

Guidance 018 Equipment Cleaning Validation For Active Pharmaceutical Ingredients

- Stability of material(s) being cleaned under the proposed cleaning conditions;
- Suitability of the cleaning agent(s) for the materials of construction of the equipment;
- Equipment surface finish (e.g., stainless steel, glass, polypropylene);
- Rationales for decisions on which materials to test, the limits for testing, and the method of verification (see Table 1); and
- Evaluation of campaign length.

2.

Equipment with the Same Design and Operating Principle may be grouped for the purpose of validation. These groupings should be documented and justified. The documentation should be approved by Site Quality Team and Production Team. If equipment grouping is used, cleaning validation should be performed using three executions of the same cleaning procedure using any combination of equipment within a group.

3.

Where Equipment is Used to Produce Only Early Intermediates (i.e., intermediates produced prior to the introduction of the API starting materials), cleaning verification is required. Validation of the cleaning procedures for these cases is not required (see Table 1).

4.

Selection of The Most Difficult To Clean Product or Process requires consideration of, at least, the following:

- Solubility of residues in cleaning agents (including cleaning and rinse solvents);
- Potential for polymers, or other side products to form during or prior to the cleaning operations;
- The Residue Acceptability Limit (RAL) required for cleaning;
- Processing Parameters (e.g., high temperature, use of carbon); and
- Cleaning history.

Selection of the most difficult to clean product or process should be documented in the validation protocol or a Cleaning Evaluation Report.

5.

Rinsate Method - if a rinsate method is used as the sampling method, a measured volume of solvent used for the final rinse should thoroughly wet all product contact surfaces, and should be circulated through all product contact lines before the rinsate is tested in the laboratory for residues.

6.

Swabbing Method - if swabbing is used as the sampling method, swabbing of product contact surfaces should be performed in locations from which there is a likelihood of transfer of residue to a subsequent product and from most difficult to clean areas (i.e., dead-legs, bottom valves, overheads, tank domes and inlets).

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

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
Cleaning Agents	Commercial Cleaning Agents	Yes ⁵	Major equipment - visual and rinsate or swabbing Minor equipment and Major equipment that can be completely disassembled and 100 percent visually inspected - visual inspection	None	RAL calculated based on lower of tox MAR, and 100 ppm Wt% of largest component (non-water)	Commercial detergents such as CIP 100, CIP 200
Dedicated Equipment	Any	No	Visual inspection	N/A	Visually Clean	Any in dedicated equipment

1. Table 1 is not intended to identify which compounds or materials are required to be tested for, only what sampling is to be performed and limits applied once the selection is made via the Cleaning Evaluation Report.
2. Swabbing shall be used only for routine verification where rinsate is not feasible and 100 percent visual inspection is not possible, unless a rationale is provided.
3. Dose MAR to be considered only if dose is known.
4. 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 must be selected.
5. Separate validation of removal of cleaning agents is not required if the removal of the cleaning agent is included in the validation of the equipment cleaning from process compounds. Validation of removal of cleaning agents is not required for equipment producing only early intermediates or other residues of chemically synthesized APIs.