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 requirements for cleaning plant and equipment used to manufacture active pharmaceutical ingredients (APIs) or their intermediates.
- To give guidance on how to assure appropriate cleaning of API plants and equipment.
- To describe when validation is applicable and what must be done to complete validation.

Scope and Applicability:

This guideline is applicable to all plants and equipment used to manufacture 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.

This guideline applies from the point of introduction of the registered starting materials into the synthesis 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 ofa 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.

API Starting Material

Maximum Daily Dose (MDD)

The maximum dose of active substance (usually mg or g) typically administered to a patient in any 24hr period (e.g. as referenced in the Core Data Sheet).

Minimal Effect Dose (MED)

The minimum dose at which there is an observable pharmacological effect in man.
Note: The MED is expressed as a weight of active substance (usually mg or g) per day.

Minimum Therapeutic Dose (MTD)

The minimum amount of active substance (usually mg or g) typically given to a patient on each occasion as referenced in the Core Data Sheet.

Mobile Equipment

Items of product contact equipment that are routinely disconnected and reconnected to plant to enable processing steps as part of an equipment train. This excludes small, easily inspected or disposable items and spares (e.g. sight glasses, small flexible lines, filter bags etc).

Multi-purpose Equipment/Plant

Non-dedicated plant or equipment used for the production of more than one intermediate or API where the potential for cross-contamination exists.

Nil Effect Dose (NED)

Based on human data, is the maximum (single or repeated) dose at which there are no observable pharmacological effects in man.

Note: The NED is expressed as a weight of active substance (usually mg or g) per day.

No Observable Effect Level (NOEL)

The dose level (usually mg or g) at which no toxicological effects are observed.

Risk Assessment Factor

A factor used when defining an acceptance limit. It is used during calculation of acceptance limits to ensure that the level of contamination is sufficiently low from a pharmacological and toxicological standpoint.

Stain

A mark (e.g. surface marking/etching/discoloration) which has appeared since the installation of new plant or equipment will be considered a stain if both physical and chemical documented procedures fail to remove it.

Trial Cleaning

Cleaning carried out prior to the use of the plant/equipment for manufacture to establish the use of clean in place devices, potential hot spots or high level 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

The Dose MAR (where applicable) and the Tox MAR (where applicable) should be calculated and compared against the weight percent limit MAR from Table 1 and the lowest of the three selected to calculate the RAL.

If a worst case limit is used for equipment producing multiple compound types (e.g., final APIs and early intermediates), the most conservative limit for all compound types produced in the equipment should be selected.

The limit for each compound or product, “A” may be calculated and used for a specific subsequent product, “B”, or a worst case limit for all A/B Combinations may be used.

Table 1 (continued from previous page):

Compound Type	Compound Type Definition	Cleaning Validation required?[6]	Verification Method to be used During Routine cleaning (after validation, if required)[2]	Additional Verification During Validation	Limits	Material Examples
'Other' residues	Generally Recognized as Safe (GRAS) compounds	No	At least visual inspection	N/A	Visually Clean	e.g., NaCl, buffers, some raw materials, reagents
	Organic Solvents		Major equipment - visual and rinsate, if required Minor equipment and Major equipment that can be completely disassembled and 100 percent visually inspected - visual inspection.		Visually Clean and analytical limit if dictated by toxicity	Organic Solvents
	All Other		Major equipment - visual and rinsate or swabbing, Minor equipment and Major equipment that can be completely disassembled and 100 percent visually inspected - visual inspection.		RAL calculated based on lower of tox MAR and 100 ppm Wt%	Some raw materials, reagents

APPENDIX I – Calculation of MAR

1) Calculate Dose MAR

(For therapeutic compounds and clinical compounds where dose information is available)

Determine Maximum Allowable Residue as mg of A per kg of B (both activity):

$$\text{Dose MAR} = \frac{T_A \text{ (mg of A)} \bullet \text{conversion } (10^6 \text{ mg of B/kg of B}) \bullet \text{(SF)}}{B_B \text{ (units)} \bullet C_B \text{ (mg of B/unit)}}$$

2) Calculate Toxicity (Tox) MAR

(For all compounds, non-therapeutic and therapeutic where toxicity information is available)

Determine Maximum Allowable Residue as mg of N per kg of B (activity):

$$\text{Tox MAR} = \frac{\text{ADI (mg of N/day)} \bullet \text{conversion } (10^6 \text{ mg of B/kg of B})}{B_B \text{ (units)} \bullet C_B \text{ (mg of B/unit)}}$$

3) Compare against Weight % MAR

(Weight% limit in Table 1)

After Dose and Tox MARs are calculated as required, compare against the Weight% limit indicated in Table 1 for the type of compound being cleaned. For equipment producing multiple compound types (e.g., final APIs and early intermediates), the most conservative Weight% limit for all the compound types produced in the equipment must be selected. Select the lowest of the MARs (Dose, Tox, Weight%) to use in the RAL (Limit) calculation in Appendix II.

For example, if the calculated Dose and Tox MARs for a therapeutic compound are both > 25 mg N or A/kg B (ppm), then use the Weight% limit of 25 ppm in the RAL calculation. If either the Dose or Tox MAR are < 25 mg N or A/kg B (ppm) for that therapeutic compound, then use the lowest calculated MAR in the RAL calculation.

