APIC Active Pharmaceutical Ingredients Committee

*ACTIVE PHARMACEUTICAL INGREDIENTS COMMITTEE (APIC)*

# GUIDANCE ON ASPECTS OF CLEANING VALIDATION IN ACTIVE PHARMACEUTICAL INGREDIENT PLANTS

*Revision April 2019 (updated in February 2021)*

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# *Table of Contents*

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# 1.0 FOREWORD

This guidance document was initially updated in 2014 by the APIC Cleaning Validation Task Force on behalf of the Active Pharmaceutical Ingredient Committee (APIC) of CEFIC.

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A revision of the guidance document was done in 2016 to bring it in line with the European Medicines Agency Guidance on use of Health Based data on setting health-based exposure limits for determining safe threshold values for the cleaning[1] . The main changes were introduced in Chapter 4, Acceptance Criteria.

A further revision has now been done in 2018 - 2019 to address comments received from industry, to align further the guidance with the EMA Q&A[2] on use of Health Based Exposure Limits (HBELs) and published articles on use of HBELs.
The subject of cleaning validation in active pharmaceutical ingredient manufacturing plants has continued to receive a large amount of attention from regulators, companies and customers alike.

[1] European Medicines Agency, EMA/CHMP/CVMP/SWP/169430/2012, Guideline on setting health-based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities.

[2] 19 April 2018, EMA/CHMP/CVMP/SWP/246844/2018, Questions and answers on implementation of risk-based prevention of cross-contamination in production and 'Guideline on setting health-based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities'
26 July 2018, EMA/288493/2018, Outcome of public consultation on Questions and Answers on implementation of risk-based prevention of cross contamination in production and 'Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities'

The integration of Cleaning Validation within an effective Quality System supported by Quality Risk Management Processes should give assurance that API Manufacturing Operations are performed in such a way that risks to patients related to cleaning validation are understood, assessed for impact and are mitigated as necessary.

It is important that the requirements for the finished manufacturing companies are not transferred back in the process to active pharmaceutical ingredient manufacturers without consideration for the different processes that take place at this stage.

For example, higher limits may be acceptable in chemical production compared to pharmaceutical production because the carry-over risk is much lower for technical and chemical manufacturing reasons.

The document reflects the outcome of discussions between APIC member companies on how cleaning validation requirements could be fulfilled and implemented as part of routine operations.

In addition, APIC has aligned this guidance with the ISPE Risk MaPP Guide[3] that follows the Quality Risk Management Processes as described in the ICH Q9 Guidance on Quality Risk Management.

The criteria of Acceptable Daily Exposure (ADE) or Permitted Daily Exposure (PDE) are recommended to be used by companies to decide if Dedicated Facilities are required or not and to define the Maximum Acceptable Carry Over (MACO) of API's in particular, in Multi-Purpose Equipment.

Chapter 6 defines factors that should be considered in controls of the cleaning processes to manage the risks related to potential chemical or microbiological contamination.

[3] ISPE Baseline® Pharmaceutical Engineering Guide, Volume 7 – Risk-Based Manufacture of Pharmaceutical Products, International Society for Pharmaceutical Engineering (ISPE), First Edition, September 2010, www.ispe.org.

The PDA Technical Report No. 29 – Points to Consider for Cleaning Validation[4] is also recommended as a valuable guidance document from industry.

The following topics are discussed in the PDA document

- Cleaning process (CIP/COP): design and qualification
- Types of residues, setting acceptance criteria, sampling and analytical methods
- Maintenance of the validated state: critical parameters measurements, process alarms, change control, trending & monitoring, training and periodic review
- Documentation

## 2.0 OBJECTIVE

This document has been prepared to assist companies in the formulation of cleaning validation programs and should not be considered as a technical standard but a starting point for internal discussions. The document includes examples on how member companies have dealt with specific areas and issues that arise when performing cleaning validation.

## 3.0 SCOPE

Six specific areas are addressed in this Guidance document:

- Acceptance Criteria
- Levels of Cleaning
- Control of the cleaning process
- Bracketing and Worst Case Rating
- Determination of the amount of residue
- Cleaning Validation Protocol

Finally, the most frequently asked questions are answered to give further guidance on specific points related to cleaning validation.

[4] Parenteral Drug Association (PDA) Guidance for Industry. Technical Report No. 29 (Revised 2012) Points to Consider for Cleaning Validation, Destin A. LeBlanc, Gretchen Allison, Jennifer L. Carlson, Koshy George, Igor Gorsky, Irwin S. Hirsh, Jamie Osborne, Greg Randall, Pierre-Michel Riss, George Verghese, Jenn Walsh, Vivienne Yankah.

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# 4.0 ACCEPTANCE CRITERIA

## 4.1. Introduction

Companies must demonstrate during validation that the cleaning procedure routinely employed for a piece of equipment limits potential carryover to an acceptable level. The limits established must be calculated based on sound scientific rational.

This section provides practical guidance as to how those acceptance criteria can be calculated. It is important that companies evaluate all cases individually. There may be specific instances where the product mix in the equipment requires further consideration.

The acceptance criteria preferably should be based on the Acceptable Daily Exposure (ADE) or Permitted Daily Exposure (PDE) calculations whenever this data is available.

The APIC Guidance refers primarily to ADE in the examples of calculations included in this chapter.

The ADE/ PDE define limits at which a patient may be exposed every day for a lifetime with acceptable risks related to adverse health effects. Calculations of ADE/ PDE of APIs and final intermediates are usually done with involvement of industrial hygienists and toxicologists, who review all available toxicology and clinical data to set the limits. The justification of the calculation should be documented.

In many cases Occupational Exposure Limits (OEL) will be defined for APIs, Intermediates and Industrial Chemicals by industrial hygienists and toxicologists and the OEL data is then used to define containment measures such that operators are adequately protected while working with the chemicals.

For API manufacture preceded by another API, when limited pharmacological/toxicological data is available, preliminary ADE/PDE with available data or TTC approach is recommended.

In other cases where availability of pharmacological or toxicological data is limited, for example for chemicals, raw materials, Starting Materials, API intermediates cleaning limits based on the Threshold of Toxicological Concern (TTC), $LD_{50}$ and/or general cleaning limits may be calculated. In these cases, carcinogenic, genotoxic and potency effect of these structures should be evaluated by toxicologists.

The acceptance criteria for equipment cleaning should be based on visually clean in dry conditions and an analytical limit.

Unlike in pharmaceutical production, where residues on the surface of equipment may be 100 % carried over to the next product, in API production the carry-over risk is much lower for technical and chemical manufacturing reasons. Therefore, all the following examples for calculating the limits can be adapted to the suitable situation by using different factors. A competent chemist with detailed knowledge about the equipment and the chemical processes and the properties of the chemicals involved such as solubility should justify this factor by evaluating the specific situation.

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## 4.2. Methods of Calculating Acceptance Criteria

### 4.2.1 Acceptance criteria using health-based data

The Maximum Allowable Carryover (MACO) should be based upon the Health-Based Exposure Limits (HBEL), which can be an Acceptable Daily Exposure (ADE) or Permitted Daily Exposure (PDE), calculated when sufficient data is available. The principle of MACO calculation is that you calculate your acceptable carry-over of your previous product, based upon the HBEL, into your next material:

$$\mathbf{MACO} = \frac{\mathbf{HBEL}_{\mathbf{previous}} \times \mathbf{MBS}_{\mathbf{next}} \times \mathbf{PF}}{\mathbf{TDD}_{\mathbf{next}} \times \mathbf{SF}}$$

| | |
|---|---|
| **MACO** | Maximum Allowable Carryover: acceptable transferred amount from the previous product into your next material (mg) |
| **HBEL** | Health-Based Exposure Limit (mg/day) of the previous compound |
| **MBSnext** | Minimum batch size for the next material(s) (where MACO can end up) (mg) |
| **TDDnext** | Maximum Therapeutic Daily Dose for the next material (mg/day) |
| **PF** | Purging Factor reflects the ability of a process to reduce the level of the previous product in the downstream synthetic route of the next material (in case the next material is not yet the final API). The default value is "1" unless R&D can provide case-specific purging ability evidence (e.g. in case of control LOD limitation.) |
| **SF** | Safety factor reflects the effects from the interaction between previous product and next material. This factor should be applied in case of a risk for patient safety. Possible risk are for example contra-indications, possible allergens, risk for children, previous products that should not be taken daily, next material which is only applied once, but with daily controlled release of the active product, etc (case-by-case specific). Assessed by a toxicologist. In case of no effects from the interaction between previous product and next material can be found the default value is "1" |

If dose ranges are available, typically the maximum therapeutic daily dose is used for the next material (TDDnext) in order to calculate a safe MACO. Instead of calculating each potential product change situation, the worst case scenario can be chosen. Then a case with most active API (lowest ADE or PDE) is chosen to end up in the following API with the smallest ratio of batch size divided with TDD (MBS/TDD ratio).

Note: for therapeutic macromolecules and peptides the determination of HBEL using PDE limits of the active and intact product may not be required (conform EMA CHMP/ CVMP/ SWP/169430/2012). An alternative approach is suggested in section 4.2.3.

#### *4.2.1.1 HBEL (Binks et al. 2003, Lovsin Barle et al. 2016, EMA guideline)*

The HBEL should be calculated as an Acceptable Daily Exposure (ADE) or Permitted Daily Exposure (PDE). They are effectively comparable with each other and represents an estimate of a daily exposure that is unlikely to cause an adverse effect if an individual is exposed, by any route, at or below this dose every day for a lifetime. They are determined to protect patients and are calculated by following formulas in mg/day:

$$\textbf{ADE} = \frac{\textbf{POD} \times \textbf{BW}}{\textbf{UFc x MF x PK}}$$

$$\textbf{PDE} = \frac{\textbf{POD} \times \textbf{BW}}{\textbf{F1 x F2 x F3 x F4 x F5}}$$

| | |
|---|---|
| **ADE** | Acceptable Daily Exposure (mg/day) |
| **PDE** | Permitted Daily Exposure (mg/day) |
| **POD** | Point Of Departure |
| **BW** | Is the weight of an average adult (e.g. 50 kg cfr EMA guideline) |
| **UFc** | Composite Uncertainty Factor: combination of factors which reflects the inter-individual variability, interspecies differences, sub-chronic-to-chronic extrapolation, LOEL-to-NOEL extrapolation, database completeness.<br>**NOAEL** No Observed Adverse Effect Level (mg/kg/day)<br>**NOEL** No Observed Effect Level (mg/day) |
| **MF** | Modifying Factor: a factor to address uncertainties not covered by the other factors |
| **PK** | Pharmacokinetic Adjustments |
| **F1-F5** | Adjustment factors to account for uncertainties. Refer to EMA Guidance [2] for further explanation. |

#### *4.2.1.2 Point Of Departure (Nielsen et al. 2008; Lovsin Barle et al. 2016)*

The point of departure is the dose-level from which the HBEL is extrapolated. The point of departure can take many forms, it might originate from animal or human data and the dose-level can correspond to different effect-levels. It is also dependent on the phase of development of the drug product at the moment of assessment. In later phase of drug development more and more data become available and several POD's can be selected. In this case the most relevant or conservative HBEL should be used. The most appropriate POD however, should be carefully selected by expert judgement.

In order to calculate an HBEL, the NO(A)EL or LO(A)EL should be available as POD, however, this is not always the case, certainly not for drugs in development. If there is no NO(A)EL or LO(A)EL available, LD50 can be used as POD. However, in this case a

conservative approach is needed and therefore more uncertainty factors need to be applied. Other available data might also be used in order to define an HBEL, but this is based on expert judgement. If no data at all is available, the TTC principle according to Dolan et al. should be applied.

Drug products and APIs should have at least one or several NO(A)EL or LO(A)EL values available. Only very occasionally, for example in early drug development stages, no NO(A)EL or LO(A)EL might be available and LD50 values can be used, but only with very conservative uncertainty factors. It is however, strongly advised to restrict the use of LD50 as POD in this case as LD50 values are not reliable for predicting long-term effects.

For intermediates where limited data may be available, HBEL determination guidance will be given by the toxicologist.

For most solvents and detergents HBELs are already determined and available in public databases: ACGIH; OSHA; MAK; NIOSH, etc.

In general, the HBEL should be determined based on following hierarchy:

- HBEL available (mostly for solvents and reagents): use most stringent HBEL
- No HBEL available, but NO(A)EL or LO(A)EL available: calculate HBEL (as described) based on NO(A)EL/LO(A)EL as POD
- No HBEL available, no NO(A)EL or LO(A)EL available: use other available numerical data as POD to determine HBEL (LD50* values, BMD)
- No HBEL available, no other numerical toxicological data available: use other available data to determine HBEL (mutagenicity, carcinogenicity, CLP, etc), but this is based on expert judgement
- No data at all available: use default (based on QSAR) or TTC or additional testing

This hierarchy should strictly be applied in setting the HBEL: the most reliable source of data available at that moment of assessment should be used to determine the HBEL.

*In cases where no other data is available and only $LD_{50}$ data is available the HBEL can be based upon $LD_{50}$ data. Calculate NOEL according to the following equation and use the result for the establishment of HBEL

$$\textbf{NOEL} = \frac{\textbf{LD}_{50} \times \textbf{BW}}{\textbf{2000}}$$

**(**2000 is an empirical constant)

#### *4.2.1.3 Threshold of Toxicological Concern (TTC) (Dolan et al. 2005)*

The Threshold of Toxicological Concern (TTC) is a level of human intake or exposure that is considered to be of negligible risk, despite the absence of chemical-specific toxicity data. The TTC approach is a scientific rationale provided to estimate acceptable daily exposure values for compounds with limited or no toxicity information available. The approach was initially developed by the Food and Drug Administration (FDA) for packaging migrants, and used a single threshold value of 1.5 µg/day (called the threshold of regulation). However, a more specific TTC approach for pharmaceutical manufacturing operations was developed by Dolan et al.

According to the Dolan principle, there are three different categories of compounds on which the TTC principles can be applied in case limited or no toxicity data is available:

(1) Compounds that are likely to be carcinogenic (ADE/PDE: 1 µg/day)
(2) Compounds that are likely to be potent or highly toxic (ADE/PDE: 10 µg/day)
(3) Compounds that are not likely to be potent, highly toxic or carcinogenic. (ADE/PDE: 100 µg/day)

For the first category, carcinogenic potential is assessed based on in vitro mutagenicity data and/or structural alerts for genotoxic potential and confirmed by an appropriate in vivo test.

The second category contains compounds with limited data indicating they may produce pharmacologic or toxic effects at very low doses, compounds that show evidence of mutagenicity in vitro studies, but not confirmed in appropriate in vivo studies or compounds with a positive in vitro study in combination with a negative in vivo study.

The third class contains compounds with no a priori evidence of unusual toxicity or potency and which are not considered to be mutagenic (no structural alerts and negative in Ames test)

When the TTC approach is applied, it is important for both risk assessors and risk managers to keep in mind that it is a probability-based screening tool and may have additional uncertainty. The TTC principle is based on oral acceptable daily intake levels but can be expanded to parenteral routes (i.e. intravenous, subcutaneous, intramuscular).

Furthermore, the thresholds are based on chronic exposure, meaning that in case of an atypical event in cleaning validation an additional margin of safety is provided.

### 4.2.2 Acceptance criteria using a General Limit

Companies may choose to have a MACO upper limit as an internal policy, if MACO calculations result are less stringent, or toxicological data for intermediates are not known, the approach of a general limit may be suitable. The general limit is often set as an upper limit for the maximum concentration (MAXCONC) of a contaminating substance in a subsequent batch.

**Procedure**

Establish MACO, based on a general limit, using the following equations.

**MACO** = **MAXCONC** x **MBS**

| | |
|---|---|
| **MACO** | Maximum Allowable Carryover: acceptable transferred amount from the investigated product ("previous"). Calculated from general ppm limit. |
| **MAXCONC** | General limit for maximum allowed concentration (mg/kg or ppm) of "previous" substance in the next batch. |
| **MBS** | Minimum batch size for the next product(s) (where MACO can end up) |

E.g. for a general limit of 100 ppm: MACO = 0.01% of the minimum batch size (MBS), and for a general limit of 10 ppm: MACO = 0.001% of the minimum batch size (MBS).
A general upper limit for the maximum concentration of a contaminating substance in a subsequent batch (MAXCONC) is often set to 5-500 ppm (100 ppm in APIs is very frequent) of the previous product into the next product depending on the nature of products produced from the individual company (e.g. toxicity, pharmacological activity,…). The general limit should be supported by a scientific/documented rationale.

*Note - If you decide to employ the concept of levels of cleaning (ref. section 5), then different safety factors (ppm limits) may be used for different levels. Especially if the product cleaned out is within the same synthetic chain and covered by the specification of the API, much higher (qualified) levels are acceptable.*

### 4.2.3 Acceptance criteria for therapeutic macromolecules and peptides

Therapeutic macromolecules and peptides are known to degrade and denature when exposed to pH extremes and/or heat and may become pharmacologically inactive. The cleaning of biopharmaceutical manufacturing equipment is typically performed under conditions which expose equipment surfaces to pH extremes and/or heat, which would lead to the degradation and inactivation of protein-based products. In view of this, the determination of HBEL of the active and intact product may not be required' (reference EMA CHMP/ CVMP/ SWP/169430/2012).

Therefore, for therapeutic macromolecules and peptides the acceptance criteria can also be set based upon 1/1000$^{th}$ of the therapeutic dose (see calculation below), typically in combination with the application of a maximum general limit of 10 ppm (which is calculated conform the principles described in section 4.2.2).

In such case, both the limit based upon the 1/1000$^{th}$ of the therapeutic dose and the general limit of 10 ppm are calculated and the lowest value is being used.

1/1000$^{th}$ of therapeutic dose calculation

Establish the limit for Maximum Allowable Carryover (MACO) according to the following equation. If ranges are available, typically the minimum therapeutic daily dose is used for TDDprevious and the maximum therapeutic daily dose is used for the next product (TDDnext) in order to calculate a safe MACO. Based on the route of administration of the next product a more stringent Safety Factor may be used, *i.e.* in the case of an oral dosage type previous product, and a parenteral type next product.

$$\mathbf{MACO} = \frac{\mathbf{TDD_{previous}} \times \mathbf{MBS_{next}}}{\mathbf{SF} \times \mathbf{TDD_{netxt}}}$$

SF = 1000 → 1/1000th

**Microbiological acceptance criteria in biopharma API manufacturing**

As biopharmaceutical manufacturing typically includes aqueous steps and given the nature of some of the standard biomanufacturing process steps (e.g. fermentation), there is typically a microbiological risk involved that should be well controlled.
Therefore, for biopharmaceutical manufacturing it is expected to have microbial samples taken during the cleaning validation.

To determine the acceptance criteria for microbiological samples (bioburden and endotoxin), the following approaches may be used:
• Leverage of product / process limits at the different process stages
• Compendia (EP, JP, US, etc.) based acceptance criteria, in which case that the EMA 158/01 'Note for Guidance on Quality of Water for Pharmaceutical Use' could be used as a basis to set an appropriate limit.

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### 4.2.4 Swab Limits

If homogeneous distribution is assumed on all surfaces, a recommended value can be set for the content in a swab. The maximum allowable carry over from one batch to another can be established based on the above sections. If the total direct contact surface is known, the target value for contamination per square meter can be calculated according equation 4.2.5-I. This can be used as basic information for preparation of a method of analysis and detection limit.

$$\text{Equation 4.2.5-I } \textbf{Target value } [\mu g/dm^2] = \frac{\textbf{MACO } [\mu g]}{\textbf{Total surface } [dm^2]}$$

Also other methods with different swab limits for different surfaces in a piece of equipment and/or equipment train can be used. If the equipment can be divided in several parts, different swab limits may be taken for the different parts building up the equipment train. If the result of one part is exceeding the target value, the whole equipment train may still be within the MACO limit. The Carry Over (CO) is then calculated according equation 4.2.5-II (see below).

During equipment qualification and cleaning validation hard to clean parts can be determined. Rather than declaring the hard to clean part as the worst case swab limit for the whole equipment train, it could be separated and dealt with as mentioned above. It should be noted that different types of surfaces (e.g. stainless steel, glass lined, Teflon) may show different recoveries during swabbing. In those cases, it may be beneficial to divide the equipment train in several parts and combine the results in a table or matrix.
When splitting up the surface of a piece of equipment in several segments (areas) having different swab results or applying different swab results for different pieces of equipment that build up an equipment train, attention should be payed to careful multiplication of the areas with the applicable swab results and subsequent summarization.
The total calculated amount should be below the MACO, and the individual swab results should not exceed the maximum expected residues established during cleaning validation / equipment qualification. Recovery studies and method validation are necessary when applying swabbing as a method to determine residues.

**Equation 4.2.5-II**

$$\textbf{CO } [\mu g] = \Sigma \left( \textbf{A}_i \, [dm^2] \times \textbf{m}_i \, [\mu g/dm^2] \right)$$

| | |
|---|---|
| **CO** | Carry Over, true (measured) total quantity of substance (possible carry over) on the cleaned surface in contact with the product, calculated from results of swab tests. |
| $\mathbf{A}_i$ | Area for the tested piece of equipment # i. |
| $\mathbf{m}_i$ | Value in $\mu g/dm^2$, for each swab per area of swabbed surface (normally 1 $dm^2$) |

Note that this equation is applicable in the case of summarizing different swab results of pieces of equipment that build up an equipment train. In the case a piece of equipment is divided in several segments each having its own specific swab result, *e.g.* because of different types

surfaces in the specific equipment (*e.g.* stainless steel and Teflon), then Ai should be read as 'Area for the tested segment of the piece of equipment. The CO in such a specific case is for the single piece of equipment alone.

#### *4.2.4.1. Setting Acceptance Criteria for Swab Limits*

For each item tested, the following acceptance criteria (AC) apply.

AC1. The cleaning result of an individual part should not exceed the maximum expected residue.

AC2. For the total equipment train the MACO must not be exceeded.

In determining acceptance limits, all possible cases of following products in the relevant equipment shall be taken into account. It is proposed that a matrix be set up in which the limits for all cases are calculated. Either acceptance criteria for each product in the equipment can be prepared or the worst case of all product combinations may be selected.

#### *4.2.4.2. Evaluation of results*

When all surfaces have been sampled and the samples have been analyzed, the results are compared to the acceptance criteria. Companies may find it easier to evaluate against the MACO. However, it is advisable to have a policy for swab limit as well. Especially because analytical methods are validated within a certain range for swab results. Another reason is that some pieces could be very contaminated, and it is not good practice to clean certain pieces very thoroughly in order to let others be dirty. Thus, limits for MACO and swabs should be set.

### 4.2.5. Rinse Limit

The residue amount in equipment after cleaning can also be determined by taking rinse samples. During equipment qualification it should be established that all direct content parts of the equipment is wetted / reached by the rinsing solvent. After the last cleaning cycle (last rinse), the equipment should be assessed as 'clean'. In some cases, it may be advisable to dry the equipment in order to do a proper assessment. Thereafter, the rinse cycle can be executed, and a sample taken (sampling rinse). The procedure for the rinse cycle and sampling should be well established and described to assure repeatability and comparability (cycle times, temperatures, volumes, *etc*.). The choice of the rinse solvent should be established during cleaning validation, taking into account solubility of the contaminations, and reactivity of the rinse solvent towards the contaminants (saponification, hydrolyses, *etc*). Method validation is needed.

In a worst-case approach, the amount of the residue in the equipment can be assumed to be equal to the amount determined by analysis of the rinse sample. This can be supported by rinse studies that show a strong decay of a residue in a piece of equipment or recovery studies of the rinse cycle.

The MACO is usually calculated on each individual product change over scenario according to the procedures outlined above and individual acceptance criteria are established using the following equation:

Target value (mg/L) = MACO (mg) / Volume of rinse or boil (L)

For quantitation a solvent sample (*e.g.* 1 L) is taken, the residue in the sample is determined by a suitable analytical method and the residue in the whole equipment is calculated according to the following equation:

CO [mg] = V*(C-Cb)

CO Carry Over, true (measured) total quantity of substance (possible carry over) on the cleaned surface in contact with the product, calculated from results of rinse tests.
V Volume of the last rinse or wash solvent portion in L
C Concentration of impurities in the sample in mg/L
Cb Blank of the cleaning or rinsing solvent in mg/L. If several samples are taken during one run, one and the same blank can be used for all samples provided the same solvent lot was used for the whole run.

Requirement: CO < Target value.

The requirement is that CO < target value. If needed, the sample can be concentrated before analysis.

The choice for swab or rinse sampling usually depends on the type of equipment. Areas to be swabbed are determined during equipment and cleaning validation (‘hard to clean areas’), and are preferably readily accessible for operational reasons, *e.g.* near the manhole. If swabbing of the indicated area is not easy, rinse sampling is the alternative. The advantage is that the whole surface of the equipment is sampled for contamination, being provided that during equipment qualification, surface wetting testing was taken into account. Thus equipment used for milling, mixing, filters, etc. are usually swabbed, whilst reactor systems are usually sampled by rinsing.

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### 4.2.6 Rationale for the use of different limits in pharmaceutical and chemical production

Unlike in pharmaceutical production, where residues on the surface of equipment may be 100 % carried over to the next product, in API production the carry-over risk is much lower for technical and chemical manufacturing reasons. Thus, higher limits may be acceptable in chemical production compared to pharmaceutical production. For example, chemical processing steps often include dissolution, extraction and filtration steps that are likely to reduce significantly any residue left from previous production and cleaning operations. A factor of 5-10 could be applied to the MACO calculated using the Acceptable Daily Exposure Limit or the secondary criteria defined in the previous sections.

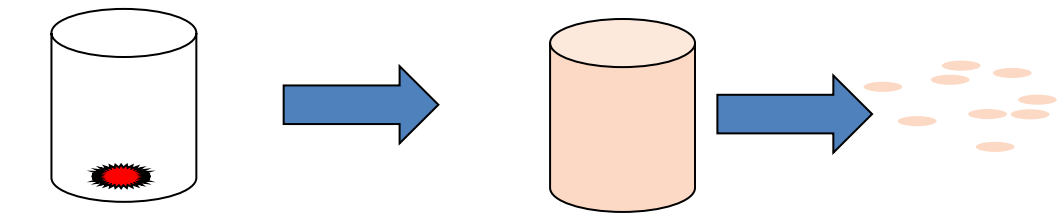
In all cases, the limits should be justified by a competent chemist with detailed knowledge about the equipment and the chemical processes, following Quality Risk Management Principles and the limits should be approved by Operations and Quality Assurance Managers.

The following description shows an example where the carry-over risk for a residue in chemical production equipment is much lower than in pharmaceutical production equipment.

Assuming that the common criteria (ADE, PDE, /ADI with SF 100-1000, 10 ppm, TTCs,…) represent the state of the art for pharmaceutical production and are considered sufficiently safe, then the calculation of limits in API manufacture must reflect the different processes in pharmaceutical production and in the chemical production of active pharmaceutical ingredients to allow comparable risk analyses to be undertaken.

**Pharmaceutical production, Chemical production physical process**

In pharmaceutical production a residue remaining on the surface of equipment after cleaning is, in the next production cycle, distributed in a mixture of active substance and excipients if it does not remain on the surface. In the worst case it will be 100 % transferred to the first batch of next product.



Residue on the surface of cleaned equipment

Contaminated mixture

Contaminated tablets

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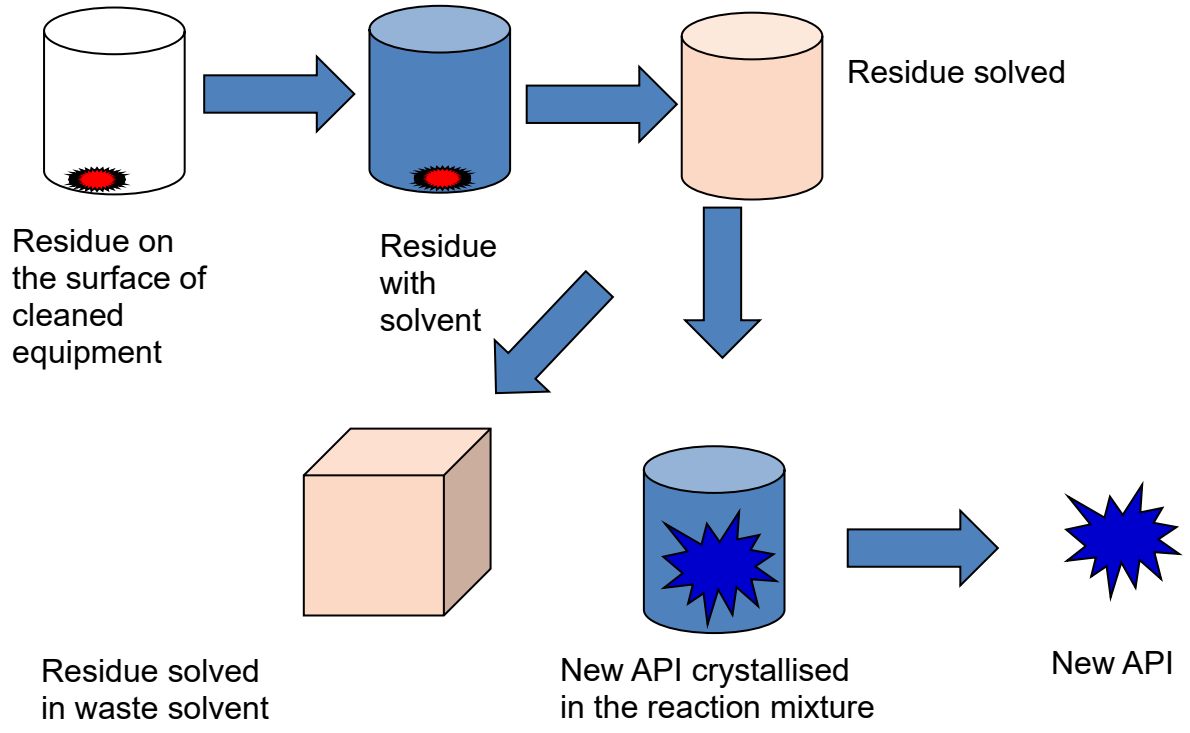
**Chemical production/processing**

In chemical production a 100 % carry-over of residue from the equipment surface to the next product to be manufactured is very unlikely based on the way the process is run and on technical considerations. The residue remaining on the equipment surface can, during the next production cycle, be carried over into the reaction mixture consisting of solvent and raw materials. In most cases, however, any residue in solution will be eliminated from the process together with the solvent, and insoluble residue by physical separation processes (e.g. filtration), so likely carry over into the end-product will be low.

The final step in a multi-step chemical synthesis is selective purification of the API (e.g. by crystallization), during which contaminants are removed from the process and/or insoluble residues are removed by physical separation). From the original reaction mixture of educt, agent and solvent there remains only a fraction of the original mass as API at the end of the chemical process.

It is also to be noted that, during subsequent pharmaceutical production, the API is further diluted through the excipients that are added.



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**Conclusion:**

Assuming that there is no intention to impose more stringent yardsticks during API production than in pharmaceutical production but that they should be approximately the same, the logical conclusion is that the limits in chemical production should be set higher than in pharmaceutical production. Based on this rationale, a factor of 5 - 10 compared to the established pharmaceutical production limits is both plausible and, in terms of pharmaceutical risk, acceptable.

**Chemical production "physical processes" (drying, mixing, filling, ...)**

Apparatus and equipment that is used for physical end-treatments such as drying, mixing or milling may either be operated together with the previous synthesis equipment or generally be used separately. During separate physical end-treatments of APIs, there is no decrease of contaminants compared to the aforementioned chemical process. Consequently, we recommend in this case that the calculation methods applied should be those normally used in pharmaceutical production, (ADE, PDE, TTC for APIs preceded by APIs, $LD_{50}$ with SF , 10 ppm,… for other changeovers of products). The Limits for carry over into the final API should be the same as those calculated in the previous sections.

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**ANNEX 1:** Examples of MACO calculations.

Example 1: ADE calculation

Product A has a $NOAEL_{50kg}$ of 100 mg/day human oral dose. Uncertainty factors applied to calculate the ADE are an $UF_S$ of 3 (extrapolation from an acute dose to sub chronic/chronic dosing) and $UF_H$ of 8.13 (the inter-individual variability based upon a PK (kinetic component) of 2.54 and PD of 3.2 (dynamic component)). The MF is 10 (extrapolation from a 'generally healthy' population to a more susceptible sick patient population). Product B is an oral product (PK = 1).

$$\textbf{ADE} = \frac{\textbf{100}\ (\text{mg/day})}{\textbf{3 x 8.13 x 10 x 1}} = \textbf{410}\ (\mu\text{g/day})$$

*Result:* **$ADE_{oral}$ is 410 µg/day**

If product B is a parenteral product and the PK is 62.5 (based upon an oral bio-availability study in human after parenteral).

$$\textbf{ADE} = \frac{\textbf{100}\ (\text{mg/day})}{\textbf{3 x 8.13 x 10 x 62.5}} = \textbf{6.6}\ (\mu\text{g/day})$$

*Result*: **$ADE_{parenteral}$ is 6.6 µg/day**

Example 2: ADE calculation

A teratogenic product A has a LOAEL of 1 mg/kg.day human oral dose (BW is 50 kg). Uncertainty factors applied to calculate the ADE are an $UF_L$ of 3 (extrapolation from LOAEL to NOAEL), an $UF_H$ of 10 (the inter-individual variability) and a MF of 10 (severity of effect: teratogenicity). Product B is an oral product (PK = 1).

$$\textbf{ADE} = \frac{\textbf{1}\ (\text{mg/kg.day}) \times 50\ \text{kg}}{\textbf{3 x 10 x 10 x 1}} = \textbf{167}\ (\mu\text{g/day})$$

*Result*: **$ADE_{oral}$ is 231 µg/day**

Example 3: Acceptance criteria based on Acceptable Daily Exposure

Product A will be cleaned out. The product has an ADE of 2 µg and the batch size is 200 kg. The next product B has a standard daily dose of 250 mg and the batch size is 50 kg. Calculate the MACO for A in B.

$$\textbf{MACO} = \frac{\textbf{0.002}\ (\text{mg}) \times \textbf{50 000 000}\ (\text{mg})}{\textbf{250}\ (\text{mg})} = \textbf{400}\ (\text{mg})$$

*Result*: **MACO is 0.4 g (400 mg)**

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# 5.0 LEVELS OF CLEANING

## 5.1 Introduction

The manufacturing process of an Active Pharmaceutical Ingredient (API) typically consists of various chemical reaction and purification steps followed by physical changes. In general, early steps undergo further processing and purification and so potential carryover of the previous product would be removed.

The level of cleaning required in order to ensure that the API is free from unacceptable levels of contamination by previous substances varies depending on the step being cleaned and the next substance being manufactured in the same piece of equipment (train).

API`s and related intermediates are often produced in multi-purpose equipment with frequent product changes which results in a high amount of cleaning. To minimize the cleaning effort the concept of using different levels of cleaning as a function of the level of risk related with the possible carryover may be applied without affecting the safety of the API.

## 5.2 Cleaning levels

It is recommended that at least three levels of cleaning in the production of a commercial product may be implemented. This approach is outlined in the table below, however it should be mentioned that additional levels might be necessary depending on the nature of the process and requirements of individual companies but should always be based on risk assessment where the characteristics of the previous and subsequent products such as solubility, recovery studies, nature of residues, process step, etc. should be considered.

| Level | Thoroughness of cleaning | Cleaning verification | | Cleaning Validation |
|---|---|---|---|---|
| | | Visual Inspection | Analytical verification | |
| 2 | Carryover of the previous product is critical. Cleaning required until predetermined stringent carry over limits are met. High risk | Yes | Yes | Mandatory |
| 1 | Carryover of the previous product is less critical. Cleaning should reduce the potential carry over to a less stringent limit as required for level 2. Medium risk | Yes | Yes | Recommended |
| 0 | Only gross cleaning if carryover of the previous product is not critical. Low risk | Yes | NO | NO |

A general approach how these levels could be established for typical product changeover situations in a multi-purpose API-plant is outlined in the figure below.

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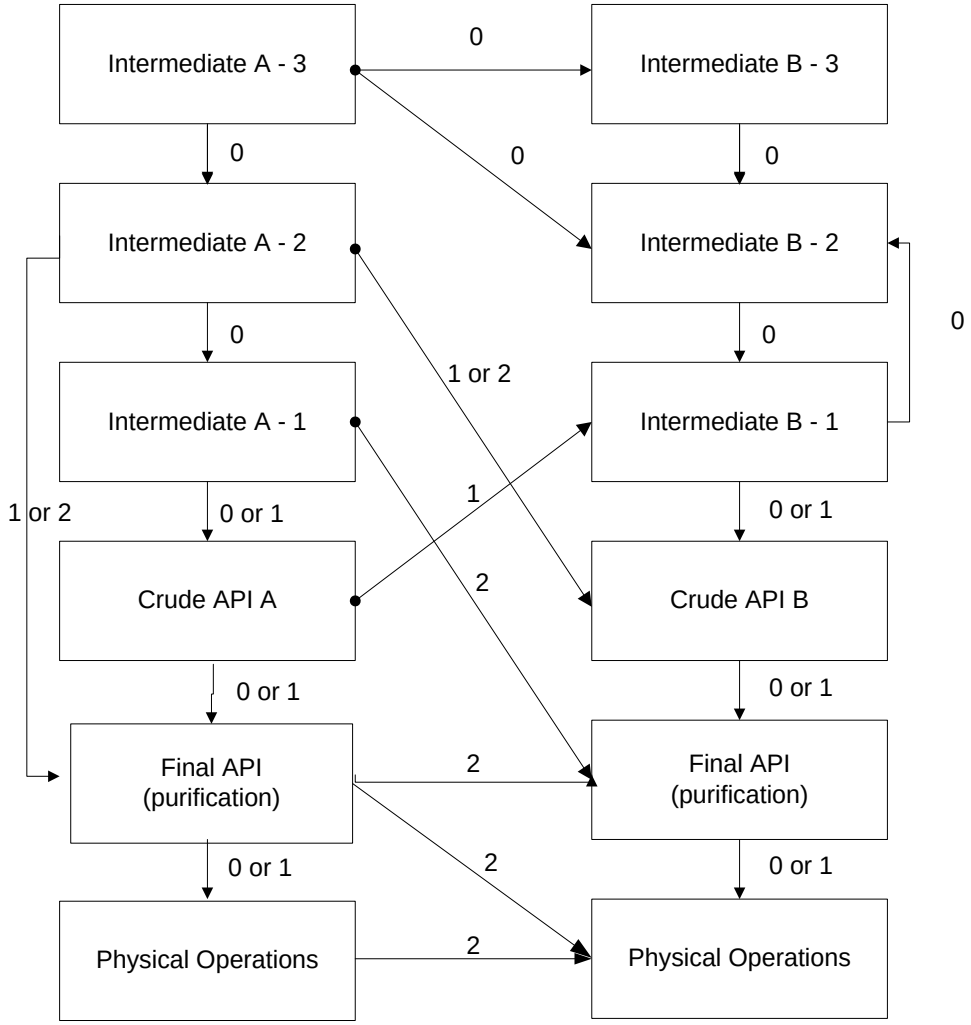
## Figure 1: Typical Product Changeover Scenarios




The levels established as shown in figure 1 are based on the approach that in general the thoroughness of cleaning will increase and the acceptable carryover of the previous product will decrease from early steps in the route of synthesis to the final API due to the fact that early steps undergo further processing and/or purification and so the potential carry over will be reduced by further processing. Physical operations, which mean e.g. powder handling such as drying, sieving or milling obviously do not reduce the potential carry over. During the risk assessment it should be taken in consideration that the residues may contribute to a degradation of the next product's quality or safety and ultimately have a detrimental effect on the final consumer.

Fig 1 shows examples of several possibilities of equipment usage patterns:

1) *The following product is the next step in the synthetic chain*
   A typical manufacturing process applied to production of Active Pharmaceutical Ingredients consists of various chemical reaction and purification steps followed by physical changes, as can be generally illustrated by the sequence of the production line of a product A or B. In this case level 0 may be applied because the previous

product is the starting material of the following manufacturing step and the analytical methods applied for the following product are usually suitable to detect the previous product which is covered and limited by the impurity profile.

2) *Between different steps of the same synthetic chain*
In general, there is a higher potential for contamination of the API if the following product in a sequence is close to the final API - step. So progression of levels from early steps to later steps in the synthetic chain is expected as outlined in figure 1. In the example of product changeover "A – 2" to "Final API A" level 2 may be chosen if "A – 2" is **not** specified in the specification of "API A" or "A – 2" is a toxic compound. If it is specified or is purged during the process or harmless, level 1 may be acceptable.

3) *Between batches of different product lines*
The level of cleaning required depends on the stage of manufacture. If the following product is an early stage in the API chain, in general lower levels are required than if it is an intermediate or final stage.
The progression of levels is outlined in figure 1, however an individual risk assessment for each potential product changeover scenario has to be performed to decide which level is applicable. This risk assessment should address the following topics:

- Easiness of cleaning
- Toxicological / pharmacological activity of the previous product, its side products or degradants
- Maximum daily dose of the following product
- Microbiological growth
- Batch size of the following product
- Solubility, experience, difficult to remove previous product
- Chemical interactions
- Campaign lengths should be evaluated and determined as part of the risk assessment.

Consideration should be given to any heels present and whether they need to be removed on a regular basis.

Instead of the investigation of each individual cleaning situation, similar situations could be grouped and classified using bracketing concepts (ref. section 7).

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## 5.3 Cleaning Verification/validation

The cleanliness status and validation of cleaning procedures is verified against pre-defined acceptance criteria.

### 5.3.1 Cleaning verification

The cleaning verification can be made by:

- visual inspection or
- visual inspection and analytical verification (e.g., swabbing and/or rinsing).

**Visual inspection:**

After cleaning procedures are performed, equipment should be dried to allow the visual inspection. No residue should then be visible. Visual inspection should be performed using the best known capabilities.
During visual inspection the following situations should be considered:

- Discoloured surfaces, worn or torn parts;
- Solid residues (for final product equipment used downstream of last filtration, the residues should be evaluated also by passing the final washing through a rough filter media (e.g. a lint-free cloth));

Visual inspection is usually applied in Level 0 where no cleaning validation is required.

**Analytical verification:**

Analytical verification should be performed with scientifically sound methods.

The analytical methods should be validated before use in cleaning validation (see 5.3.2), unless they are compendial methods (see chapter 8.2).

### 5.3.2 Cleaning validation

The cleaning validation involves a series of stages over the lifecycle of the product and cleaning process: cleaning process design, cleaning process qualification and continued cleaning process verification. Details on the work to be performed and acceptance criteria should be defined in a protocol. The cleaning procedure can be prepared per equipment or set of equipment and should include detail enough to reduce operator's variability (see chapter 7.3).

The strategy should be defined and taken in consideration in the validation activities.

The validation consists in successive applications of the cleaning procedure complying with the acceptance criteria defined, in a minimum of 3 successful applications. The success of the applications should be consecutive unless the cause of failure is clearly identified as not related to the process or procedure.

Depending on the individual product changeover situation it may take some time to finalize the cleaning validation with the third application (see chapter 8 bracketing and worst case rating). In these cases, cleaning verification using validated analytical methods has to be performed in the meantime.

At this stage analytical methods should be validated and suitable to quantify at the acceptance criterion level. The limit of detection must be lower than or equal to the acceptance criterion level. Blanks must be evaluated to ensure that there is no significant interference with the recovery of the analyte. In dedicated facilities, validation of cleaning procedures is not normally required but a risk assessment should be performed to make sure that there is no potential for degradation and or microbial contamination that may adversely impact the quality of the product.

For both dedicated and multi-product facilities, the frequency with which the cleaning procedure should be performed should be validated to assess risks related to potential degradation and microbiological contamination.

The validation of the Dirty Hold Time (DHT) should be an outcome of the cleaning validation. Whenever the DHT is exceeded, analytical verification should be performed and the extension of the DHT should be handled through change control procedure.

#### *5.3.2.1. Cleaning process design*

Cleaning process design intends to design, develop and understand the cleaning process residues and to establish the strategy for the cleaning process control.
The main activities in this stage are evaluation of the chemical and physical properties of the residue; determination of the most difficult to clean residue; evaluation of residue solubility and stability.

#### *5.3.2.2. Cleaning process qualification*

In this stage it should be demonstrated that the cleaning procedure works as expected. The following activities are included among others: qualification of specific equipment used in the cleaning such as Clean In Place (CIP) systems, cleaning operational parameters (e.g. temperature, flow rates, pressure, etc.); identification of the most difficult cleaning locations; training of operators.

#### *5.3.2.3 Continued cleaning process verification*

In this stage it should be demonstrated that the cleaning process remains in control throughout the product lifecycle.
The following should be considered in this stage: Post validation monitoring; Change control; Periodic management review.

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**Post validation monitoring**

After cleaning validation, the analytical verification may be omitted or replaced by simpler analytical methods (e.g. conductivity; pH; etc.) that have proven to be suitable for the intended use. However, visual inspection should be maintained in the dried equipment and no visible residues should be observed.

The confirmation of the validation status should be performed periodically according to the periodicity defined in the validation report.

**Change control**

Any change to the cleaning procedure, analytical methods, manufacturing process, equipment, etc. during the execution of the cleaning validation protocol or after the validation is concluded should be handling through the change control procedure in place in the organization. The impact on the cleaning validation process should be evaluated.

**Periodic management review**

Deviations, non-conformances, changes in the cleaning procedure and/or product manufacturing process, trends should be periodically reviewed with the aim to continuously improve the cleaning process, reduce variability and to assess the validation status of the procedure.

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## 6.0 CONTROL OF CLEANING PROCESS

In order to validate a cleaning process, the cleaning process needs to be repeatable and sufficiently robust for the to-be-cleaned load. It should be clear which steps are considered part of the production process/ unit operation and which are part of the cleaning process, for example if the pre-rinse or wash-out which may be routinely applied to bring the equipment in a good starting position is part of the overall cleaning process or not. Another example is the cleaning of chromatography columns, which are typically cleaned with buffers prior to the chromatography skid cleaning.
To assure repeatability and robustness of the cleaning, adequate cleaning instructions are required.
For manual cleaning, this is typically accomplished by sufficiently detailed cleaning instructions, including an unambiguous description of the attributes to be used and how to handle these, together with adequate training.

The detailed description should consider:

1. the system boundaries
2. cleaning agents/solvents to be used
3. volumes and or concentrations
4. reflux or rinse times, and temperatures
5. the sequence of cleaning steps or pre-defined repeats
6. in process analyses
7. description of pumps used (if needed)
8. sample instructions (if needed)

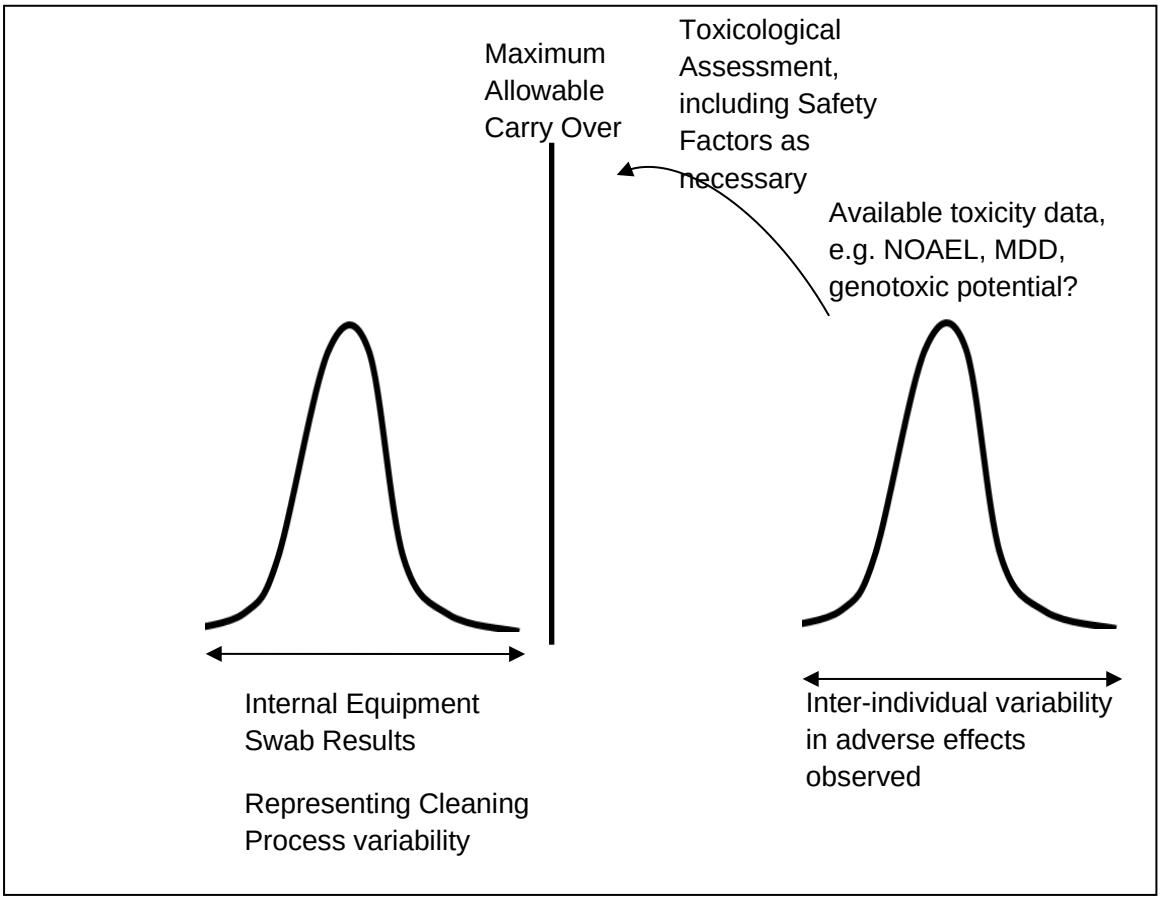
For automated cleanings, this should be ensured by the equipment design together with the cleaning software, cleaning recipe and built-in control mechanisms.

For automated systems, it is expected that a cleaning instruction covers:

1) The applied cleaning phases, for example once-through versus re-circulating versus soak versus reflux-mode rinse/wash phases
2) The sequences of the cleaning phases
3) Time of each of the cleaning phases
4) Action applied during the cleaning process. Note that the mechanical action/impact is often flow/pressure related (e.g. if spray balls are being used).
5) Used cleaning agents and/or cleaning solvents
6) The concentrations and/or quality of the used cleaning agents and/or cleaning solvents
7) Temperatures applied during the various cleaning phases

Because of the uncertainties on cleaning parameters, like a.o. flow, time, temperature, detergent concentration and starting conditions (inclusive Dirty Hold Time and soiling), and the geometric aspects of the cleaned system, the cleaning process is susceptible to variability/ spread. The mean effectiveness of the cleaning process together with its spread should be adequately removed from the edge of failure of the cleaning process, which can be established by performing the MACO calculations as discussed in the previous chapters. At minimum, the

level of cleaning should support a cleaning result (including the spread) below the obtained MACO level. Schematically, this can be depicted as:




The level of cleaning should be commensurate to the level of risk that the cleaning process poses in relation to the related production processes. Notice that the cleaning risk can be further reduced either by:

1) improving the cleaning cycle to improve cleaning effectiveness and shift the mean cleaning result further away from the MACO level, which typically requires cleaning development studies;
2) reducing process variability, which is typically established by increasing the level of control on the cleaning process parameters. An improved level of control on cleaning parameters such as flow, temperature and time, may not only result in more robust cleaning processes with smaller process variability, but may also create cleaning optimization opportunities (e.g. reduced chemical and water consumption).

For automated systems, the level of control can often be enhanced by applying in-line measurements together with enhanced controlling capabilities. Improved monitoring capabilities often results into enhanced cleaning process knowledge and may be used in a Process Analytical Technology (PAT) framework.

Where control measures cannot adequately assure that the potential contamination is consistently controlled to a level below that of the HBEL then the products concerned should be manufactured in dedicated facilities.

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# 7.0 BRACKETING AND WORST CASE RATING

## 7.1 Introduction

The cleaning processes of multiple product use equipment in API facilities are subject to requirements for cleaning validation. The validation effort could be huge. In order to minimize the amount of validation required, a worst case approach for the validation can be used.

- By means of a bracketing procedure the substances are grouped.
- A worst case rating procedure is used to select the worst case in each group.

Validation of the worst case situation takes place. However, it is of utmost importance that a documented scientific rational for the chosen worst cases exists.

This chapter gives an overview of the suggested work to be carried out, the acceptance criteria and the methodology for evaluation of the data. It should be emphasized that this is only an example to give guidance. The equipment, the substances produced and the procedures in place may vary; and this results in other solutions than those given in this example.
The worst case rating priority will then support a conclusion that the cleaning procedures are effective for all drug substances and other chemicals within the bracket, including those not individually tested.

## 7.2 Bracketing Procedure

The objective of a bracketing project is for the company to demonstrate that it has a scientific rationale for its worst case rating of the substances in the cleaning validation program. The first thing to do is to make groups and sub groups - which we will term “bracketing”, from which worst cases will later be selected based on the results from the rating. The bracketing procedure should be included in a company policy, or an SOP or an equivalent document on cleaning validation. A multipurpose facility, Clean Company, is presented as an example we will follow.

### a) Equipment Train

The Clean Company is a multipurpose site for synthesis and isolation of organic substances *(see figure 1)*. It is divided into six equipment trains separated from each other and intended for different use (earlier API steps, final API purification, drying etc.). In TrainA 9 substances can be produced, in TrainB 9 substances can be produced, in TrainC 8 substances can be produced, in TrainD 8 substances can be produced, in TrainE 10 substances can be produced, and in TrainF 11 substances can be produced. With no bracketing and worst case rating, cleaning validation studies would be required for each of the 55 substances.

The first grouping criteria is that the substances in a group are produced in identical equipment trains and cleaned out following the same cleaning procedure/SOP. The ideal with regard to cleaning validation (as will be discussed in 7.3) each train could be considered as a group. Then 6 worst cases would ideally be identified. In reality, the number of worst cases identified will often be something between these two extremes (more than 6, but less than 55).

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CleanCompany

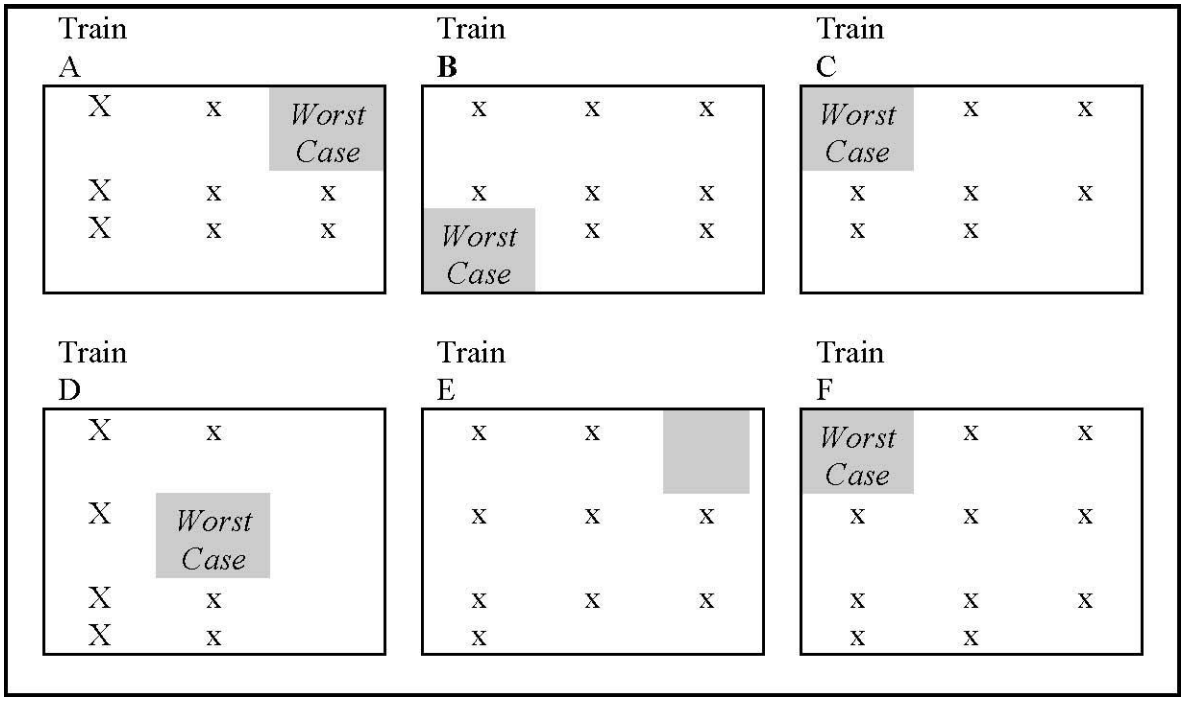


*Figure 1 CleanCompany's ideal example (1 train considered as 1 group) gives 6 worst cases.*

In this example the main classes in this bracketing are based on the different Trains. The following equipment classes are maintained:

- TrainA
- TrainB
- TrainC
- TrainD
- TrainE
- TrainF

**b) Substances**

If the company has two or more trains used for the same purpose (such as earlier API steps, final API purification, drying etc.) a choice of which products to be produced in each of the trains used for the same purpose is done. The combination of substances (starting materials, intermediates or APIs) in a train can be chosen based on one or more of the following strategies, or combinations of them:

- Produce in the same train substances with the same cleaning procedure;
- Produce in the same train substances with very low therapeutic doses and/or low batch sizes (and the opposite);
- Produce in the same train substances with very low ADE values (and the opposite).

Also, a choice of maximum flexibility can be used, but this could result in low limits for residues (for example if the substance to be cleaned out has a very low ADE/PDE, and the following substance has a small batch size and/or a very high daily dose) and thus longer cleaning times. Advantages and disadvantages with several cleaning procedures, compared to one cleaning procedure, will be discussed in section 7.3. More explanations on effects of different strategies will be evident from section 7.4.

### 7.3 Cleaning Procedures

For one train, in which several substances are being produced, several cleaning procedures often exist. In order to be able to defend the bracketing into groups, the second criterion is that the same cleaning procedure (method) shall be used for the substances within a group.
Cleaning procedures (before change of products) can for example be considered to be the same if:

1. Same or equivalent issued cleaning batch records/cleaning SOPs;

2. Same solvent, solubility or similar properties.

Advantages and disadvantages with several cleaning procedures, compared to one cleaning procedure, are presented in the following table.

**The same cleaning procedure for all substances (chosen to clean out the most difficult substance)**

| | | | |
|---|---|---|---|
| + | Minimum number of cleaning validation studies (perhaps only one) | - | Not optimal cleaning procedures for each substance → longer clean out times on average as well as higher consumption of solvents. |
| | | - | Normally a low limit for residues valid for all substances |

**Optimised cleaning procedures for each substance**

| | | | |
|---|---|---|---|
| + | Minimum clean out time on average | - | Maximum number of cleaning validation studies (as many as there are cleaning procedures) |

In the example the Clean Company has evaluated the cleaning procedures. The cleaning procedures have been examined and categorised into different classes. Substances in the same class are cleaned in the same way, using the same solvents and usually exhibit some chemical similarity with each other (*e. g.* salts, chemical structure etc.). In this example, totally, four cleaning procedure classes are included:

- Class I water soluble substances.
- Class II methanol soluble substances.
- Class III acetone soluble substances.
- Class IV separate class for special substances with defined solubility

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## 7.4 Investigations and Worst Case Rating (WCR)/Risk assessment

A worst-case rating study/Risk assessment will prioritise existing drug substances, in a cleaning validation program, based on information on applicable criteria chosen by the company. Clean company chose the following criteria which are relevant to the molecule preparation in their facility (companies should evaluate individual situations):

a) Hardest to clean: experience from production;
b) Solubility in used solvent;
c) Lowest Acceptable Daily Exposure or Permitted Daily Exposure ( If ADE / PDE data are not available, other data may be used (see chapter 4))

In order to present documented evidence supporting the scientific rating for each criterion, investigations (a formalized Risk assessment) should be carried out and formal reports should be written. For each criterion groups of rating with corresponding descriptive terms should be presented. When available, the descriptive terms can be chosen from the scientific literature on the subject (i.e. for solubility and toxicity). For other cases the rating is based on scientific investigations carried out by the company and collecting experience regarding details on the cleaning processes (i.e. "experience from production").

Clean Company chose to execute the WCR according to a formal protocol, in which the rating system was identified and the rating documented. In a Risk assessment report the results including the WCR were summarised, as well as conclusions.

### a) Hardest to Clean out - Experience from Production

One criterion which can be used is, experience from production with regard to how difficult a substance is to clean out. The study is recommended to be in the form of interviews with operators and supervisors. A standardised sheet with questions could be used in which the answers are noted. Hard-to-clean substances are identified and the difficulty of cleaning could be rated according to the three categories suggested below. The opinions of the personnel are subjective, and therefore should be supported by a scientific rationale.

**Category:** 1 = Easy
2 = Medium
3 = Difficult

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**b) Solubility**

A solubility-rating should be carried out based on the solubilities of the substances in the solvents used for cleaning. Suggested rating numbers, with explanations, are presented in the table below. The descriptive terms are given in [1] - page 53 - USP 24 under —Reference Tables (Description and Solubility, 2254).

| ***Group*** | ***Included descriptive terms*** | ***Approximate quantities of solvent by volume for 1 part of solute by weight*** |
|---|---|---|
| 1 | Very soluble<br>Freely soluble | less than 1 part<br>from 1 to 10 parts |
| 2 | Soluble<br>Sparingly soluble | from 10 to 30 parts<br>from 30 to 100 parts |
| 3 | Slightly soluble<br>Very slightly soluble<br>Practically insoluble<br>Insoluble | from 100 to 1 000 parts<br>from 1 000 to 10 000 parts<br>more than 10 000 parts - |

**c) ADE or PDE concept**

The Acceptable Daily Exposure or Permitted Daily Exposure define limits at which a patient may be exposed every day for a lifetime with acceptable risks related to adverse health effects (see chapter 4).

An example of rating numbers, with explanations, is presented in the table below.

| ***Group*** | ***ADE / PDE*** |
|---|---|
| 1 | >500 µg |
| 2 | 100 - 500 µg |
| 3 | 10 – 99 µg |
| 4 | 1 – 9 µg |
| 5 | <1 µg |

If ADE / PDE data are not available, other data may be used (see chapter 4).

### d) Therapeutic Doses

An investigation of therapeutic doses is typically based on oral and/or parenteral data. In the cases where the therapeutic doses are not available, corresponding values based on the toxicity could be used (recalculated according to company procedure). An example of rating numbers, with explanations, are presented in the table below.

| ***Group*** | ***Include dose intervals (smallest therapeutic dose)*** |
|---|---|
| 1 | >1 000 mg |
| 2 | 100 - 1 000 mg |
| 3 | 10 – 99 mg |
| 4 | 1 – 9 mg |
| 5 | <1 mg |

## 7.5. Worst Case Rating

The substances are scientifically matrixed by equipment class (train/equipment) and cleaning class (procedure). Each existing combination of the classes is considered as a group. When this bracketing has been carried out, the - "Worst Case Rating (WCR)"- can start. For at least one worst case in each group, cleaning validation studies shall be carried out. The rating procedure for CleanCompany presented as an example could be used.

### a) Rating Procedure

During a worst-case rating, the results of the investigations are summarised for each substance in each equipment class. If the evaluation of the cleaning procedures indicates that some of the substances have unique cleaning procedures, then each of those substances will be considered as a group (with one group member which is the worst case).

If all the substances in a cleaning class (train/equipment) will be tested, then individual limits may be used for each substance. In case of groups, where only some "worst cases" are tested, the strategy described below shall be followed. The following methodology shall normally be applied when a priority based on a worst case shall be used.

<u>Choice of common, general residual limit</u>

Evaluate if the lowest calculated limit is reasonable to apply on all substances. If that is the case, this limit shall be valid as a common general limit for the specific equipment. If the lowest limit is found to be too low as common limit for all substances, then the second lowest limit is evaluated and so on.

<u>Criteria for the validation of the cleaning processes:</u>

1. For the substances with common, general limit, it is required that the substance with the lowest solubility (in the cleaning solvent/solution) shall be tested for each

cleaning method. If more than one substance fulfils this criterion, then the substance shall be chosen which, based on experience is most difficult to clean.

2. Any substance which does not fall within this 'bracket' must be validated individually.

**b) Evaluation of Rating**

The worst case rating can be executed according to an issued protocol in which the methods and procedures for the rating will be identified. The applicable investigations presented in section 7.4 a-d would then be used (and could be enclosed to the protocol or a report, to support the rationales for the rating). A matrix system, for each equipment class (such as a dryer), can be set up as evident from the following table where TrainA of CleanCompany has been chosen. In this case a formal rating matrix has been filled in for TrainA. Altogether two cleaning classes were identified for the substances produced in TrainA. All the categories are introduced as columns in a matrix.

| Substance | Cleaning Method Class | a): Hardest to clean[(1)] | b): Solubility | c): ADE / PDE [(2)] | d): Alternative toxicity data |
|---|---|---|---|---|---|
| Esubstance | III | 2.3 | 1 | 4 | 3 |
| Fsubstance | III | 2.2 | 1 | 2 | 4 |
| Csubstance | III | 2.1 | 1 | 3 | 2 |
| Lsubstance | III | 1.9 | 1 | 3 | 3 |
| **Osubstance** | III | **2.8** | **2** | 2 | 3 |
| Msubstance | III | 2.5 | 2 | 2 | 3 |
| Psubstance | I | 2.2 | 1 | 2 | 3 |
| **Rsubstance** | I | **2.6** | **2** | 3 | 3 |
| Tsubstance | I | 1.8 | 1 | 2 | 3 |

(1) Each figure is the mean value for different questions answered by operators and supervisors.

(2) For APIs.

For the products in this train two cleaning methods (Class I and III) are used.
Therefore, two groups have to be validated.
The worst-case product (for the validation study) for class III is Osubstance (Solubility 2 and Hardest to clean* 2.8).

The worst case product (for the validation study) for class I is Rsubstance (Solubility 2 and Hardest to clean* 2.6).

In both cases the limit should be calculated with the most toxic substance (ADE/PDE 4).
If ADE / PDE data are not available, the limit should be calculated with the most toxic substance determined by alternative methods, according section 4 (Alternative toxicity 4).

If the limit calculated with ADE / PDE 4 or Alternative toxicity 4 is achievable for all products, this limit can be chosen for both groups.
If the limit calculated with ADE 4 or Alternative toxicity 4 is too low and not achievable for

all products, Esubstance and Fsubstance should be considered as separate groups or produced in dedicated equipment.
The limit for the remaining group should be calculated with the next most toxic substance (ADE / PDE 3 or Alternative toxicity 3).
In case a substance of top priority is not produced regularly, the substance with the second highest priority will be tested in order to show that the cleaning procedure is sufficient for all the other substances in that class. The substance of top priority will then be tested at the first possible occasion.
The WCR/Risk assessment could typically result in a report including a priority, based on the rating, for the substances in the cleaning validation program. It is recommended that the applicable background investigations shall be completed, approved and enclosed to the cleaning protocol or the report.

**c) Re-rating**

Change control should be applied to the WCR. If the conditions for the rating are changed, then a re-rating procedure should be carried out. The following listing gives examples where a formal re-rating procedure may be required:

- Changed cleaning method
- Changed process
- Changed / additional new product
- Changed / new equipment

After re-rating, it is recommended to issue an official controlled document including a worst case listing or table, with the same type of result presented for the involved substances/ equipment/methods, as for the original rating.

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# 8.0 DETERMINATION OF THE AMOUNT OF RESIDUE

## 8.1 Introduction

This section provides a practical guidance for the determination of the amount of residue in cleaned equipment based on the requirements from regulatory authorities[5] and current guidelines on analytical validation.[6] Specific requirements for the validation of analytical and sampling methods for cleaning validation purposes are provided in this section, in addition to examples of sampling methods and the appropriate use of analytical methods.
The carryover acceptance limit (Mper or Permitted Carry Over) is a calculated figure that represents the specification limit for the equipment cleanliness (see Section 4.0, Acceptance Limits), however, the determination of the actual amount of residue (M or Carry Over) remaining in the equipment following cleaning must be achieved using appropriate methods *i.e.* for both the sampling method and the quantitation of the contaminant in the sample.
Since the decision on the acceptable cleanliness of the equipment bears a potential risk to product quality, the method(s) used for the determination of M must be validated[1] and the specificity, sensitivity and recovery of the method(s) should be determined as a minimum.

## 8.2 Validation Requirements

### 8.2.1 General

The requirements for analytical method validation are defined in *ICH Q2(R1), Validation of Analytical Procedures: Text and Methodology, November 2005*. There are four types of analytical methods with principally different validation requirements; these are identification tests, tests for impurities (both quantitative and limit tests) and assay tests. The validation requirements for each method type are shown **Table 1**.

The list should be considered typical for the aforementioned analytical procedures; however, exceptions should be dealt with on a case-by-case basis. It should be noted that robustness is not listed in the table and should be considered at an appropriate stage in the development of the analytical procedure.

In practice, it is usually possible to design the experimental work such that the appropriate validation characteristics can be considered simultaneously to provide a sound, overall knowledge of the capabilities of the analytical procedure, for instance; specificity, linearity, range, accuracy and precision.

The validation of an analytical method should occur in compliance with pre-established acceptance criteria that should be documented in a written general policy or Validation Plan. However, there should be one validation report per validated method that summarises the specific results.

[5] FDA Guide to Inspections Validation of Cleaning Processes, http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074922.htm
[6] ICH Q2 (R1), Validation of Analytical Procedures: Text and Methodology, November 2005

| Characteristic | Type of Analytical Procedure | | | |
|---|---|---|---|---|
| | Identification | Testing for Impurities | | Assay |
| | | Quantitative | Limit | |
| Accuracy | – | + | – | + |
| Precision | | | | |
| Repeatability | | + | – | + |
| Intermediate Precision | – | +[1] | – | +[1] |
| Specificity[2] | + | + | + | + |
| Detection Limit | – | –[3] | + | – |
| Quantitation Limit | – | + | – | – |
| Linearity | – | + | – | + |
| Range | – | + | – | + |
| Key | – Signifies that this characteristic is not normally evaluated.<br>+ Signifies that this characteristic is normally evaluated.<br>1 In cases where reproducibility has been performed, intermediate precision is not needed.<br>2 Lack of specificity of one analytical procedure could be compensated by other supporting analytical procedure(s).<br>3 May be needed in some cases. | | | |

**TABLE 1** Requirement List for Analytical Validation

The requirements for 'Testing for Impurities' are typically employed for the validation of analytical methods specific to cleaning validation.

The requirements for 'Quantitative Testing for Impurities' can apply, for example, in cases where a method should be suitable for several possible acceptance limits and therefore quantitation of the residue over a certain range may be necessary *e.g.* the measured amount of residue M must be compared with acceptance limits between 5 and 750 g/equipment. This is possible when the method will be used for several changeovers.

The requirements for 'Limit Testing for Impurities' can apply, for example, in cases where the method should be suitable for one specific acceptance limit *e.g.* the measured M must be compared with Mper ≤ 105 g/equipment.

### 8.2.2 Analytical Method Validation for Cleaning Validation

In the following sections, aspects of analytical method validation specific to cleaning validation are emphasised. For further details refer to ICH Q2 (R1).

Specificity is a basic requirement for all analytical methods (see **Table 1**), however, in the case of cleaning validation it may occur, that not all potential impurities are clearly specified. It is important to note that in such a situation a **specific method may not always detect all impurities**. Studies should be performed to characterise the unknown impurities, develop and validate suitable analytical methods. However, this can be an unacceptably time consuming task. In this case a method that detects **all** potential impurities together can be suitable, even when it is not specific for each of the impurities. For example, in a situation where **only non-volatile** impurities occur, a dry residue determination method that is specific for the sum of non-volatile impurities could be used, provided that the validation requirements according to **Table 1** are satisfied. In order to consider the equipment acceptable for use it must be assumed

that the dry residue consists of the worst case impurity (most toxic, most active *etc*.). In some cases a combination of several methods can achieve the necessary specificity.

After the completion of a cleaning validation study an unspecific method (*e.g*. dry residue) may be used for the routine verification of equipment cleaned by the validated cleaning procedure provided that it is shown that the unspecific method is suitable for the intended purpose. If possible, the sensitivity of impurity detection for cleaning validation should be determined for both the sampling and analytical methods together (see **Section 7.2.4**).

### 8.2.3 Detection and Quantification Limits

Measured values below limit of quantification (LOQ) should be reported as the LOQ value (worst case approach). For example, if the LOQ is 10 mg/l, the measured blank is 7 mg/l and the measured residue amount is 3 mg/l, the reported value for the sample should be equal to the LOQ *i.e.* 10 mg/l.

Usually it can be assumed that, for quantitative impurity determination, the LOQ should approximately be 0.5 of the specification *i.e.* for cleaning validation 0.5 of the acceptance limit or lower. LOQ should never be higher than the acceptance limit. In the following sections three methods of LOQ/LOD determination are outlined:

• **Based on Visual Evaluation**

Visual evaluation may be used for non-instrumental methods but may also be used with instrumental methods. Frequently this approach is used for TLC.

• **Based on Signal-to-Noise Approach**

This approach can only be applied to analytical procedures which exhibit baseline noise (*e.g.* GC, HPLC). A signal-to-noise ratio (S/N) between 3 or 2:1 is generally considered acceptable for estimating the detection limit (LOD) and a typical ratio for acceptable quantitation limit is 10:1 (LOQ). The value for S/N can be calculated according to **Equation 1** and **Figure 1**:

**Equation 1:** $$\frac{(2 \times H)}{h_n}$$

where: **H** is the height of the peak from the mean baseline.

$h_n$ is the maximum deviation of the baseline within the range of 5 to 20 fold width of peak at half height.

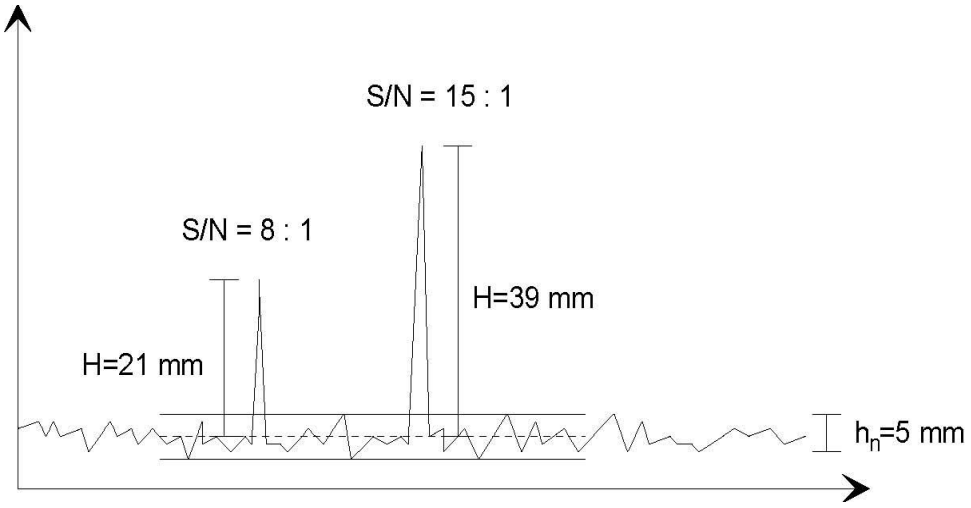


**FIGURE 1** Detection Limit Base on Signal to Noise Approach

• **Based on the Standard Deviation of the Response and the Slope**

The detection limit may be expressed by Equation 2 and the quantitation limit by Equation 3.

**Equation 2:** $$\mathbf{LOD} = \frac{\mathbf{3.3 \times \sigma}}{\mathbf{S}}$$

**Equation 3:** $$\mathbf{LOQ} = \frac{\mathbf{10 \times \sigma}}{\mathbf{S}}$$

### 8.2.4 Determination of Recovery

If possible, the recovery of impurity detection for cleaning validation should be determined for the sampling and analytical methods together at least for recovery and sensitivity (Limit of Quantitation - LOQ, or Limit of Detection - LOD). This can be achieved, for example, by spiking a surface equivalent to the equipment surface (*e.g.* material, polish grade) with different known amounts of the impurity. The impurity can then be recovered and analysed using the same sampling and analytical methods that will be used for the cleaning validation study. The overall results from this procedure are then compared to criteria for detection or quantitation limits as defined in ICH Q2 (R1). Validation of the limits may be achieved by the analysis of samples known to be near at the limits.

The measured results are then compared to the actual amount applied to the surface. The recovery is typically determined during the accuracy determination and should be reported as a percentage of the known applied amount of the impurity.

As an example, quantitative impurity determination recoveries of ≥ 90 % are usually regarded acceptable. For cleaning validation, recoveries of ≥ 90 % do not need to be taken into account for the calculation of the true value for M. Recoveries of < 90 % must be included in the calculation for M (see **Equation 4**) and recoveries of < 50 % should be omitted.

**Equation 4:** $$\mathbf{M} = \frac{\mathbf{M_{res}}}{\mathbf{R}}$$

Where: M: True value for the amount of residue remaining in the equipment after cleaning;
$M_{res}$: The measured amount of residue, the measured Carry Over (sampling and then analytical measurement);
R Recovery in % divided by 100 (*e.g.* for 75%, 75/100 = 0.75).

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### 8.2.5 Validation Requirements for Quantitative Testing of Impurities

The requirements for the validation of quantitative testing of impurities according to ICH Q2 (R1) are shown in **Table 2**, including proposed acceptance criteria (as an example only). Alternative acceptance criteria may be established based on sound scientific rationale.

It is important to note, that the summarised requirements should be used for the validation of quantitative testing for impurities during cleaning validation studies. Validation of quantitative testing for impurities is usually applied when the analytical method will be used for several specifications of the residue amount in the equipment.

The lowest foreseen acceptance limit is referred to as $M_{perMin}$ (or Minimal permitted Carry Over) and the highest limit as $M_{perMax}$ (Maximal permitted Carry Over) in **Table 2**. For only one specific acceptance limit normally limit testing for impurities and the corresponding validation of the analytical method is sufficient. If the validation of quantitative testing for impurities will be used for one specific acceptance limit, then $M_{perMin} = M_{perMax} = M_{per}$.

For the experimental work described in **Table 2**, the samples can be spiked with appropriate levels of the impurities (when standards are available) or compared with another well-characterised procedure (when standards are not available) to obtain the true value of the analyte concentration.

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| Experiments | Possible Acceptance Criteria |
|---|---|
| ***Accuracy:*** | |
| Perform a minimum of 9 determinations over a minimum of 3 concentration levels covering the specific range (*e.g.* 3 concentrations/3 replicates each of the total analytical procedure). Determine analyte with respect to the total amount of residue in the sample (*e.g.* weight/weight). Report: | |
| □ Accuracy as percent recovery or | 90.00 – 110.00 % |
| □ Difference between the mean and the accepted true value. | ≤ 10.00 % (P = 95 %) |
| □ Confidence intervals. | |
| ***Precision:*** | |
| Investigate using homogenous, authentic samples or (if not possible) artificially prepared samples. Perform a minimum of 9 determinations covering the specified range for the procedure (*e.g.* 3 concentrations/3 replicates each) or a minimum of 6 determinations at 100 % of the test concentration. | |
| ***Repeatability (intra-assay precision):*** | |
| Establish precision under the same operating conditions over a short interval of time. Report: | |
| □ Standard deviation (interdependent with $S_{rel}$) | see $S_{rel}$ |
| □ Overall relative standard deviation over the whole range of the method | ≤ 10.00 % |
| □ Relative standard deviation within one concentration level | ≤ 20.00 % |
| □ Confidence interval | |
| ***Intermediate Precision (may include robustness, ruggedness):*** | |
| Establish precision on different days, for different analysts, on different equipment and after variation of method parameters (= robustness, e.g. stability of solutions, variations of pH, of mobile phase composition, of flow rate, of temperature, of columns etc.). It is not necessary to study these effects individually. Experimental design (matrix) may be applied. **Report:** | |
| □ Standard deviation (interdependent with relative standard deviation) | see $S_{rel}$ |
| □ Relative standard deviation | 3 × $S_{rel}$ from repeatability or 10 % whichever is greater |
| □ Confidence interval | |
| ***Specificity:*** | |
| Demonstrate the discrimination of the analyte in the presence of the other impurities: | |
| □ Test samples containing the analyte and other impurities. Obtain positive and correct results for the analyte. | Specify acceptable deviation |
| □ Test samples without the analyte. | Negative results |
| □ For chromatographic procedures use representative chromatograms to document specificity. Label individual components appropriately. | Specify acceptable resolution of peaks |

**TABLE 2** Validation Requirements

| Experiments | Possible Acceptance Criteria |
|---|---|
| ***Linearity:*** | |
| Measure a minimum of 5 concentrations across the range of the procedure (dilute standard stock solution or prepare synthetic mixtures). Plot the signals as function of concentration. Evaluate the plot: | |
| □ Visually | Linear |
| □ Statistically (*e.g.* regression line by the method of least squares) | |
| correlation coefficient | ≥ 0.99000 |
| y-intercept | Confidence band (P = 95 %) contains 0 |
| slope of the regression line | |
| residual sum of squares | |
| ***Range:*** | |
| Confirm that the analytical procedure provides an acceptable degree of linearity, accuracy and precision within or at the extremes of the specified range. Minimum specified ranges: | |
| □ From the reporting level to 120 % of $M_{perMax}$. The reporting level for cleaning validation reasonably will be the LOQ. However, the reporting level must be below $M_{perMin}$ and should be below or at 80% of $M_{perMin}$. | From LOQ or 80 % of $M_{perMin}$ to 120 % of $M_{perMax}$ |

## 8.3 Sampling Methods

In order to demonstrate that the plant equipment is verified clean and meets the pre-defined acceptance criteria, sampling and analysis should be carried out using the methods described in the following sections. Justification should be provided for the selection of the appropriate verification technique on a case by case basis. A combination of the two methods is generally the most desirable. For all methods the sampling points should be fixed in a manner such that the true contamination of the equipment will be reflected.

### 8.3.1 Swab sampling (Direct Surface Sampling)

Swab sampling of the direct surface is designed to test small sections of the equipment surface for the presence of residues. Samples should be taken from all main equipment items and since swab sampling does not cover the entire equipment surface area, justification should be provided for the choice of the area for swabbing.

Typically, a small area of the cleaned equipment is swabbed with a material according to a pre-defined method *i.e.* swab material, solvent and technique. The swab sample can then be extracted and examined using a suitable analytical method.
The quantified residue obtained from the sample is then extrapolated to the whole equipment (see **Equation 6**).

It is important:

- That the validation of the swab sampling is performed on the same surface (material, polish grade, **area in dm$^2$**) and with the same materials as the routine sampling of the equipment.
- That the choice of swabbing material considers extractable materials that could interfere with the expected residue.
- To ensure that the sampling points represent the true worst case areas of the equipment. Also, an approach dividing a piece of equipment in several segments having their own specific recovery rate may be chosen.

The disadvantage of this sampling method for often complex API equipment is that difficult to reach areas (*e.g.* sealings, condensers, transfer pipework) may not be accessible by swabbing. Nevertheless, these areas may be the critical areas for the determination of the amount of residue in the equipment.

**Equation 6**: $$\mathbf{CO} = \left(\frac{\mathbf{1}}{\mathbf{WF}}\right) \times \left[\mathbf{F_{tot}} \times \sum\left(\frac{\mathbf{M_i/F_i}}{\mathbf{N}}\right)\right] = \left(\frac{\mathbf{1}}{\mathbf{WF}}\right) \times \left[\mathbf{F_{tot}} \times \sum\left(\frac{\mathbf{(C_i - C_{Bi})\,/F_i}}{\mathbf{N}}\right)\right]$$

| | |
|---|---|
| CO | Carry Over, amount of residue in the cleaned equipment in mg. |
| WF | Recovery rate for the whole chain swab/analytical method (e.g. 0.8 for 80%). |
| $F_{tot}$ | The entire inner surface of the equipment in dm$^2$ |
| Mi | Amount of residue (e.g. previous product) in the sample i in mg. |
| $C_i$ | Gross amount of residue in the sample i in mg. |
| $C_{Bi}$ | Blank of the sample i in mg. To establish the blank, a swab (or several swabs) can be treated in the similar way as a sampling swab except swabbing of the contaminated surface. Usually one and the same blank can be used for all N sampling swabs. |
| $F_i$ | Area swabbed by the swab i in dm$^2$. |
| N | Number of swab samples. |
| i | Sample identifier (current number from 1 to N). |

The first production batch of the following product may be sampled and analysed for impurities (for preceding product) since chromatographic analytical methods will typically be used (e.g. HPLC, GC, TLC).

### 8.3.2 Rinse or Wash Solvent Sampling

In cases where swabbing is not possible, for example restricted access, swabbing may be substituted by the analysis of final rinse solutions. Rinse samples can be used to determine the carryover of residues over a large surface area and cover all main process items including transfer pipework. In cases where swab sampling is not practical, it is acceptable to analyse only rinse samples, however this should be justified as part of the validation study.

This section outlines the quantitation of the amount of residue remaining in the equipment after cleaning based on the amount of residue in the last rinse of the routinely used cleaning procedure.

The residue amount in the equipment can be assumed to be equal to the amount of residue in the last wash or rinse solvent portion. The assumption is based on the worst case consideration

that a further rinse (or any reaction) would not remove more than the same amount of residue present in the analysed rinse sample. Recovery studies of the rinse sampling can also be performed.

The advantage of the rinse sampling method is the whole equipment will be reached by the solvent, including difficult to reach locations that cannot be disassembled. Therefore, if appropriately designed, this method will give the best indication of the amount of residue remaining in the equipment.
For quantitation, a solvent sample (*e.g.* 1 litre) is removed and the residue in the sample is determined by a suitable analytical method, which can then be extrapolated to the whole equipment according to **Equation 5**.

**Equation 5**: $\mathbf{CO\ [mg] = V \times (C - C_B)}$

| | | |
|---|---|---|
| Where | CO | Carry Over, amount of residue in the cleaned equipment in mg. |
| | V | Volume of the last rinse or wash solvent portion in litres. |
| | C | Concentration of impurities in the sample in mg/l. |
| | $C_B$ | Blank of the cleaning or rinsing solvent in mg/l. If several samples are taken during one run, one and the same blank can be used for all samples provided the same solvent lot was used for the whole run. |

### 8.3.3 Stamps

In this exceptionally used sampling method, “coins” (or stamps) are placed on appropriate sampling points in the equipment **during the manufacture of the previous product** and **during cleaning**. After cleaning, the contamination on the coins can be analysed and the overall contamination can be calculated by extrapolation to the whole equipment. For quantitation, the coins may be firstly swabbed followed by further analysis of the samples.

## 8.4 Analytical Methods

A sample isolated by either of the sampling methods discussed in Section 8.3 should be analysed by a suitable analytical method (e.g. HPLC, GC, GC-MS, TLC, dry residue, TOC, UV, titration, conductivity or pH). The suitability of the method can be documented by appropriate validation as detailed in **Section 8.2**.

A combination of analytical methods can be used if appropriate. For example, evaporation of the solvent sample and analysis of the dry residue by another method (e.g. HPLC) can enhance the sensitivity of the final analytical method by a factor $10^6$. Alternatively, the use of several methods (e.g. titration, HPLC) can provide the required specificity.

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# 9.0 CLEANING VALIDATOIN PROTOCOL (example)

PREPARED BY (DEPT.): _____ DATE:_____

REVIEWED BY (DEPT.) : _____ DATE:_____

APPROVED BY (DEPT.) : _____ DATE:_____

APPROVED BY (DEPT.) : _____ DATE:_____

APPROVED BY (DEPT.) : _____ DATE:_____

**TITLE:**

PROTOCOL NO:_____

PROTOCOL ISSUE DATE: _____

CLEANING SOP REFERENCE AND ISSUE NO : _____

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**TABLE OF CONTENTS**



## 9.1 Background

Equipment X is routinely cleaned after product Y (or group of products*) according to procedure XXX.....
**If group of products describe rational for choosing this grouping strategy.*
Describe: Equipment
Cleaning method
Cleaning agents.

## 9.2 Purpose

The purpose of this study is to demonstrate that remaining product residues previous in a piece of equipment are always within the established acceptance criteria if the equipment is cleaned by a defined cleaning method.

## 9.3 Scope

A visual test and a chemical evaluation of the equipment will be performed after a clean to demonstrate that product residue(s) (active ingredient, intermediates and / or excipients) and cleaning agent residues (exclude solvents used in process) have been removed to levels within the acceptance criteria.

The equipment cleanliness will be proven by testing and evaluation of samples in accordance with this protocol from *Z** consecutive cleans. (**Z: Generally three consecutive cleans are acceptable, however, companies should determine the number adequate for their operation.)*

At least a visual revision of the working areas will be performed to minimize the risk of cross contamination that results from e.g. contamination on the surface of the process room.

In order for the cleaning procedure to be deemed valid, all data generated during the study should be within the acceptance criteria detailed in section 9.7 of this protocol.

A report will be written assessing the data generated and thus determining the validity of the cleaning process.

*The equipment should not be used to process another product until clearance indicating that the equipment is adequately clean has been received from the validation department in accordance with process transfer SOP AAA (or detail whatever system is in-place to ensure that equipment is not used).*

## 9.4 Responsibility

The responsibility for completion of this study lies as follows (for example):

| | |
|---|---|
| Scheduling: | *Manufacturing, QA, QC and Engineering.* |
| Cleaning of equipment: | *Manufacturing* |
| Removal of samples: | *QA* |
| Testing of samples: | *QC* |
| Review of data and approval of study: | *Validation / Manufacturing / QC* |

## 9.5 Sampling Procedure

Remove swab and rinse samples from the equipment as detailed in section 8.3 of this guidance document.

**SWAB SAMPLES:**

See attached equipment sampling diagram (It is important to show clearly where the sampling locations are). Definition of sampling locations should be based on a Risk Assessment.

Swab samples should be removed according to swabbing procedure SOP BBB (or if there is no SOP in place describe in the text the validated sampling technique for the QA sampler).

The swab sampling locations are as follows:

Product residue samples: list of sample locations and no of swabs to be removed.

Cleaning agent samples: list of sample locations and no of swabs to be removed.

*Samples should be removed from the locations on the equipment deemed to be 'worst case' i.e. most difficult to clean locations and therefore where product is most likely to reside if cleaning has not been adequate. It is important that these locations have been determined scientifically and can be rationalised if necessary.*

**RINSE SAMPLES:**

Rinse samples should be removed according to procedure SOP CCC (or if there is no SOP in place describe the sampling technique for the QA sampler).
The volume of liquid used to rinse the equipment should be detailed (volume must be shown to be sufficient to cover all product contact surfaces of the equipment). The volumes of the rinse samples should also be stipulated in the protocol.

**MICROBIOLOGICAL TESTING**

See attached equipment sampling diagram (It is important to show clearly where the sampling locations are)
Microbiological test samples should be removed according to procedure SOP DDD (or if there is no SOP in place describe the sampling technique for the QA sampler).

The microbiological testing locations are as follows:
List of sample locations and no of microbiological tests samples to be removed

All sampling details (swab, rinse and microbiological) should be referenced in Table Samples should then be sent to the QC department for analysis. Any relevant sample transfer conditions should be noted.

## 9.6 Testing procedure

Rinse samples should be tested for:
- Product residues in accordance with analytical protocol
- Cleaning agent residues in accordance with analytical protocol

Swab samples should be tested for:
- Product residues in accordance with analytical protocol
- Cleaning agent residues in accordance with analytical protocol

Microbiological test samples should be tested for:
-Total germ number

Note the limits of quantitation and detection as well as the % recovery for the tests being performed.

***The analytical protocol should include a calculation to convert the amount of residue detected in the sample to 100% (i.e. if the analytical validation results indicate that only 50% of spiked active / cleaning agent is recovered using the swabbing / rinse method of choice, the amount of active cleaning agent recovered per sample should be multiplied by 2 to bring result to 100%).***

All data generated should be attached to this study and returned to the Validation

department where calculations and adherence to acceptance criteria is determined.

### 9.7 Acceptance criteria

The visual cleanliness of the equipment must be checked and verified after cleaning according to the procedure xxx:

Equipment is visually clean: Signed (manufacturing): _____ Date: _____

Verified (QA): _____ Date: _____

The swab / rinse sample acceptance criteria for product and cleaning agent residues as well as the microbiological test acceptance criteria should be detailed along with a rational for the figures quoted.

(Unlike product residues, it is expected that no (or for ultra-sensitive analytical test methods - very low), detergent levels remain after cleaning. Detergents are not part of the manufacturing process and are only added to facilitate cleaning. Thus, they should be easily removed. Otherwise a different detergent should be selected.)

Reference: Please see chapter 4 of this guidance document for examples of calculating acceptance criteria.

In addition, a sample calculation detailing how the residual levels of active ingredient / cleaning agent for the entire equipment are computed should be given.

**POINTS TO CONSIDER:**

Surface area calculations should be performed, verified and kept on file for all equipment evaluated (photos may be incorporated into the protocol to ensure samples are taken from the correct position).

When the worst case result recorded is less than the limit of quantitation but greater than the limit of detection for the test method, the value denoting the limit of quantitation should be used to perform the calculations.

When the worst case result recorded is less than the limit of detection for the test being performed the value denoting the limit of detection should be used to perform the calculations.

Dirty Hold Times and Clean Hold Times

The period and when appropriate, conditions of storage of equipment before cleaning, commonly referred to as The Dirty Hold Time (DHT) and the time between cleaning and equipment re-use, prior to additional cleaning, commonly referred to as The Clean Hold Time (CHT), should form part of the validation of cleaning procedures. This is to provide confidence that routine cleaning, drying and storage of equipment does not allow potential for buildup of degradation products that may not be removed by the standard cleaning procedure and does not allow potential for microbial contamination of equipment and to ensure that these potential risks are properly assessed and controlled.

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**TABLE 1: SAMPLE REFERENCE TABLE**

| **Sample** | **To be tested for** | **Area swabbed** | **Total surface area (cm2)** | **Sample ref.** | **signed / date** |
|---|---|---|---|---|---|
| swab sample | Active | | xxx | | |
| swab sample | Cleaning agent | | xxx | | |
| swab sample | Active | | xxx | | |
| swab sample | Cleaning agent | | xxx | | |
| swab sample | Active | | xxx | | |
| swab sample | Cleaning agent | | xxx | | |
| swab sample | Active | | xxx | | |
| swab sample | Cleaning agent | | xxx | | |
| swab sample | Active | | xxx | | |
| swab sample | Cleaning agent | | xxx | | |
| **Sample** | **To be tested for** | **Sample volume** | **total volume of rinse** | **Sample ref.** | **signed / date** |
| rinse sample | Active | | | | |
| rinse sample | Cleaning agent | | | | |
| **Sample** | **To be tested for** | **Sample ref.** | | | **signed / date** |
| swab sample | Microbial contamination | | | | |
| swab sample | Microbial Contamination | | | | |

## 9.8 Training

The personnel involved in cleaning, sampling and testing of processing equipment should be effectively qualified in the relevant procedures.

Typical procedures are (not limitative):

- Cleaning of equipment (e.g. manually or clean-in-place (CIP))

- Visual inspection of equipment
- Sampling techniques (i.e. swab and rinse samples)
- Applied analytical methods
- Sanitization of equipment and rooms (where appropriate)

### 9.9 Deviations

Please indicate whether deviations occurred during the completion of this Validation Protocol and give details especially with regard to impact on the effectiveness of the cleaning validation and with regard to corrective and preventive actions.

### 9.10 Revalidation

Define the revalidation strategy for cleaning processes.

Signed: _____ Verified: _____

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## 10.0 VALIDATION QUESTIONS

**Question 1: When should a company validate/ revalidate cleaning procedures? When is validation not required?**

***Advice:*** *Ref. Section 7.0 and 10.0*
*Companies should look at each situation individually and determine the need for validation. Section 7.0 provides a basic template, which may be used as a starting point in this evaluation. The necessity to revalidate cleaning procedures should be determined under change control parameters - See Section 10.0.*
*If routine verification procedures are used, these should be monitored to ensure that the procedure is in control. Companies should consider a periodic evaluation of cleaning procedures , which are subject to variation (i.e. manual procedures etc.), as an additional precaution to assure that the procedures are still valid.*

**Question 2: When is it appropriate to use Prospective, Concurrent or Retrospective Validation**

***Advice:*** *Ref. Section 9.0*
*Retrospective Validation of cleaning is not condoned by regulatory Authorities Prospective Validation is the ideal method of validation.*
*In situations where very few runs are manufactured in any given period and/ or a business decision has been taken to release the next material manufactured after cleaning based on a high level of testing of the equipment (i.e. Validation level,) concurrent release of material may take place.*

**Question 3: What level of testing is needed after cleaning validation?**

***Advice:*** *Ref. Section 5.3*
*The answer to this question depends on individual situations. Typically, companies perform visual inspection and take rinse samples to monitor the effectiveness of the cleaning in pre-defined intervals (time or number of batches).*
*If after validation company decides to perform always cleaning verification non-specific scientifically sound analytical methods may be used.*
*A practical approach for monitoring the effectiveness of cleaning after completion of cleaning validation in an effective, scientific sound and inexpensive way is given below:*

*1.) Visual inspection of the cleaned equipment. Only after this check is considered satisfactory, proceed with the next step.*
*2.) Take a rinse and/or swab sample (one liter of rinsing liquid is usually required)*
*3.) Determine the dry residue by evaporating about 500 ml to dryness in a small flask using a rotary evaporator. This unspecific test covers also inorganic salts, known or unknown organic products and will detect the total residues.*

*(this test might be omitted for the drying equipment, in this instance we have a pure API or intermediate and typically no potential for side products, degradation, etc.)*

*4.) If the result meets the specification, proceed to specific (chromatographic) technique. Start with a TLC-limit test (inexpensive and fast to validate, broad detection range – UV and specific derivatization – if these techniques are combined, the method is very specific for the different impurities potentially present in the sample. Apply 2 samples: the last washing liquid (to see all potential residues), the rinsing liquid (to look for the residue) and two standards: one of the suspected residual product at a concentration that is the limit accepted, and a 1:2 dilution of the standard. If the main spot in the rinsing liquid has lower intensity than the standard, the equipment is clean. The second standard is for confirmation of detection.*

*5.) If TLC is not the appropriate technique, revert to HPLC or GC.*

**Question 4: What critical parameters need to be looked at during cleaning validation?**

***Advice:*** *Ref. Section 8.2 for details*
*It is vital that the equipment design is evaluated in detail in conjunction with the product residues to be removed, the available cleaning agents and the cleaning techniques. Also the ruggedness and reproducibility of the cleaning procedure should be covered.*

**Question 5: What number of cleans should be run in order to validate a cleaning procedure?**

***Advice:*** *Ref. Section 9.0*
*A validation program generally encompasses three consecutive successful replicates. However, companies should evaluate each situation individually.*

**Question 6: Is it acceptable for a validated cleaning procedure to be continued until the analytical results demonstrate it is clean?**

***Advice:*** *Regulatory authorities do not condone this practice.*

*When the analytical result does not meet the acceptance criteria an investigation to determine the possible root cause should be performed. If needed re-training of the operators should be performed and/or adjustment of the cleaning procedure to solve the issue.*

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**Question 7: Is it necessary for companies to validate a maximum time allowed for a piece of equipment to be dirty before cleaning?**

***Advice:*** *Companies should have SOPs in place, which require cleaning to be performed immediately after production has stopped. This scenario should be validated. However, if for some reason immediate cleaning is not always possible, companies should consider the effect of time on the material deposited on the equipment. It may be possible to 'Group' or 'Bracket' products and validate a worst case scenario.*

**Question 8: Is it necessary for companies to validate a maximum time allowed for a piece of equipment to be left clean before re-use?**

***Advice:*** *Companies should have SOPs in place to ensure that pieces of equipment are adequately protected from any contamination after cleaning has taken place i.e. ensure that the equipment is adequately covered, closed from dust etc. If the company feels that there is any risk of contamination during 'idle time' after cleaning, validation should be considered.*

**Question 9: Is it necessary to establish time limits for cleaning if equipment is not used frequently?**

***Advice:*** *Please see previous advice to question 8.*

**Question 10: What is the maximum time allowed after cleaning with water as last rinse?**

***Advice:*** *Equipment should <u>not</u> be left with water in it after cleaning. The last step of the cleaning procedure involve drying with solvent or flushing with Nitrogen, thus ensuring that there is no opportunity for microbial growth.*

**Question 11: Is it possible that a deterioration of equipment may take place over time, thus invalidating the original validation results?**

***Advice:*** *Materials used to manufacture equipment for the pharmaceutical / chemical industry is of a very high standard. However, equipment materials used should be evaluated to ensure their durability over time as part of the preventative maintenance programme. The possibility of surface roughness and any possible effects that it may have on cleaning should be considered. Companies employing verification methods after validation should monitor analytical data generated as part of this process.*

**Question 12: If a company has validated a worst case scenario (grouping or bracketing regime), should they also need to validate a 'less' worst case?**

***Advice:*** *When grouping products and determining worst case situation scenario for validation, companies should determine whether or not the worst case being*

*validated is one, which is appropriate for routine manufacture. For operational reasons it may be beneficial to validate a "less" stringent cleaning procedure for some products.*

**Question 13: In a case of a dedicated plant with no degradants, is there a need to validate?**

***Advice:*** *Ref. Section 7.0*
*Companies should consider each situation individually and validate where there is a potential for contamination. In the above situation, there may not be a need. However, consideration should be given to the number of runs being performed prior to full cleaning.*

**Question 14: Should cleaning validation be part of a development programme?**

***Advice:*** *While it is not a requirement of ICH that cleaning validation be performed during development phase the following should be considered:*

*If the equipment being cleaned after the development product in question is used to manufacture commercial product or product for human use for example clinical trials, it is essential to verify the appropriate cleanliness of the equipment prior to re-use.*

*Development of the Cleaning procedure for the product should take place at development phase for validation when the product becomes commercially available. The cleaning procedure validation should be performed or at least should start with the process validation campaign.*

**Question 15: Is it necessary to include microbiological testing / aspects in the cleaning validation programme?**

***Advice:*** *Ref. Section 8.1*

*Yes, if the following product needs to have a low microbiological load, also depending on the cleaning agent used, if there is any risk for microbiological contamination of the subsequent product (e.g. if water is used for final cleaning).*

**Question 16: Which analytical methods should be used in cleaning validation studies (is only HPLC -testing acceptable?) and to which extend should these methods be validated?**

***Advice:*** *Ref. Section8.0 of this "Guidance on Aspects Document"*

*Any analytical method suitable for its intended use could be used. In general limit tests are performed in cleaning validation studies which result in less stringent validation requirements. (as outlined in ICH-Q2A and Q2B).*
*However, if a company decides to validate analytical methods, suitable for the determination of the residue over a certain range (e.g. decay-curve, to prove the success of cleaning during proceeding of a defined cleaning procedure consisting of individual cleaning steps) also less stringent validation requirements for e.g.*

*linearity and accuracy could be established compared with figures typically required in the validation of API release testing methods.*

**Question 17: Do we have to wait for swab and rinse samples to be approved prior using the equipment for production?**

***Advice:*** *During cleaning validation studies it is recommended to wait for completion of all planned tests prior to release equipment for further use (to be able to perform an investigation if tests fail). In routine operations (after validation has been completed) the release of equipment pending testing results (verification, monitoring status of the tests) could be done. Responsibilities and circumstances for using equipment pending release should be defined within the company.*

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## 11.0 REFERENCES


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# 12.0 GLOSSARY

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|---|---|
| **$A_i$** | Area for the tested piece of equipment # i. |
| **ADE** | Acceptable Daily Exposure (mg/day) |
| **CO** | True (measured) total quantity of substance (possible carryover) on the cleaned surface in contact with the product, calculated from results of swab tests. |
| **CONC** | Concentration (kg/kg or ppm) of "previous" substance in the next batch. Based on MACO calculated from therapeutic doses and/or tox data. |
| **LD50** | Lethal Dose 50 in g/kg animal. The identification of the animal (mouse rat etc.) and the way of entry (IV, oral etc.) is important. |
| **LOD** | Limit of detection. |
| **LOQ** | Limit of quantification. |
| **$m_i$** | Quantity (in weight/area) for each swab per area of swabbed surface (normally 1 $dm^2$). |
| **MACO** | Maximum Allowable Carryover: acceptable transferred amount from the investigated product ("previous"). |
| **MAXCONC** | General limit for maximum allowed concentration (kg/kg or ppm) of "previous" substance in the next batch. |
| **MBS** | Minimum batch size for the next product(s) (where MACO can end up). |
| **NOEL** | No Observed Effect Level. |
| **NOAEL** | No Observed Adverse Effect Level |
| **PDE** | A substance specific dose that is unlikely to cause an adverse effect if an individual is exposed at or below this dose every day for a lifetime (mg/day) |
| **Rinsing cycle** | Sometimes rinsing cycles/runs may follow the washing cycles. The rinsing cycles may be part of the routine cleaning procedure (e.g. to rinse out the washing solvent) or may be used for sampling purposes (e.g. rinsing with water after washing with detergents). Rinsing cycles that are not part of the routine cleaning procedure may be used for enhanced sampling during the cleaning validation exercise. |
| **SF** | Safety factor. |
| **$S_{rel}$** | Relative standard deviation, coefficient of variation. |
| **$TDD_{next}$** | Standard therapeutic dose of the daily dose for the next product. |
| **$TDD_{previous}$** | Standard therapeutic dose of the investigated product (in the same dosage form as **$TDD_{next}$** |
| **Washing cycle** | Usually the API equipment will be washed thoroughly with several portions of solvent one after the other by the same repeated process. One cleaning process repetition with one of these portions is termed washing cycle (run). |

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## 13.0 COPYRIGHT AND DISCLAIMER



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