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 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.

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 óplaceboô 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 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.

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). Surface area calculations for plant must be documented

Three risk levels need to be considered depending on the type of changeover. The flowchart (Appendix 1) shows the changeover scenarios within and between two synthetic sequences

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.

For new plant or product it may be necessary to sample all hot spots. Where experience has been built up over several cleaning batches that demonstrate the

5.2.5.3 Sampling Methods

The most suitable sampling method or combination of methods should be chosen to verify, validate and/or monitor the effectiveness of cleaning on a case by case basis. The two most commonly used methods of sampling are swab sampling and rinse sampling although other approaches can be taken if scientifically justified (e.g. the use of placebos and the use of coupons (test pieces made of the same material as the plant)).

The advantage of rinse sampling for API cleaning is that it contacts the vast majority of the many inaccessible and difficult to clean surfaces in API plant that cannot be swabbed (e.g. transfer lines, condensers, vapour uplifts and small inaccessible vessels). If well designed (taking account of solubility in the wash solvent and the kinetics of dissolution i.e. how much time is required for effective dissolution of residue) rinse sampling will give the best picture of the amount of residue remaining in the plant (with the exception of certain hot spots e.g. ball valves).

The advantage of swabbing is that it directly samples the surface and measures the actual residue left on the equipment. Additionally residues that are ódried outô or insoluble can be sampled by physical removal. Swabbing can be particularly effective in sampling hot spots where the action of refluxing solvent washes may be ineffective (e.g. vessel roofs, complex manifolds and ball valves). It is unlikely to offer any advantage over rinse sampling for large surfaces well contacted by solvent rinse washes (e.g. vessel side and base walls) and can be impractical in much API plant (e.g. transfer lines).

The greatest risk of carryover of residue comes from material hold up in hot spots. The first step in an effective sampling plan is to identify potential hot spots (see section 5.2.5.1) and to ensure these are closely monitored (see appendix 1 ï typical hot spots in API plant). Risk assessment may be a suitable approach to identify which hot spots to sample and inspect or test. In some cases it may be most effective to remove and clean such hot spots or to replace them with like-for-like clean equipment (e.g. transfer pumps or ball valves).

During the establishment and validation phase a combination of rinse sampling with inspection and swab sampling (and/or removal and physical cleaning) of hot spots must be used. After validation the effectiveness of cleaning should be monitored with at least rinse sampling (final wash only) and visual inspection. Following cleaning validation, inspection and swab sampling (and/or removal and physical cleaning) of selected hot spots may be retained.

When selected as a sampling technique, swabbing procedures should define the area to be monitored, use of any solvents, details of the technique and equipment to be used and how a quantitative residue result is then derived, taking into account the area to be swabbed, recovery from swabbing, size of equipment etc.

These procedures should be sufficiently detailed to ensure adequate consistency in the swabbing technique between analytical method validation and on plant

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

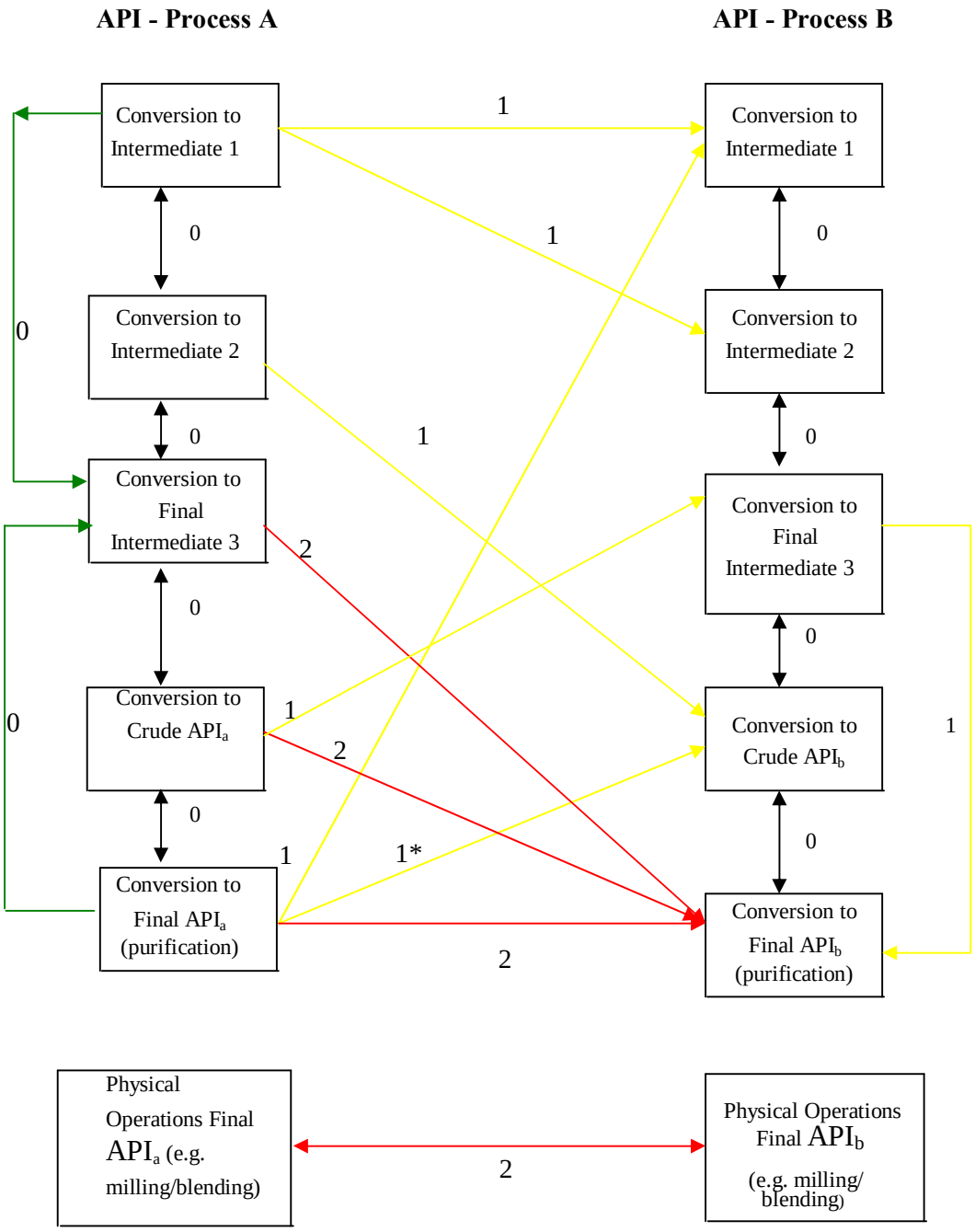
For a multi purpose plant it is acceptable to use a bracketing approach for cleaning validation. Bracketing may be applied to the guiding substance(s) and/or the plant.

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 and ACQ.

5.3.3.2 Bracketing of Plants and Equipment

Appendix 1 – Product Changeovers and Risk Levels



Appendix 3 – Typical API Plant Hot Spots

- Baffles with thermotips
- BRO valves
- Discharge assemblies/valves on pressure filters
- Pressure filter spray rings, door seals, inlets and vent lines
- Pipe manifolds
- Tight bends
- Dead legs
- Long pipe runs
- Condensers (particularly carbon block)
- Sampling systems (including dip legs, valves and pumps)
- Agitators (particularly where cladded)
- Valves (particularly ball valves and butterfly valves)
- Uplifts/charge chutes etc

