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 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.

2 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.

3 Definitions

3.1 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

3.2 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

3.16 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.

3.17 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.

3.18 No Observable Effect Level (NOEL)

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

3.19 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.

3.20 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.

3.21 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).

3.22 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.

4 Responsibilities

4.1 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

If the mobile equipment is multi purpose:

- There should be separately maintained records of equipment use, cleaning or maintenance with the appropriate cross-references to batch records.
- Such equipment must be considered as a part of the total equipment train with respect to risk for cross-contamination and cleaning, i.e. when assessing the acceptable ACQ and verifying the level of cleanliness all mobile equipment must be included. When configuring more than one item of mobile equipment (individually cleaned to a specified limit for different products) into the same equipment train an assessment must be made as to the suitability for use of the equipment both as individual items and as part of the overall equipment train.

  Mobile equipment, including spare parts, that has been cleaned and is not in use must be stored to prevent contamination (e.g. in cabinets providing a clean environment, or by sealed covers or other appropriate means).

  Small items (e.g. sight glasses) are not considered as separate items of equipment and are cleaned along with the equipment that they are connected to.

5.2.4 Establishment of Acceptance Criteria for Carryover Limits

5.2.4.1 Application of a risk based approach to product changeovers (risk levels)

In order to prevent cross contamination of API that will be incorporated in a dosage form for administration to patients, residues must be quantified after cleaning and ACQ specified. The ACQ is determined to ensure that the level of residue after cleaning will not have a clinically significant pharmacological or toxicological effect at the maximum daily dose of the subsequent product.

The choice of the guiding substance(s) must be recorded and justified. Typically it will be the last material prepared in the vessel, though other components of the contamination matrix should be considered, e.g. catalysts, toxic reagents, solvents, degradedness or by-products of the last material.

The amount of a specific contaminant actually present in the equipment to be used for the manufacture of an API is determined by summing the amount present in the rinse washes or swabs of all the equipment to be used in the manufacture.

For the calculation a worst-case assumption is taken that the amount of contaminant remaining is equal to the amount that has been recovered by swabbing or rinse analysis.
It is not necessary to add results from rinses and swabs, unless they are measuring separate
parts of the equipment train, in the

calculation of residual guiding substance(s). The most appropriate method to give the final result should be selected based on consideration of the equipment, guiding substance properties and knowledge of the cleaning procedure (see section 5.2.5.3).

$$ACQ = \frac{MBS \times MDD_{APIb}}{MDD_{APIb}}$$

ACQ	=	Acceptable carryover quantity (mg) into APIb
MBS	=	Minimum batch size of APIb (mg)
MDD_{APIb}	=	Maximum daily dose of APIb(mg)

If there is other information in addition to the Ames result (i.e. the guiding substance is a known genotoxic material or subsequent testing shows that a compound that gave an Ames positive result is/is not genotoxic) then the cleaning limit should be assessed on a case-by-case basis. DSORC should ratify the assessment in order to ensure that the approach is consistent across sites.

5.2.4.3 Use of ACQ for a Level 0 or 1 Change Over (see Appendix 2)

Generally it is not possible to use the calculation approach for level 0 or 1 because therapeutic dose information is not available. However, in some circumstances a calculated ACQ, or where this is not possible a more stringent ACQ, may be applied to level 0 or 1 changeovers.

Examples:

Change over of plant between the manufacture of a crude and pure API from the same series (general guidance risk level 0) where the crude process uses a highly toxic reagent or metal catalyst. In such circumstances an ACQ may be calculated using the API therapeutic data and the reagent/metal toxicological data.

Change over from a pure API to a crude API from another series (general guidance risk level 1). Data may be available for both APIs to enable a calculated ACQ for comparison with the default minimum acceptance criteria of 100ppm.

5.2.5 Inspection, Sampling and Determination of Residue

5.2.5.1 Inspection and Sampling Plan

Due to the complexity of a chemical plant an effective plan must be devised and documented prior to inspection and sampling. Key to this activity is an understanding of the plant layout and equipment paying particular attention to hot spots.

A critical assessment of the equipment and its configuration to assess all potential hot spots should be performed. This assessment of hot spots should involve QA, the plant engineer, the plant operator, the production manager and include a review of line diagrams along side physical plant inspection. For new plants a list of potential hot spots should be included in the hand over documentation.

Cleaning validation requirements vary according to the changeover type and the subsequent risk to API contamination.

Plant Use/ Risk Level	Risk Considerations	Minimum Requirements
Dedicated Plant - no changeovers	No risk of cross contamination. Campaign length and any engineering cleaning should be assessed (see sections 5.2.6 and 5.2.7)	No formal validation required. Verify removal of gross contamination at justified periodic intervals
Level 0	No technical restrictions limiting carryover If sequence of stages or products change then the risk should be revisited.	Verify removal of gross contamination at changeover.
	Technical restrictions limiting carryover.	Demonstrate plant/equipment is visibly clean (or cleaned to a technically justified level) for three changeovers
Level 1	Risk of cross contamination between product families at stages prior to final API purification.	ACQ maximum 100ppm demonstrated for three changeovers.
Level 2	Risk of cross contamination into final API	Level of carryover at or below ACQ (see section 5.2.4) demonstrated for three changeovers.

5.3.2 Cleaning Validation Documentation Requirements

There must be a documented cleaning process approved by QA prior to validation. The validation must be documented (e.g. in a validation program/protocol and report). The detailed requirements for the validation documentation must be described in site policies and procedures.

5.3.3 Bracketing Approach for Cleaning Validation

For a multi purpose plant it is acceptable to use a bracketing approach for cleaning validation. Bracketing may be applied to the guiding substance(s) and/or the plant.

5.3.3.1 Bracketing of Guiding Substances

If bracketing the guiding substances all of the substances contacting the equipment must be reviewed and a representative substance or substances selected. The selection of a representative substance(s) for cleaning validation must include worst case example(s) based on solubility, difficulty of cleaning, potency, toxicity, stability

* See section 5.2.4.3

Each box represents the process to convert to the named intermediate or API. The envelope for the
cleaning is all the equipment used to manufacture the named intermediate or API. The guiding
substance is likely to be the intermediate/API manufactured at that stage of the process (e.g. Conversion to Intermediate 2, the equipment will be contaminated with intermediate 2 or a chemical used in this step)

Appendix 2 – Risk Level Minimum Acceptance Criteria

Risk Level	Risk Consideration	Minimum Acceptance Criteria for the Equipment Train
0	Carry over of material within the same synthetic sequence represents the lowest risk.	The acceptance criteria must be based on technical considerations (impact on chemistry and API purity profile) and can be assessed through risk assessment. The minimum acceptance criterion (i.e. if there are no technical restrictions on the acceptable level of carry over) is that the equipment must be free from gross contamination.
1	Carry over of the intermediate/crude API into a different synthetic sequence or into final purification step of the same synthetic sequence represents a higher risk to product quality. The carry over of material into the subsequent purified API will be reduced through attrition (e.g. loss to mother liquors, screening filtrations).	Theoretically toxicological/pharmacological data could be used to calculate the ACQ, however the carry through to the following final APIb will depend on the yields of the subsequent reaction/purification steps, the relative solubility of the contaminant and the stability of the contaminant under the conditions of the succeeding steps. As all the information required to calculate an ACQ is unlikely to be available adefault minimum acceptance criteria of 100 ppm w/w carry over for the guiding substance is applied (e.g. 100 mg of carry over per kg of the next product).
2	Carry over of an intermediate or an API into the purification step of an API (or post final purification step such as milling and blending) from a different synthesis represents the highest risk because of the potential for unrelated toxicity/activity effects. The likelihood of attrition is reduced as there is only one processing step (there will be some reduction in equipment in contact with solvent such as dissolution vessels and crystallisers, however there will be none in dryers and mills).	The acceptance criterion is calculated from toxicity/activity data. If there is no data available then a default acceptance criterion of 10 ppm w/w carry over of the guiding substance is applied (e.g. 10 mg of carry over per kg of next product). If the calculated acceptance criterion is greater than 100ppm w/w then a default limit of 100ppm w/w must be applied. If the calculated acceptable carry over limit is between 10ppm and 100ppm then the calculated limit must be applied.

