Supplementary Training Modules on Good Manufacturing Practice

Validation

Validation

- Part 1. General overview on qualification and validation
- Part 2. Qualification of HVAC and water systems
- Part 3. Cleaning validation
- Part 4. Analytical method validation
- Part 5. Computerized system validation
- Part 6. Qualification of systems and equipment
- Part 7. Non sterile product process validation
Supplementary Training Modules on Good Manufacturing Practice

Cleaning Validation

Part 3

Validation

Objectives

To discuss principles and approaches to cleaning validation including:
- Protocols and reports
- Personnel and equipment
- Use of detergents
- Microbiology
- Sampling
- Analytical methods and
- Acceptable limits
Principle

- The objectives of GMP include prevention of possible contamination and cross-contamination.

- Contamination by a variety of substances:
  - contaminants (e.g. microbes, previous products (both API and excipient residues), residues of cleaning agents, airborne materials (e.g. dust and particulate matter), lubricants and ancillary material, such as disinfectants)

- Also decomposition residues from product or detergents.
Validation

Principle (2)

- Adequate cleaning procedures important
- Documented evidence needed - cleaning procedure will provide clean equipment, suitable for intended use.
- What is the objective of cleaning validation?
  - product, detergent and microbial residues
  - prevent possible contamination and cross-contamination
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Principle (3)

- Where is cleaning validation required?
  - Not necessarily for non-critical cleaning, e.g. between batches of the same product (or different lots of the same intermediate in a bulk process), or of floors, walls, the outside of vessels, and following some intermediate steps.
  - Considered important in multiproduct facilities - should be performed, e.g. for equipment, sanitization procedures and garment laundering.
Scope

- Guidelines: General aspects of cleaning validation
- Excluding specialized cleaning or inactivation
  - e.g. for removal of viral or mycoplasmal contaminants in the biological manufacturing industry.
- Normally cleaning validation needed for critical cleaning, e.g.
  - between manufacturing of one product and another
  - contact surfaces (products, drug products and API).
Validation

General

- Written SOPs for cleaning processes – validated

- Cleaning policy and cleaning validation procedure to cover:
  - contact surfaces;
  - cleaning after product changeover;
  - between batches in campaigns;
  - bracketing products for cleaning validation; and
  - periodic evaluation and revalidation of the number of batches manufactured between cleaning validations.
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General (2)

- The company has to prove consistency
- What are the variables when a cleaning procedure is followed?
- How many consecutive applications of the cleaning procedure should be performed?
- Training of personnel
Cleaning validation protocols

- Approved by QC or QA and to cover, e.g.
  - disassembly of system;
  - pre-cleaning;
  - cleaning agent, concentration, solution volume, water quality;
  - time and temperature;
  - flow rate, pressure and rinsing;
  - complexity and design of the equipment;
  - training of operators; and
  - size of the system.
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Cleaning validation protocols (2)

- The cleaning validation protocol should include:
  - objectives, responsible people;
  - description of the equipment including the make, model, serial number or other unique code;
  - time intervals; bioburden; cleaning procedures;
  - equipment used for routine monitoring (e.g. conductivity meters, pH meters and total organic carbon analysers);
  - number of cleaning cycles; sampling procedures (e.g. direct sampling, rinse sampling, in process monitoring and sampling locations) and the rationale for their use
The cleaning validation protocol should include (2):

- *data on recovery studies (efficiency of the recovery of the sampling technique should be established)*;
- *analytical methods*;
- *acceptance criteria (with rationale for setting the specific limits) including a margin for error and for sampling efficiency*;
- *cleaning agent to be used*;
- *revalidation requirements*. 
Cleaning validation protocols (4)

- Cleaning agent used, scientifically justified and based on:
  - the solubility of the materials to be removed;
  - the design and construction of the equipment and surface materials to be cleaned;
  - the safety of the cleaning agent;
  - the ease of removal and detection;
  - the product attributes;
  - the minimum temperature and volume of cleaning agent and rinse solution; and
  - the manufacturer's recommendations
Cleaning validation protocols (5)

Bracketing:

- Very similar cleaning procedures for products and processes - no need for individual validation. “Worst case” may be acceptable and should be justified.

- Consider type of products and equipment; allowed only where products are similar in nature or property and processed on the same equipment; and identical cleaning procedures used.
Cleaning validation protocols (6)

Bracketing:

- Representative product - most difficult to clean.

- Equipment - only when it is similar or the same equipment in different sizes (e.g. 300 l, 500 l and 1000 l tanks).
  - *Alternative approach may be to validate the smallest and the largest sizes separately.*
Cleaning validation reports

- The relevant cleaning records – *(signed by the operator, checked by production and reviewed by quality assurance)* – and source data *(original results)* should be kept.

- The results of the cleaning validation should be presented in cleaning validation reports stating the *outcome and conclusion*. 
Cleaning of contact surfaces to be validated, with consideration to “non-contact” parts. Critical areas should be identified.

Dedicated equipment for:

- products which are difficult to clean,
- equipment which is difficult to clean,
- products with a high safety risk where it is not possible to achieve the required cleaning acceptance limits using a validated cleaning procedure.
Equipment (2)

- If one SOP for cleaning a piece of equipment, review:
  - products being produced,
  - cleaning in a large campaign,
  - cleaning between batches of different products.

- The design of equipment may influence the effectiveness of the cleaning process.

- Consider design, e.g. V-blenders, transfer pumps or filling lines.
Basic Principles of GMP

- Which are the critical areas for sampling?
- What would be considered an appropriate approach for cleaning validation for this piece of equipment?
Basic Principles of GMP

- Which are the critical areas for sampling?
- What would be considered an appropriate approach for cleaning validation for this piece of equipment?
Detergents

- Released by quality control and meet food standards or regulations
- Composition known
- Easily removed with rinsing - demonstrated - with acceptable limits defined
- If persistent residues (e.g. cationic detergents) - avoided
- Consider also detergent breakdown
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Microbiology

- Prevent microbial growth and remove contamination
- Documented evidence
  - routine cleaning
  - storage of equipment
- The period and conditions
  - storage of unclean equipment before cleaning
  - between cleaning and equipment reuse
- Equipment stored in a dry condition after cleaning (no stagnant water)
- Control of bioburden important
Basic Principles of GMP

- What is important about cleaning validation for components/parts of equipment?

- Consider also the different materials, e.g. stainless steel contact surfaces, silicon seals and others
Sampling (General)

- Clean as soon as possible after use
  - especially topical products, suspensions and bulk drug or
  - where the drying of residues will directly affect the efficiency of a cleaning procedure

- Two methods of sampling:
  - direct surface sampling and
  - rinse samples

- Combination of the two - most desirable
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Sampling (General) (2)

- Re-sampling:
  - *not to be done before or during cleaning*

- Constant re-testing and re-sampling:
  - *can show that the cleaning process is not validated*
  - *may indicate presence of unacceptable residue and contaminants resulting from an ineffective cleaning process*
Direct surface sampling (direct method)

- Most commonly used method
- Use “swabs” (inert material) - type of sampling material should not interfere with the test
- Factors to be considered include:
  - supplier of the swab,
  - area swabbed, number of swabs used, whether they are wet or dry swabs,
  - swab handling and swabbing technique
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Direct surface sampling (direct method) (2)

- Other factors include:
  - *location from which the sample is taken (including worst case locations, identified in the protocol)*
  - *composition of the equipment (e.g. glass or steel)*

- Critical areas (hardest to clean)
  - *e.g. in semi-automatic/fully automatic clean-in-place systems*

- Use appropriate sampling medium and solvent
Rinse samples (indirect method)

- Allows sampling of:
  - a large surface
  - areas that are inaccessible or that cannot be routinely disassembled

- Provides an "overall picture"

- Useful for checking for residues of cleaning agents

- In combination with other sampling methods such as surface sampling
Rinse samples (indirect method) (2)

- The manufacturer has to provide evidence that samples are accurately recovered
- What is considered acceptable in terms of recovery?
> 80% is considered good
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Recovery

> 80% is considered good

> 50% is considered reasonable
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> 80% is considered good

> 50% is considered reasonable

< 50% is considered questionable
Batch placebo method

- A placebo batch is manufactured and checks are done for carry-over of the previous product
  - Expensive and laborious process
  - Little assurance that the contaminants are dislodged
  - Particles not necessarily uniformly dispersed
  - Method used in conjunction with rinse and/or surface sampling method(s)
  - Samples taken throughout the process of manufacture
  - Sensitivity of the assay may be greatly reduced by dilution of the contaminant
Validated analytical methods – able to detect residuals or contaminants:

- *specific for the substance(s) being assayed*
- *at an appropriate level of cleanliness (sensitivity)*

Sensitive and specific - may include:

- *chromatographic methods (e.g. high pressure liquid chromatography (HPLC), gas chromatography (GC), and high pressure thin-layer chromatography (HPTLC)). Others include (alone or in combination), e.g. total organic carbon (TOC), pH, conductivity, ultraviolet (UV) spectroscopy, and ELISA*
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Analytical methods (2)

- Validation of the analytical method should include, e.g.
  - precision, linearity and selectivity (the latter if specific analytes are targeted);
  - limit of detection (LOD);
  - limit of quantitation (LOQ);
  - recovery, by spiking with the analyte; and
  - reproducibility

- Detection limit (sufficiently sensitive) to detect the established acceptable level of residue / contaminants
Establishing acceptable limits

- Limits: Practical, achievable and verifiable
- Rationale: Logical, based on knowledge of materials
- Each situation assessed individually
- Principal reactant and other chemical variations
- Screening (thin-layer chromatography) in addition to chemical analyses where necessary
Establishing acceptable limits (2)

There should be no residue from:

- Previous product
- Reaction by-products and degradants
- Cleaning process itself (e.g. detergents or solvents)

*Remember: Uniform distribution of contaminants is not guaranteed*
Establishing acceptable limits (3)

- The limit-setting approach can:
  - be product-specific
  - group products into families and choose a worst case product
  - group products into groups according to risk, e.g. very soluble products, products with similar potency, highly toxic, or difficult to detect products
  - use different safety factors for different dosage forms based on physiological response (this method is essential for potent materials)
Establishing acceptable limits (4)

- Limits may be expressed as:
  - a concentration in a subsequent product (ppm),
  - limit per surface area (mcg/cm\(^2\)), or
  - in rinse water as ppm.

- Limits for carry-over of product residues should meet defined criteria.

- What are the three most commonly used criteria?
Establishing acceptable limits (5)

The three most commonly used criteria are:

- **Visually clean** No residue visible on equipment after cleaning. Spiking studies to determine the concentration at which most active ingredients are visible. (May not be suitable for high potency, low-dosage drugs.)

- **No more than 10 ppm** of one product will appear in another product (basis for heavy metals in starting materials).

- **No more than 0.1%** of the normal therapeutic dose of one product will appear in the maximum daily dose of a subsequent product.
Establishing acceptable limits (6)

- The most stringent of three options should be used.
- Certain allergenic ingredients and highly potent material should be undetectable by the best available analytical methods.
  - e.g. penicillins and cephalosporins
  - e.g. anovulent steroids, potent steroids and cytotoxics
- Dedicated manufacturing facilities needed.
Validation

- Group session