Regulatory Basis:
FDA Quality Systems Regulations

Reference: FDA CFR - Code of Federal Regulations Title 21

1 Purpose

The Purpose of this guideline is to define the minimum requirements for cleaning and validation of cleaning processes for formulated product. It also covers post validation monitoring of the effectiveness of cleaning processes.

2 Scope and Applicability

This document is applicable to all commercial and investigational formulated products manufactured within a R&D and Operations facilities. It sets standards for cleaning and cleaning validation that suppliers of formulated products should be assessed against. Cleaning for primary packaging operations is also included.

This guideline applies to the validation of cleaning procedures for equipment used in manufacture of pharmaceutical products, but excludes Active Pharmaceutical Ingredients (API) and their intermediates.

Microbiological aspects of cleaning and determination of effectiveness are not considered in this document. Such activities should be treated on a case-by-case basis with due consideration given to manufacturing operations, area classifications, dosage forms etc.

3 Definitions

3.1 Hot Spot

A surface which is judged to be difficult to clean, or where microbiological growth may be foreseen, such as bends, valves, feed controls, sleeve couplings, bushing and hidden surfaces.

3.2 Limit of Detection

The lowest amount of a given substance in a sample that can be detected but not quantified with the selected analysis procedure.

3.3 Limit of Quantification

The lowest amount of a given substance in a sample that can be quantified with suitable accuracy and precision with the selected analysis procedure.

3.4 Cleaning Validation

Establishing documented evidence that a specified cleaning procedure will provide a high degree of assurance that it can be used to consistently clean a piece of equipment or a facility to a predetermined acceptable level of cleanliness.

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Each site/plant shall ensure that the analytical methods used for the determination of residual contaminants are validated.

Each site/plant shall issue and maintain procedure(s) based upon this guideline.

4.2 Operations Sites

Each Operations site/plant shall put in place validated cleaning procedures and generate data to confirm the validation of all product/equipment changeovers.

4.3 R&D Sites

Each R&D site/plant shall put in place appropriate cleaning validation or cleaning verification (including appropriate analytical method validation) that provide a high degree of assurance that cross contamination is avoided.

5 Guideline

5.1 General Principles

In Operations records for each changeover, confirming compliance with the pre-determined acceptance criteria shall be produced and retained.
In R&D, during early development phases, when a worst-case cleaning validation approach (see section 5.2) or cleaning verification is employed, records for each changeover should be documented in process equipment log books to confirm that the equipment has been cleaned using the validated procedure or that verification has been successful before it can be used for the next product.

During later development phases, when replicate clinical trial batches of the same product are being manufactured and the formulation and process are fixed validated cleaning procedures should be undertaken and recorded more formally.

The exact approach taken shall be described in R&D SOPs. When Operations facilities are used to manufacture products for clinical trials the approach adopted shall be documented and include a supporting rationale.

Each site/plant shall consider all product/equipment combinations. Grouping into product families (e.g. utilizing highest active agent variant, or other worst case example) and identical equipment groups is acceptable.

For product dedicated equipment, a rationale and supportive data shall be generated to justify time limits or maximum campaign lengths between cleaning. 'Test until clean' (i.e. cleaning until an Acceptable Carryover Quantity (ACQ) is achieved) procedures should not be used. The level of cleaning required/number of repeat washings should be established during the technology transfer phase of product development, and cleaning validation work for the product and equipment in question. Cases where additional cleaning is required following the routine cleaning procedure should be reported via the site/plant deviation reporting system.

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The cleaning method should utilize the most appropriate combination of these sampling procedures to confirm the adequacy of the specific cleaning procedure.

5.1.3.1 Visibly Clean

Although not strictly a sampling technique visual inspection is a key requirement and the foundation of the cleaning process, during cleaning verification, during validation and for all subsequent routine cleaning operations. Diagrams and/or checklists to represent areas to be cleaned/examined should be developed and completed during the cleaning operation/inspection. Ancillary equipment such as UV lamps may be used to detect fluorescent compounds. Cameras may be used to examine inaccessible areas such as pipes and hoses.

5.1.3.2 Swab Testing

Surface sampling via swab testing is a direct method for assessment of cleanliness. This technique permits the hot spots and critical sites to be sampled and measures the actual residues left on the equipment. Swab procedures should define the area to be monitored and solvent, if used. Procedures shall be in place for quantitative calculation of the residue product result, taking into account area swabbed, recovery of product from the surface and swab, total area of the equipment. The time between cleaning and swabbing also needs to be considered. The swab technique can be used to assess effectiveness of Clean In Place (CIP) systems after defined CIP cycles.

5.1.3.3 Rinse Wash Testing

Rinse solutions are an indirect method for assessment of cleanliness. This technique samples a greater surface area but measures removal rather than residual product (hence indirect). This approach assumes that residual product is not greater than product removed. This method allows larger areas/more complex equipment/CIP systems to be evaluated. Analytical methodology should measure the product specifically, however following validation non product-specific measures may be employed as part of routine monitoring.

5.1.4 Testing Methods

A suitable quantitative method should be selected appropriate to the sampling method and acceptance criterion. The limit of detection must be lower than the ACQ. Preferably, the limit of quantification should also be below the ACQ otherwise it is necessary to clean to ‘none detected’. Qualitative methods are generally not acceptable. Non-specific techniques such as Total Organic Carbon (TOC) determination may be applied for certain products, providing there is scientific justification that these will give worst-case results (i.e. they could detect additional contamination).

5.1.5 Acceptance Criteria for Carryover

The scientific rationale for derivation of ACQ for a changeover is based upon the premise that 'The maximum daily dosage of one product must not contain a level of

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Surface sampling via swabs is the preferred method for assessment of cleanliness during validation. Visibly clean must apply. Rinse testing may be used to provide additional assurance or to indicate readiness for swab sampling.

Following successful completion and documentation of validation, it is not necessary to routinely use all these methods (e.g. use visual inspection only), provided that the documented cleaning procedure is followed.

5.2.2 Analytical Methodology

Analytical methodology shall be appropriately validated and documented in order to provide sufficient assurance of cleanliness relative to the acceptance criterion for the product changeover.

During the Technology Transfer of a new product from R&D to Operations, R&D shall provide the validated analytical methods to Operations for use in Cleaning Validation. The analytical method validation should take into account the method of sampling, proven level of recovery from swabs and surfaces, and interactions with other materials present in the sample matrix (e.g., solvents, swab extractives, cleaning agents, other active ingredients, etc.).

5.2.3 Bracketing (Matrixing) of Products, Equipment and Cleaning Methods

It is acceptable, with documented rationale and data, to group (also known as ‘bracket’ or ‘matrix’) together product 'families' (i.e. different strengths of the same formulation), or products/active ingredients with similar physico-chemical characteristics (e.g. solubility) to perform cleaning validation studies on the 'worst case' example, where the same equipment and cleaning method is used.

Bracketing studies may also be based upon other criteria. Examples of such criteria could be: type of equipment, type of material in contact with product, type of process (e.g. wet or dry manufacturing), ability to perform visual inspection, method of cleaning (eg manual or automated), etc.

The rationale and criteria for any use of bracketing shall be justified and documented and the validation of such bracketing must encompass worst-case conditions (e.g. active ingredients, equipment etc).

5.2.4 Cleaning Validation Documentation

Operation or R&D sites shall have a procedure describing how to validate cleaning. Cleaning validation should be included in the Validation Master Plan.

The cleaning validation documentation shall explain how the validation of the cleaning procedure shall be conducted. The documentation shall, as a minimum, include the following:

- The objective of the validation
- Description of the equipment and material specifications
- Cleaning procedure to be used including all cleaning parameters and cleaning agents

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