Regulatory Basis

FDA CFR Sec. 211.67 Equipment cleaning and maintenance.

Reference: CFR - Code of Federal Regulations Title 21

Purpose

The purpose of this guideline is to define the criteria that should be considered when grouping Active Pharmaceutical Ingredient (API) and Drug Product (DP) equipment or product for the purposes of cleaning validation.

The ability to group products or equipment for the purpose of reducing the amount of sampling and testing during cleaning validation is dependent on scientific, documented rationale. Similarly, scientific, documented rationale is also required when determining a worst-case product for the purposes of cleaning validation of API and DP manufacturing equipment.

Scope and Applicability

This guideline is applicable to all plants and equipment used to manufacture medicinal products and APIs and/or their intermediates (excluding biotechnology processing) within Operations and R & D.

Microbiological aspects of cleaning are not considered in detail in this guideline. The risk of microbiological contamination and the associated actions to mitigate this risk should be assessed on a case-by-case basis, eg generally equipment is not left water wet. Such risk assessments should consider manufacturing and cleaning operations; materials used in production and cleaning; facility design and controls; API susceptibility to microbial growth and the use of the API.

Note: R&D do not carry out formal cleaning validation during development(owing to the limited number of batches and changing processes/equipment), but cleaning verification must be carried out.

Definitions

Cleaning Validation

> Cleaning validation is a validation program to verify that the processes and procedures used to clean product residue from process equipment and components, will consistently and significantly reduce the amount of active and/or excipient(s) and cleaning agent(s) to a concentration within calculated acceptance limits

Drug Substance (DS) or Active Pharmaceutical Ingredient (API)

> Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product that when used in the production of a drug becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body. Note: Also known as Bulk drug or Drug Substance.

Acceptable Carryover Quantity (ACQ)

> The maximum quantity of guiding substance that can be carried over into subsequent manufacture.

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cleaning procedures. Such cleaning may include the use of 'placebo' contaminants (e.g. lactose).

Visibly Clean

A state of cleanliness characterized by the absence of any residues visible to the naked eye assessed following a written procedure. This can be quantified (e.g. as part of analytical method validation) where a quantitative result (based on the worst case level for visibly clean) is required for carry over calculation.

Responsibilities

All Operations and R&D sites are responsible for developing an approach to cleaning of plant and equipment used to manufacture APIs that is justified and consistent with the requirements of this guideline and current GMP.

Each site shall put cleaning procedures in place. Each site shall ensure that analytical methods used for the determination of residual contaminants are appropriately validated.

Each site shall generate sufficient supporting data to support cleaning verification, establishment or validation as appropriate.

Operations Sites

Each Operations site shall implement validated cleaning procedures as required in this Guideline.

General Discussion

The primary objective of grouping related items in validation is to be able to identify a 'worst case' or representative item that allows the results of a particular validation exercise using that item to be applied to the remainder of the items in that group. In doing so, the overall burden of validation is reduced while at the same time objective evidence is obtained that supports validation of grouped products or equipment.

Equivalent Cleaning Procedures

Any plan to group products or equipment for the purpose of cleaning validation should be based on the premise that the items grouped share the same cleaning procedure. Use of the term 'same' in this context means equivalent and applies to the cleaning methodology and parameters. If two or more procedures or automated programs share the same methodology and parameters, but have different titles, document numbers or program identifiers then it should be possible to apply the results of the cleaning validation across all those procedures. When determining if two procedures are equivalent, the following points should be considered as to their criticality in achieving the final result:

- Cleaning agent and cleaning agent concentration
- Liquid used for rinsing
- Temperature

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Types and examples of equipment grouping include:

Identical Equipment (Grouped by type and similar or identical utilities and accessories)	Reactors (vessels with heating, cooling and a condenser); Receivers (tanks with no heating, with or without agitation) cleaned by an individual procedure. Blenders or Mixers (same configurations/accessories with respect to cleaning). Tablet Presses (same cleaning procedures/accessories/ parameters)
Grouped by gross function	Where one individual cleaning procedure is used for all product cleanups (e.g., Centrifuges and dryers, or Fitzmills and Comils, Granulators). This applies where there is mostly manual disassembly.
Grouping Minor Equipment	For example, scoops, shovels, filter plates, filter housings, spatulas. Relatively small equipment that is manually cleaned and has no moving parts can usually be cleaned by the same procedure.

- Equipment design (e.g., Heating/cooling, Mixing, gross function) and geometry (e.g., shape and size)

- The ability of an individual procedure to produce expected results, i.e., uses the same cleaning instructions.
  - A change in the sequence of cleaning cycles constitutes a different cleaning recipe and should not be considered equivalent for the purpose of validation.
- CIP design including spray device pattern, pump size, and supply line diameter.

- Process piping routing and aggregate surface area is sufficiently similar. Pipe routing and size should be considered and appropriate test cases identified. If a scientific rationale can be justified with approval by site Quality, that a set of piping is sufficiently similar, a worst test case selection is appropriate for the purpose of validating the set. Otherwise, multiple piping configurations should be represented within the test cases to represent the variability inherent in the pipe sets.

  Verify if all equipment groupings and cleaning procedures are being included on the selected test cases for each family group. If not, add additional test conditions to include all equipment and cleaning procedure considerations. This process may result in several combinations selected as “worst cases” for each group of products, and also to include the different equipment and cleaning procedure considerations.

During any failure investigation activity, consider the possibility of an inappropriate grouping strategy as the root cause of failure, and revise the rationale for the grouping strategy as necessary. For example, if the failure rate for an equipment unit is higher than the failure rate for the other equipment in the same group, the equipment grouping should be re-
evaluated to determine if it is defendable.

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