1 Purpose

The Purpose of this guideline is to define the minimum requirements for cleaning and validation of cleaning processes for formulated product. It also covers post validation monitoring of the effectiveness of cleaning processes.

2 Scope and Applicability

This document is applicable to all commercial and investigational formulated products manufactured within a R&D and Operations facilities. It sets standards for cleaning and cleaning validation that suppliers of formulated products should be assessed against. Cleaning for primary packaging operations is also included.

This guideline applies to the validation of cleaning procedures for equipment used in manufacture of pharmaceutical products, but excludes Active Pharmaceutical Ingredients (API) and their intermediates.

Microbiological aspects of cleaning and determination of effectiveness are not considered in this document. Such activities should be treated on a case-by-case basis with due consideration given to manufacturing operations, area classifications, dosage forms etc.

3 Definitions

3.1 Hot Spot

A surface which is judged to be difficult to clean, or where microbiological growth may be foreseen, such as bends, valves, feed controls, sleeve couplings, bushing and hidden surfaces.

3.2 Limit of Detection

The lowest amount of a given substance in a sample that can be detected but not quantified with the selected analysis procedure.

3.3 Limit of Quantification

The lowest amount of a given substance in a sample that can be quantified with suitable accuracy and precision with the selected analysis procedure.

3.4 Cleaning Validation

Establishing documented evidence that a specified cleaning procedure will provide a high degree of assurance that it can be used to consistently clean a piece of equipment or a facility to a predetermined acceptable level of cleanliness.

3.5 Acceptable Carryover Quantity (ACQ)

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

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

3.11 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.

3.12 Maximum Daily Dose (MDD)

The maximum dose of product typically administered to a patient in any 24hr period.

Note: The MDD is normally expressed as a weight of active ingredient (usually mg or g) per day. For the purpose of the ACQ calculation it may be more appropriate to use the gross weight of drug product (mg or g) per day if the minimum batch size used in the ACQ calculation is based on weight of drug product rather than weight of active ingredient.

3.13 Safety Factor

The Safety Factor is the safety margin used when defining an acceptance limit for product carryover. It is applied during calculation to ensure that the level of product carryover is sufficiently low that there will not be a pharmacological effect due to any product carried over into the subsequent product.

3.14 Swab

Swab means a piece of inert absorbent material used for sampling a predetermined surface area of equipment.

3.15 Visibly Clean/ Absence of visible residues

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 Sites/Plants

Each site/plant shall document the rationale for their adopted approach (e.g. product/plant matrices, revalidation frequency etc.) and for the setting of maximum acceptable limits for carryover, including the medical rationale.

Each site/plant shall ensure that the analytical methods used for the determination of residual contaminants are validated.

reproducible process that results in carryover remaining below a scientifically derived limit. Whilst attempts should be made to optimize the efficiency of all cleaning processes, it is not necessary to clean until the carryover is below the analytical limit of detection (i.e. none detected). The acceptance criteria for carryover must be related to the pharmacological effect of the carryover product or to a defined default limit if this pharmacological effect information is not available.

If the acceptance limit for a changeover is lower than the analytical limit of detection, the equipment must either be dedicated, or an alternative, more sensitive method of detection be developed.

Cleaned equipment should be stored dry and protected against contamination. Cleaning validation for packaging operations shall be considered in the same manner as for manufacturing or processing operations. Cases where cleaning validation is not undertaken shall be justified.

Cleaning from a microbiological viewpoint is not considered within this document. The need for microbiological evaluation should be considered within the cleaning protocol. When not undertaken, justification should be supported by a documented rationale.

For certain products (e.g. penicillin, cytotoxics) it may not be permissible or practical to routinely perform cleaning to the required levels for prevention of cross contamination.

For new products introduced to an Operations site/plant, cleaning information (e.g. validated analytical methodology for determination of product residues, outline cleaning methods, etc.)shall be part of the technology transferred from the development function to the site/plant, and form the basis of the site validation.

For established product technology transfer, the transferring Operations site shall ensure data is available for inclusion in receiving Operations site cleaning validation protocols.

5.1.1 Design Requirements

Design documents, such as piping and instrument diagrams, equipment specifications and product contact material specifications, should be reviewed to evaluate that the equipment can be cleaned and that the design meets current GMP requirements. Such review shall be documented and should include identification of potential hotspots or critical sites requiring evaluation during cleaning.

5.1.2 Cleaning Methods

The preferred methods of cleaning are vacuum or wet cleaning methods, using water or the most appropriate solvent and cleaning agent for the product. Site/plants should develop specific procedures during the transfer process.

All cleaning procedures shall specify the cleaning parameters, such as wash

Acceptance criteria for carryover shall include absence of visible residues.
The most stringent of the following limits shall also be applied.

Either:
ACQ = (Therapeutic Dose of residue product) x (Smallest batch size of next product)
(Safety factor) x (MDD of next product)

Therapeutic Dose of residual product = NED, MED or MTD, in this order of preference depending on availability of the relevant therapeutic dose information.

Safety factors for equipment train or individual equipment respectively:

	Equipment Train	Individual Equipment
NED (This allows for the uncertainty associated with the carryover measurement)	10	100
MED (This allows for uncertainty associated with carryover measurement and makes an additional allowance of 10 fold for use of MED instead of NED)	100	1,000
MTD (This allows for uncertainty associated with carryover measurement and makes an additional allowance 10-100 fold for use of MTD instead of NED)	100 - 1,000a	1,000 ï 10,000 a
ñppmò Allowed carryover of previous product to appear in any subsequent product	10ppm	1ppm

a An appropriate safety factor within the range should be selected if MTD is used. For some products the therapeutic effect is the lead pharmacological effect and the MTD is effectively the same as the MED hence the lower safety factor (same as MED) is appropriate. For other products the lead pharmacological effect may not be the therapeutic one and the MED is lower value than the MTD and hence the higher safety factor is appropriate. The use of the lower safety factors should be justified, however in R&D (for development compound cleaning where NED and MED are most often not available) the lower safety factors can be used without justification.

5.1.5.1 Acceptance Limits for Dedicated Equipment

Cleaning between batches of the same stage for the same product (e.g. several granulation batches later blended together in a tablet process) or for dedicated equipment used for one stage of one product, should not normally be required, unless there is evidence from Development or Technology Transfer of any

problems (e.g. degradation). In both these cases, time limits should be established defining intervals between cleaning. Where cleaning is carried out in dedicated equipment, visibly clean is the minimum acceptance criterion.

5.1.6 Determination of Carryover Levels

Surface sampling (swab testing) provides quantitative data for residues remaining on a given surface. Individual swab test results should be combined to yield an overall Measured Carryover (MC) for comparison to the calculated ACQ for the product changeover. The MC must be less than ACQ.

Usually swabs will be taken from different equipment surfaces and the individual swab results are then combined to obtain the final MC. The following guidance should be used to calculate the MC.
Note:
Swab test results must be corrected for recovery

5.1.6.1 Permitted Amount for Each Swab

Based on the assumption of uniform distribution of carryover product in the equipment it is possible to calculate the amount of product that would be obtained for each swab if the carryover amount equal the ACQ.

$$\text{Permitted amount (Per swab)} = \frac{\text{ACQ x Area of equipment sampled (per swab)}}{\text{Total surface area of equipment}}$$

If all swab results are below this permitted amount then the MC is also below the ACQ and the equipment is clean.

Where individual swab result(s) is/are greater than this amount it is then necessary to calculate the MC to demonstrate cleanliness. It is allowable for individual swabs results to be greater than the permitted amount so long as the MC is less than the ACQ. However, it is recommended that no individual swab should be greater than x10 the permitted amount for each swab (x10 is safety factor built into the ACQ calculation to cover uncertainty in the sampling and determination of carryover).

5.1.6.2 Measured Carryover (MC)

Measured Carryover is calculated by adding the individual swab results. This may be done on an equipment basis:

$$MC = \frac{\text{(Sum of swab values) x (Total surface area of whole equipment)}}{\text{(Total surface area sampled by all swabs)}}$$

Or, this may be done on an individual surface basis:

$$MC = \text{Sum of: } \frac{\text{(Swab value) x (Total surface area of the individual surface)}}{}$$

- The carryover product to be detected
- Worst case conditions, including the rationale for selection
- Sampling methods, including the rationale for selection
- Sampling plan covering identified sampling spots, including the rationale for selection
- Validated test methods
- The acceptance criteria including the rationale for ACQ
- Responsibilities for performing the validation work
- A statement requiring that a validation report shall be written

5.2.5 Post Validation Requirements for Cleaning Processes

This should be taken into account in the relevant Cleaning Validation report. Following cleaning validation, there should be a periodic reassessment of the continued suitability and validity of the cleaning against the original validation. Manual cleaning processes should be evaluated more regularly than a CIP process.

The frequency of periodic monitoring for different cleaning operations should be documented including how it will be performed. This may include repeating all or selected parts of the original validation, or by monitoring by alternative methods.

Note: Visual checks for absence of visible residues are mandatory for every changeover.

Each site/plant should aim to routinely achieve the standards of cleaning demonstrated during cleaning validation. This may result in setting action limits below the scientifically derived acceptable limits. To aid consistency of routine operations a common action limit may need to be applied to similar cleaning procedures on a site/plant.

5.2.5.1 Change Control

Cleaning routines, analytical methods, equipment, cleaning solutions and production process should be defined and documented in connection with the validation. In case of changes, change control in accordance with local procedures and Quality & Compliance international procedures and guidelines should be applied.

Revalidation should be evaluated on a case-by-case basis following formal changes to plant.

