guidance for Industry-Sterile Drug Products Produced by Aseptic Processing —Current Good Manufacturing Practice

- **First Air (USP definition)-the first air exiting a HEPA filter in a unidirectional air stream that is essentially particle free**

Nonunidirectional or Turbulent Airflow

- **Airflow which does not meet the definition of unidirectional airflow**
- **Edges, Solid flat surfaces, Person or Equipment Moving**

Subpart C – Building and Facilities 211.42

Design and Construction Features

10. **Aseptic processing to include, *as appropriate*:**

    iv. **A system for monitoring environmental conditions**

    (Monitoring generally conducted under “as built”, “at rest” and “operational or dynamic” conditions)

Cleanroom

- **An isolated environment, strictly controlled with respect to:**
  - **Airborne particles of viable and non-viable nature**
  - **Temperature**
  - **Humidity**
  - **Air pressure**
  - **Air flow**
  - **Air motion**
  - **Lighting**

As-Built Cleanroom

- **A cleanroom (facility) that is complete and ready for operation, with all services connected and functional, but without equipment or operating personnel in the facility**
- **Can achieve very low particle counts**
- **Reflects quality of supply air and removal efficiency of the HVAC system**

At-Rest Cleanroom

- **A cleanroom (facility) that is complete with all services functioning and with equipment installed and operable or operating, as specified, but without operating personnel in the facility**
- **Smoke testing should demonstrate unidirectional air flow over critical equipment surfaces**
- **If areas of air disturbance are observed, may require movement of equipment or adjustment of air velocities**

Operational Cleanroom

- **A cleanroom (facility) in normal operation, with all services functioning and with equipment and personnel, if applicable, present and performing their normal work functions**

- **Validation studies should demonstrate that Class 100 is maintained in critical zones during routine operations**

Operational Cleanroom

Subpart C – Building and Facilities 211.42

Design and Construction Features

10. **Aseptic processing to include, *as appropriate*:**

    v. **A system for cleaning and disinfecting the room and equipment to provide aseptic conditions**

Subpart C – Building and Facilities 211.42

Design and Construction Features

10. **Aseptic processing to include, *as appropriate*:**

    vi. **A system for maintaining any equipment used to control the aseptic conditions**

Subpart C – Building and Facilities

- 211.44 Lighting
- 211.46 Ventilation, air filtration, heating and cooling
- 211.48 Plumbing
- 211.50 Sewage and Refuse
- 211.52 Washing and Toilet facilities
- 211.56 Sanitation
- 211.58 Maintenance

Subpart C – Buildings & Facilities Sections 211.48, 211.50, and 211.52 Plumbing, Sewage and Refuse, Washing and Toilet Facilities

- **Potable water supplied under continuous positive pressure in plumbing system free of defects *that could contribute to product contamination***
- **Adequately sized and designed drains (air break or mechanical device) *to prevent back-siphoning***
- **Safe/sanitary disposal of sewage, trash, and other refuse**

Subpart C – Buildings & Facilities
Sections 211.56 and 211.58
Sanitation and Maintenance

- **Buildings maintained in clean/sanitary condition**
  - **Free of infestation by rodents, birds, insects, and other vermin**
  - **Trash and organic waste held and disposed of in a timely and sanitary matter**
- **Written sanitation procedures to include schedules, methods, equipment materials for cleaning of buildings and facilities**

Subpart C – Buildings & Facilities
Sections 211.56 and 211.58
Sanitation and Maintenance

- **Written procedures for use of suitable rodenticides, insecticides, fungicides, fumigation agents and cleaning and sanitation agents *to prevent contamination***
- **Sanitation procedures also apply to contractors and temporary employees as well as full-time employees during the ordinary course of operations**

Subpart D – Equipment
211.63-Equipment Design, Size and Location

“Equipment used in the manufacture, processing, packing, or holding of a drug product shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and its cleaning and maintenance.”

- **ISPE Good Practice Guide, Applied Risk Management for Commissioning and Qualification**
- **ISPE Baseline Guide, Commissioning and Qualification**

Equipment Qualification Terms

- **Installation Qualification (IQ)**
- **Operation Qualification (OQ)**
- **Performance Qualification (PQ)**

Installation Qualification

- **This term is associated with equipment**
- **Conducted according to an approved Installation Qualification protocol or plan**
- **Identify and document equipment**
- **Verify proper installation**
  - **Are critical components installed correctly and in accordance with design documentation requirements (i.e., specification, purchase orders, contracts)**
  - **Including integration with other equipment and utilities**

Installation Qualification

- **Documentation of the results**
- **Includes:**
  - **Operating manuals**
  - **Blueprints**
  - **Equipment drawings**
  - **P&ID (piping & instrumentation diagram)**
- **The installation should be checked against the construction drawings and any deviations should be recorded and evaluated.**

Acceptance Testing

- **Factory Acceptance Test (FAT)- documented evidence that a piece of equipment or system has been adequately tested at the manufacturer's facility and performed to the end user's expectations prior to delivery to the end user.**

- **Site Acceptance Test (SAT)- documented evidence that a piece of equipment or system has not been affected in the transportation and has been adequately tested at the end user's facility and performed to end user's expectation.**

Operation Qualification

- **Also associated with equipment**
- **ISPE Baseline Guide, Volume 5- Commissioning and Qualification definition:**
  - ***"The documented verification that all aspects of a facility, utility, or equipment that can affect product quality operated as intended throughout all anticipated ranges."***

Operation Qualification

- **Performed to verify operation within specified parameters such as temperature, pressure, flow, etc.**
- **Should be accomplished via established and approved protocol that describes all aspects of the testing of the equipment in detail**
- **Involves the verification of the proper operation of controllers, indicators, recorders, alarms and interlocks**

Operation Qualification

- Confirmation that the equipment or system can sequence through its operating steps
- That key functions and process parameters are checked
- Assure they meet the operating specifications
- Ensure there are no undesirable operations
- Assure the system appropriately responds under fault or failure conditions

Operation Qualification

- For new processes, this may also include scaling-up from product development to actual manufacturing equipment
- Optimize the process by testing different operating parameters
- Assuring that the critical components and systems are capable of operating within established limits and tolerances

Operation Qualification

- **“Worst case” (Proven Acceptable Range) demonstration that the equipment will perform as expected while operating at the extremes of the proposed range of operation.**

Performance Qualification

- **Documents needed to conduct the PQ**
  - **P&IDs**
  - **Approved SOPs (system operation, operation of test equipment, sampling, analytical)**
  - **Load configuration diagrams (autoclaves, washers, etc.)**
  - **Test method for samples collected**
  - **Calibration certificates**

Performance Qualification

- **Should be accomplished via an established and approved protocol that describes the acceptance criteria to be met to successfully accomplish the performance qualification.**

Performance Qualification

- **Integrates procedure, personnel, systems, and materials to verify that the pharmaceutical grade utility, environment, equipment, or support system produces the required output**
- **Production is done under conditions that simulate those planned to be used during actual manufacturing**
- **Should include a final report that addresses any out-of-specification results, outlying data points, deviations, or non-conformances encountered during validation.**

To Recap

- **IQ is a verification of alignment with design specifications**
- **OQ is a verification of alignment with functional specifications**
- **PQ is a verification of the ability of a process to meet with user required specifications**

More Subpart D – Equipment

- 211.65 Equipment construction
- 211.67 Equipment cleaning and maintenance
- 211.68 Automatic, mechanical and electronic equipment
- 211.72 Filters

Subpart D – Equipment
Sections 211.63 and 211.65
Design, Size, Location, Construction

- **Equipment of *appropriate* design, adequate size, and suitably located *to facilitate operations for its intended use and for its cleaning/maintenance***
- **Constructed so that**
  - **Surfaces that contact components, in-process materials, or drug products are *not reactive, additive or absorptive***
  - **To *prevent contact with substances required for operations such as lubricants and coolants***

Subpart D – Equipment
Sections 211.68
Automatic, Mechanical & Electronic Equipment

- **Routinely calibrated, inspected or checked as per written program *to assure proper performance***
- **Appropriate controls over computer and related systems *to limit changes made to master production/ control records and other records* to authorized personnel**
- **Computer input/output checked for accuracy**

Subpart D – Equipment
Section 211.68
Automatic, Mechanical & Electronic Equipment

- **Backup data file or written record of computer program maintained with validation data unless certain data (i.e., calculations) performed in connection with lab analysis are eliminated by computerization or other automated processes**

- **Hardcopy or alternate systems maintained to assure that backup data are exact, complete, and secure from alteration, inadvertent erasures, or loss**

Other CGMP Sections Referring to Equipment

- **211.105 Equipment Identification**
  - **Major equipment**
  - **Equipment and containers contents and stage of production identified at all times**

- **211.182 Equipment Cleaning and Use log**

Cleaning Validation

- **It's a process…involving production cleaning procedures, and data, as well as laboratory procedures, and data.**

- **How clean is clean?**

Subpart D – Equipment
Sections 211.63 and 211.65
Design, Size, Location, Construction

- **Equipment of *appropriate* design, adequate size, and suitably located *to facilitate operations for its intended use and for its cleaning/maintenance***

- **Constructed so that**

  Surfaces that contact components, in-process materials, or drug products are *not reactive, additive or absorptive*

  To *prevent contact with substances required for operations such as lubricants and coolants*

Subpart D – Equipment
Section 211.67
Equipment Cleaning and Maintenance

- **Cleaning and maintenance activities are *to prevent malfunctions which could lead to contamination of a drug product***
- **Written procedures for cleaning and maintenance of equipment should be established and followed**
- **Records SHALL be kept for cleaning, sanitizing, maintenance and inspection**

Subpart D – Equipment
Section 211.67 (b)
Equipment Cleaning and Maintenance

- **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**

Added FDA Expectations

- **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**

FDA Expectations

- ***"Guide to Inspections of Validation of Cleaning Processes"***
  - **Intended for FDA inspection consistency and uniformity**
  - **Cleaning Validation: Establishing documented evidence that the equipment is consistently cleaned of product, microbial and cleaning agent residues to predetermined, acceptable levels**

Cleaning Validation - Main Topics

- Objective of the cleaning process
- Equipment design
- Cleaning procedures and documentation
- Detergents/Cleaning agents
- Validation protocol
- Sampling
- Analytical methods
- Establishing limits
- Cleaning of chemical residues and micro

“Test Until Clean” is not considered Cleaning Validation

The Starting Point

- **The starting point for cleaning validation is the cleaning procedure itself….**
- **Analytical methods, limits, etc. are the tools supporting the effectiveness of the cleaning procedure.**
- **The objective of the exercise is to prove that the cleaning procedure is adequate.**

Inspectional Approach

- **Cleaning Validation approach (e.g. matrix or product-specific, dedicated vs. non-dedicated equipment, campaigns, CIP or disassembly)**
- **Is some equipment more difficult to clean (e.g. mills, centrifuges, fluid bed dryers, piping, rubber gaskets, etc.)?**
- **Identify types of products manufactured, e.g. drug products, industrial chemicals, pesticides**

Other Information

- **Were there any OOS results or trends during cleaning validation studies**
- **Were there unknown peaks in unrelated laboratory chromatograms**
- **Be alert to auxiliary equipment or containers that may be re-used and/or not included in the cleaning validation**

Inspectional Approach

- **Identify critical pieces of equipment for evaluation of cleaning validation based on previously gathered information, including past difficulty with achieving clean status, adverse trends observed, hazard to intended patient population, potency or toxicity of drug product, degradants, excipients, etc.**

Cleaning Procedures

- **Cleaning procedures must be specific**
  - **Cleaning tools (brushes, wipes, sponges, etc.)**
  - **Sequence of cleaning steps**
  - **Critical steps identified, including rationale (often found in validation protocol)**
  - **Specific instructions for disassembling and assembly of equipments or parts**
    - **Type of valves, gaskets and seals used**
    - **How residues will be removed**

Cleaning Procedures

- **Cleaning procedures must be specific (cont.)**
  - **Use of dedicated vs. multi-product equipment**
  - **Cleaning between batches of same or different products**
  - **Clean-In-Place (CIP)**
    - **Identification of piping and valves**
    - **Valves and pumps should be of sanitary design**

Cleaning Procedures

- **Cleaning procedures must be specific (cont.)**
  - **Type, amounts, concentration and temperature of cleaning agents and how they should be applied**
  - **Temperature and quality of water**
  - **Washing, rinsing or scrubbing methods and times**

Cleaning Procedures

- **Cleaning procedures must be specific (cont.)**
  - **Instructions like this will get attention:**
    - **Rinse, if needed**
    - **Rinse if specifications are not met. Then resample.**
    - **Use rag or brush, as needed**
  - **Drying and storage**
  - **Instructions to perform at least a visual inspection after every cleaning**

Cleaning Procedures

- **Cleaning procedures must be specific (cont.)**
  - **Time between processing and cleaning (dirty hold times)**
    - **Residues may dry out becoming more difficult to clean**
    - **May also increase microbiological bioburden**

Sampling

- **Direct Surface Sampling (swab)**
  - **Areas hardest to clean can be evaluated**
- **Rinse Sampling**
  - **Greater surface coverage**
  - **Inaccessible areas can be sampled**
  - **Should be direct measurement of residue**
  - **Insoluble residues are not tested**

Analytical Method

- **Recovery studies should be representative of all major product contact surfaces (i.e. stainless steel, teflon, tygon, etc) and sampling methods (rinse or swab)**

Analytical Method

Challenge the analytical method in combination with the sampling

- **Specificity**
- **Sensitivity**
- **Recovery**

Analytical Method

- **Specific assay test methods such as HPLC**
- **Total Organic Carbon (TOC)**
  - **Advantage - less analysis time**
  - **Disadvantage - lack of specificity**
  - **Can be used if TOC is sensitive to the compounds being cleaned away**

Establishment of Limits

- **Limit should be based on scientific rationale**
- **A good scientific rationale should be logical, practical, verifiable, safe and achievable**

Establishment of Limits

"How clean is clean"?-no clear answer

Actual numerical limit should be based on one or more of the following:

- **Therapeutic dosage levels**
- **Toxicity**
- **Solubility of the residue (detergent)**
- **Batch size and nature of other products made in the same equipment**

Establishment of Limits

- **Nature of the Dosage Form**
  - **Parenteral**
  - **Ophthalmic**
  - **Topicals**
  - **Liquids**
  - **Solid Oral**
  - **Research Compound**

Inspectional Approach

Validation Protocol

- **Who is responsible for doing the cleaning validation?**
- **Who approves it**
- **Acceptance criteria defined**
- **Cleaning procedures defined**
- **Sampling Plan (specific)**
- **Analytical Methods to be used**
- **Revalidation requirements**

Inspectional Approach

Evaluation of cleaning validation studies

- Review the cleaning validation Report
- Review cleaning records
- Review raw data for swab &/or rinse samples
- Verify that acceptance criteria were met
- Confirm that all deviations/OOS results were adequately investigated
- Verify batch to batch consistency

Significant Issues and Concerns

Significant Issues and Concerns

- Cleaning procedures too vague
- Operator's performance and reproducibility; training
- Inadequate investigations and corrective actions for unknown peaks in cleaning validation samples

Significant Issues and Concerns

- **Re-cleaning, re-sampling and retesting of equipment (“Test Until Clean”) without investigating the root cause for the OOS results**
- **Failure to evaluate/improve cleaning procedures and/or operator performance**
- **Failure to properly disassemble equipment for cleaning**

Significant Issues and Concerns

- **Failure to specify and validate dirty hold times, or equipment remains dirty for extended periods exceeding those validated**
- **Interview of operators disclosed that cleaning procedures are not always followed**

Significant Issues and Concerns

- **Worst-case surfaces, e.g., gaskets, rubber seals, difficult to clean spots, not always sampled**
- **Use of common equipment to manufacture potent (e.g., steroids) and non-potent drugs w/o adequate cleaning**

Summary

- **Review the Cleaning Validation Protocol/Report**
- **Review raw data for swab and/or rinse samples**
- **Verify that the cleaning procedures are specific and were followed during the C.V. studies**
- **Verify that pre-determined acceptance criteria were met**

Summary

- **Confirm that all deviations/OOS results were adequately investigated and corrective actions implemented**
- **Verify batch to batch consistency**
- **Cleaning logs/records**
- **Change control records**
- **Training**
- **Laboratory Controls**

Questions?

Evaluation: surveymonkey.com/r/CGMP-D1S5

Remember

- **Equipment is qualified**
- **Processes are validated**

Pharmaceutical Inspection & CGMP Reference Sources

FDA References at www.fda.gov

- **Inspectors Operations Manual**
- **Compliance Policy Guides**
- **Compliance Program Guidance Manuals**
- **FDA Enforcement Reports**
- **Guidance for Industry**