# Guidance on aspects of cleaning validation in active pharmaceutical ingredient plants

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APIC Active Pharmaceutical Ingredients Committee

A Sector Group of CEFIC

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# 1.0 Foreword

This document has been prepared by the cleaning validation task force within the active pharmaceutical ingredient committee (APIC) of CEFIC.

In recent years the subject of cleaning validation in active pharmaceutical ingredient manufacturing plants has received a large amount of attention from regulators, companies and customers alike. 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.

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.

It should be read in conjunction with the APIC document entitled „Cleaning Validation in Active Pharmaceutical Ingredient Manufacturing Plants“

# 2.0 Objective

This document has been prepared only to assist companies in the formulation of cleaning validation programmes and should not be considered 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

Five specific areas are addressed in this Guidance document, namely:

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

Finally the most frequently asked questions are answered.

# 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. That limit established must be calculated based on sound scientific rational.

This section provides practical guidance as to how that 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 require further consideration.

## 4.2 Methods of Calculating Acceptance Criteria

### *4.2.1 Based on Therapeutic Daily Dose*

The principle for the requirement is that the standard Therapeutic Daily Dose (TDD) of the following substance (‘contaminated’ substance, in this case called "next") may be contaminated by no more than a certain proportion (usually 1/1000 part) of the TDD of the substance investigated in the cleaning validation (contaminating substance, in this case called "previous"). This method only applies when the therapeutic daily dose is known. It is generally used for final product changeover API Process “A” to API Process “B.

**Procedure**

Establish the limit for *Maximum Allowable Carryover* (MACO) according to the following equation.

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

| | |
|---|---|
| **MACO** | Maximum Allowable Carryover: acceptable transferred amount from the investigated product ("previous") |
| **TDD**$_{\text{previous}}$ | Standard therapeutic dose of the investigated product (in the same dosage form as **TDD**$_{\mathbf{next}}$) |
| **TDD**$_{\mathbf{next}}$ | Standard therapeutic dose of the daily dose for the next product |
| **MBS** | Minimum batch size for the next product(s) (where MACO can end up) |
| **SF** | Safety factor (normally 1000 is used in calculations based on TDD) |

Example 1:

Product A will be cleaned out. The product has a standard daily dose of 10 mg and the batch size is 200 kg. The next product B has standard a daily dose of 250 mg and the batch size is 50 kg. Both A and B are administrated orally and SF is set to 1000. Calculate the MACO for A in B!

$$\mathbf{MACO} = \frac{\mathbf{10}\ (\text{mg}) \times \mathbf{50\,000\,000}\ (\text{mg})}{\mathbf{1000} \times \mathbf{250}\ (\text{mg})} = \mathbf{2\,000}\ (\text{mg})$$

*Result*: **MACO is 2 g (2000 mg)**

Example 2:

Now product B in example 1 will be cleaned out. The following product is product A in example 1. Calculate the MACO for B in A!

$$\mathbf{MACO} = \frac{\mathbf{250}\ (\text{mg}) \times \mathbf{200\,000\,000}\ (\text{mg})}{\mathbf{1000} \times \mathbf{10}\ (\text{mg})} = \mathbf{5\,000\,000}\ (\text{mg})$$

*Result:* **MACO is 5 kg (5 000 000 mg)**

In API manufacture it is possible to obtain a very high MACO figure. In example 2, the figure obtained is clearly unacceptable. Although there would be no effects expected, the equipment would be obviously dirty and a general GMP limit should be chosen (see 4.2.3 - page 7 - how to select limits).

Instead of calculating each potential product change situation, the worst case scenario can be chosen. Then a case with most active API (lowest TDD) is chosen to end up in the following API with the smallest ratio of batch size divided with TDD (MBS/TDD ratio). This could be done if the safety factor is the same for all products (otherwise the lowest MBS/(TDDxSF) ratio should be chosen).

### *4.2.2 Based on Toxicological Data*

In cases in which a therapeutic dose is not known (e.g. for intermediates and detergents), toxicity data may be used for calculating MACO.

**Procedure**

Calculate the so called NOEL number (No Observable Effect Level) according to the following equation and use the result for the establishment of MACO. (See [3] – page 53 - for reference.)

$$\mathbf{NOEL} = \frac{\mathbf{LD_{50}}\ \text{(g/kg)} \times \mathbf{70}\ \text{(kg a person)}}{\mathbf{2000}}$$

From the NOEL number a MACO can then be calculated according to:

$$\mathbf{MACO} = \frac{\mathbf{NOEL} \times \mathbf{MBS}}{\mathbf{SF} \times \mathbf{TDD_{next}}}$$

| | |
|---|---|
| **MACO** | Maximum Allowable Carryover: acceptable transferred amount from the investigated product ("previous") |
| **NOEL** | No Observed Effect Level |
| **$LD_{50}$** | 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. |
| **70 kg** | 70 kg is the weight of an average adult |
| **2000** | 2000 is an empirical constant |
| **$TDD_{next}$** | Largest normal daily dose for the next product |
| **MBS** | Minimum batch size for the next product(s) (where MACO can end up) |
| **SF** | Safety factor |

The safety factor (SF) varies depending on the route of administration. Generally a factor of 200 is employed when manufacturing APIs to be administered in oral dosage forms. SF can vary depending on substance/dosage form according to (suppose tox values from oral administration) as for example as presented on the next page.

| | | |
|---|---|---|
| Safety factors: | Topicals | 10 – 100 |
| | Oral products | 100 – 1000 |
| | Parenterals | 1000 – 10 000 |

Remarks: API`s in development may require higher safety factors due to lack of knowledge.

To calculate MACO values from tox data is frequently done when therapeutic dosage data is not available or not relevant. It is generally employed if the previous product is an intermediate and the following product an API.

### *4.2.3 General Limit*

If the calculation methods based on therapeutic doses or toxicological data (see 4.2.1 or 4.2.2, page 4 – 7) result in unacceptably high or irrelevant carryover figures, or toxicological data for intermediates are not known, the approach of a general limit may be suitable. Companies may chose to have such an upper limit as a policy. The general limit is often set as an upper limit for the maximum concentration (MAXCONC) of a contaminating substance in a subsequent batch.

The concentration (CONC) of the investigated substance which can be accepted in the next batch, according to dose related calculations, is:

$$\mathbf{CONC} = \frac{\mathbf{MACO}}{\mathbf{MBS}}$$

| | |
|---|---|
| **MACO** | Maximum Allowable Carryover: acceptable transferred amount from the investigated product ("previous"). Calculated from therapeutic doses and/or tox data. |
| **$\text{MACO}_{\text{ppm}}$** | Maximum Allowable Carryover: acceptable transferred amount from the investigated product ("previous"). Calculated from general ppm limit. |
| **CONC** | Concentration (kg/kg or ppm) of "previous" substance in the next batch. Based on MACO calculated from therapeutic doses and/or tox data. |
| **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) |

A general upper limit for the maximum concentration of a contaminating substance in a subsequent batch (MAXCONC) is often set to 5-100 ppm depending on the nature of products produced from the individual company (e.g. toxicity, pharmacological activity, 10 ppm in APIs is very frequent).

*Note - If you decide to employ the concept of levels of cleaning (ref. section 5, page 16), 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.*

If the calculated concentration (CONC) of the previous product (based on MACO calculated from therapeutic doses/tox data) exceeds the general upper limit (MAXCONC), then MAXCONC level will be the limit.

**Procedure**

Establish $\mathrm{MACO}_{\mathrm{ppm}}$, based on a general limit, using the following equations.

$$\mathbf{MACO_{ppm}} = \quad \mathbf{MAXCONC} \times \mathbf{MBS}$$

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).

Remarks: The ICH impurity document (Q 3) indicates that up to 0.1% of an individual unknown or 0.5% total unknowns may be present in the product being tested.

Example 3:

A product B will be cleaned out. The product has a standard daily dose of 250 mg and the batch size is 50 kg. The next product A has a standard daily dose of 10 mg and the batch size is 200 kg. The general limit of the company is 10 ppm. Calculate the $\mathrm{MACO}_{\mathrm{ppm}}$ for B in A!

$$\mathbf{MACO_{ppm}} = \quad \mathbf{0.00001}\ (\mathrm{mg/mg}) \times \mathbf{200\,000\,000}\ (\mathrm{mg}) \quad = \mathbf{2000}\ (\mathrm{mg})$$

*Result*: **$\mathbf{MACO_{ppm}}$ is 2 g (2 000 mg)**

In the worst case a maximum of 2 g of B may appear in API A. This is more reasonable than the limit 5 kg calculated in example 2.

### *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. This can be used as basic information for preparation of a method of analysis and detection limit.

**Procedure**

Establish the target value for swab limit for the whole equipment train, using the following equation:

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

Also other methods with different swab limits for different surfaces in a piece of equipment and/or equipment train can be used. Using this approach, the total amount found on the equipment train has to be below the MACO (see 4.2.4.2 - page 12 - how to evaluate this).

#### 4.2.4.1 Setting Acceptance Criteria for Swab Limits

For each item tested, normally two acceptance criteria (AC) are set.

AC1. The acceptance criterion “no visible residue” shall always be applied.

AC2. The most stringent of the following swab limits are normally used for swab tests:

- Swab limit based on therapeutic dose or tox calculations (see 4.2.1, page 4 and 4.2.2, page 6)
- Swab limit based on a general "ppm limit" (see 4.2.3, page 7)

AC3. The MACO must not be exceeded for the total equipment train (see 4.2.4.2, page 12).

Usually either AC2 or AC3 is used (swab limits are calculated from MACO). However, both can be used and then different swab limits can be set for different types of equipment. Some swab limits can be higher than the target value, if others to compensate are lower. This as long as the total calculated amount is below the MACO (see 4.2.4.2, page 12).

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.

Example 4:

Several substances are produced in the same equipment train (Dryer X), as presented in the following table. Any of the other six substances can be produced after Substance C. Substance C can be administered both in oral and parental dosage form. The company policy is based on three requirements:

1. No product shall contain more than 10 ppm of a contaminating substance from a previous batch.
2. No patient shall be exposed to more than 1/1000 of the therapeutic dose (TDD for the same dosage form) of another API.
3. If the TDD is not known for the same dosage form, then no patient shall be exposed to more than 1/10000 of the NOEL for another API (with not known TDD for the same dosage form).

Calculate the MACO value and swab limit for Substance C! In this case the same swab limit shall apply to all surfaces.

*Data table:*

| Area: 1500 $dm^2$ | **MBS kg** | **TDD mg** | | | **Safety factor (SF)** | | **NOEL mg** | | |
|---|---|---|---|---|---|---|---|---|---|
| Dryer X | | Oral | Par | Inhal | Oral | Par | Oral | Par | Inhal |
| Substance A | 200 | 10 | 375 | | 1000 | 1000 | | | |
| Substance B | 50 | 250 | | | 1000 | 10000 | | 2500 | |
| Substance C | 200 | 40 | 120 | | 1000 | 1000 | | | |
| Substance D | 120 | 40 | 40 | | 1000 | 1000 | | | |
| Substance E | 200 | | 400 | | 10000 | 1000 | 8000 | | |
| Substance F | 1000 | | 400 | | 10000 | 1000 | 11000 | | |
| Substance G | 50 | 15 | 35 | | 1000 | 1000 | | | |

*Calculation of upper general limit (10 ppm):*

The next batches may contain maximum 10 ppm of Substance C. The upper general limit for Substance C is calculated (from equation in 4.2.3, page 8) from the lowest MBS of the possible "substance of next batches"; in this case 50 kg valid for Substance B and G:

$$\mathbf{MACO_{ppm}} = \quad \mathbf{10} \times \mathbf{10^{-6}}\ (\text{kg/kg}) \times \mathbf{50}\ (\text{kg}) = \mathbf{5} \times \mathbf{10^{-4}}\ (\text{kg}) = \mathbf{500}\ (\text{mg})$$

<u>This corresponds to a swab limit equal to a target value (from equation in 4.2.4, page 9):</u>

$$\textbf{Target value}\ [\mu g/dm^2] = \frac{\textbf{MACO}}{\textbf{Total surface}} = \frac{\textbf{500 000}\ [\mu g]}{\textbf{1500}\ [dm^2]} = \textbf{333}\ [\mu g/dm^2]$$

So the general upper MACO is 500 mg - corresponding to a swab limit of 333 [$\mu g/dm^2$]. This has to be compared to the limits calculated based on doses / NOELs.

*<u>Matrix calculations of swab limit according to requirement based on therapeutic dose/NOEL:</u>*

For each possible "next product", the MACO is calculated according to the equation in 4.2.1 – page 4 - (when TDD is known) or according to the equation in 4.2.2 – page 6 - (NOEL is used when TDD is not known). The corresponding concentration in ppm is calculated in accordance with the equation in 4.2.3 – page 7. Then a target value for swabs is calculated according to 4.2.4 – page 9.

The safety factor for Substance C is 1000 both for oral and parental use, and will be constant in all calculations. The $TDD_{previous}$ is 40 mg for all the "oral calculations" and 120 mg for all the "parental calculations". For the "next substance", batch size and $TDD_{next}$/NOEL have to be collected from the data table for each substance in each dosage form. The results are inserted in the following table (two valid figures in the results). The worst cases for MACO and swab limits are indicated with bold. The total worst case comparing oral and parental calculations are indicated with bold on the last line of the table.

| **Substance** | **MACO [mg]** | | | **CONC [ppm]** | | | **Target value for swabs [$\mu g/dm^2$]** | | |
|---|---|---|---|---|---|---|---|---|---|
| | Oral | Par | Inhal * | Oral | Par | Inhal | Oral | Par | Inhal* |
| Substance A | 800 000 | 64 000 | - | 4000 | 320 | - | 530 000 | 43 000 | - |
| Substance B | 8 000 | **2 400** | - | 160 | 48 | - | 5 300 | **1 600** | - |
| Substance D | 120 000 | 360 000 | - | 1000 | 3000 | - | 80 000 | 240 000 | - |
| Substance E | **1 000** | 60 000 | - | 5 | 300 | - | **670** | 40 000 | - |
| Substance F | 3 600 | 300 000 | - | 4 | 300 | - | 2400 | 200 000 | - |
| Substance G | 130 000 | 170 000 | - | 2700 | 3400 | - | 89 000 | 110 000 | - |
| Worst case | **1000** | 2 400 | - | - | - | - | **670** | 1 600 | - |

* The symbol '-' indicates that these values are missing, because no product is administrated by inhalation.

The lowest swab limit occurs, according to dose calculations (670 µg/dm$^2$), when Substance E is manufactured after the Substance C. This also results in the lowest MACO (1000 mg = 1 g). As evident from the table, the corresponding CONC is 5 ppm. This value is below the general limit because the MBS for Substance E (200 kg) is larger than the MBS for the worst case (50 kg).

A comparison, of MACO and swab limit, for values based on the general 10 ppm limit and values based on TDD/NOEL calculations, is presented in the following table.

| Value of | 10 ppm limit | TDD/NOEL based limit | Most stringent case |
|---|---|---|---|
| **MACO** | 500 mg | 1000 mg | 500 mg |
| **Target value swabs** | 330 µg/dm$^2$ | 670 µg/dm$^2$ | 330 µg/dm$^2$ |

As evident from the comparison, the most stringent requirements result from the calculations based on the 10 ppm limit.

*Result*: **The swab limit for Substance C in Dryer X will be 330 µg/dm$^2$ and the MACO will be 500 mg.**

Note that in example 4, the limits for Substance C were calculated. To determine the limits for the other substances, a matrix must be set up for each substance. Then for each substance, MACO and target values are calculated. For each Substance a similar comparison against the limit calculated from MAXCONC should be done and the most stringent limits to be selected.

#### 4.2.4.2 Evaluation of results

When all surfaces have been sampled and the samples have been analysed, then the results are compared to the acceptance criteria. Below the case when a MACO is set as an acceptance criteria is used. In this case the total amount shall be calculated, and this implies that some results can be above the target limit, if of course others are below.

**Procedure**

Establish the possible *Carry Over* (CO) from the swab results, using the following equation:

$$\mathbf{CO}\ [\mu g] = \mathbf{\Sigma}\ (\ \mathbf{A_i}\ [dm^2] \times \mathbf{m_i}\ [\mu g/dm^2]\ )$$

**CO** True (measured) total quantity of substance (possible carryover) on the cleaned surface in contact with the product, calculated from results of swab tests.

**$A_i$** Area for the tested piece of equipment # i.

**$m_i$** Quantity, in µg/dm$^2$, for each swab per area of swabbed surface (normally 1 dm$^2$)

Example 5:

A company has carried out a cleaning validation study according to an approved protocol. The results of the swabs are presented in the following table. The individual swab results have been calculated as well as the CO.

| **Swab #** | **Swab position** | **Swab result non compensated (mg/dm$^2$)** | **Swab result comp-ensated for 95% recovery (mg/dm$^2$)** | **Area of part of dryer (dm$^2$)** | **Amount on part of dryer (g)** |
|---|---|---|---|---|---|
| Swab 1 | Inlet valve | 0.30 | 0.32 | 2 | 0.0006 |
| Swab 2 | Outlet valve | 0.40 | 0.42 | 2 | 0.0008 |
| Swab 3 | Dryer roof | 0.20 | 0.21 | 249 | 0.052 |
| Swab 4 | Dryer bottom | 0.20 | 0.21 | 250 | 0.053 |
| Swab 5 | Dryer centre left | 0.24* | 0.25* | 997 | 0.25* (calculated from worst case) |
| Swab 5 | Dryer centre right | 0.20 | 0.21 | | |
| **-** | **Total area** | **-** | **-** | **1500** | **0.36** |

* When several swabs are taken on the same surface, the worst case result is used to calculate the CO.

Now it is time to evaluate the results. Do that for case a) and b) below!

a) If the acceptance criterion is a swab limit of 0.33 mg/dm$^2$: are the results acceptable?

b) If the acceptance criterion is a MACO of 0.50 g: are the results acceptable?

*Answer a)*: The results are not acceptable. The swab of the outlet valve is not approved. This must be treated as a deviation, and action must be taken. The current cleaning procedure is not qualified for the outlet valve (however, for the other areas).

*Answer b):* The results are acceptable since the total amount is lower than the MACO.

As evident from the different results in a) and b), 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 other be dirty. One <u>example</u> of policy, to set limits for both MACO and swabs, is to have the following acceptance criteria:

AC 3: The MACO must not be exceeded for the total equipment train (see 4.2.4.2, page 12).

AC 2: The most stringent of the following swab limits:

Swab limit based on therapeutic dose (see 4.2.1, page 4) or NOEL (see 4.2.2, page 6).
Swab limit based on a general "ppm limit" (see 4.2.3, page 7)
AC 2.1 For all areas except for valves: the calculated swab limit.
AC 2.2 For valves: 10 times the calculated swab limit if AC 3 can still be fulfilled.

As mentioned before, AC 2.2 implies that in order to have a higher swab limit on valves or other pieces of equipment, the swab results for other areas have to be lower than the target value, in order for the CO to be below the MACO.

### *4.2.5 Rinse Limits*

The residue amount in the equipment can be assumed to be equal to the amount of residue in the last wash /boil) or rinse solvent portion. The assumption is based on the worst case consideration, that a further washing or rinsing run (or any reaction) would not wash more than the same amount of residue out of the equipment as the analysed solvent portion did.

The MACO is usually calculated on each individual product change over scenario according to the procedures outlined in chapter 4.2.1 – 4.2.3 (page 4 – 8) and individual acceptance criteria are established using the following equation:

$$\textbf{Target value}\ [\mathrm{mg/l}] = \frac{\textbf{MACO}\ [\mathrm{mg}]}{\textbf{Volume of rinse or boil}\ [\mathrm{l}]}$$

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:

$$M = V * (C - C_B)$$

| | |
|---|---|
| $M$ | Amount of residue in the cleaned equipment in mg. |
| $V$ | Volume of the last rinse or wash solvent portion in l. |
| $C$ | 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. |

Requirement: $M <$ Target value.

# 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 amount or as we will call it here, 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. During the course of this chapter the reader will be introduced to the concept of using different levels of cleaning, thereby giving the opportunity to minimize the amount of cleaning and cleaning validation required without effecting the safety of the API.

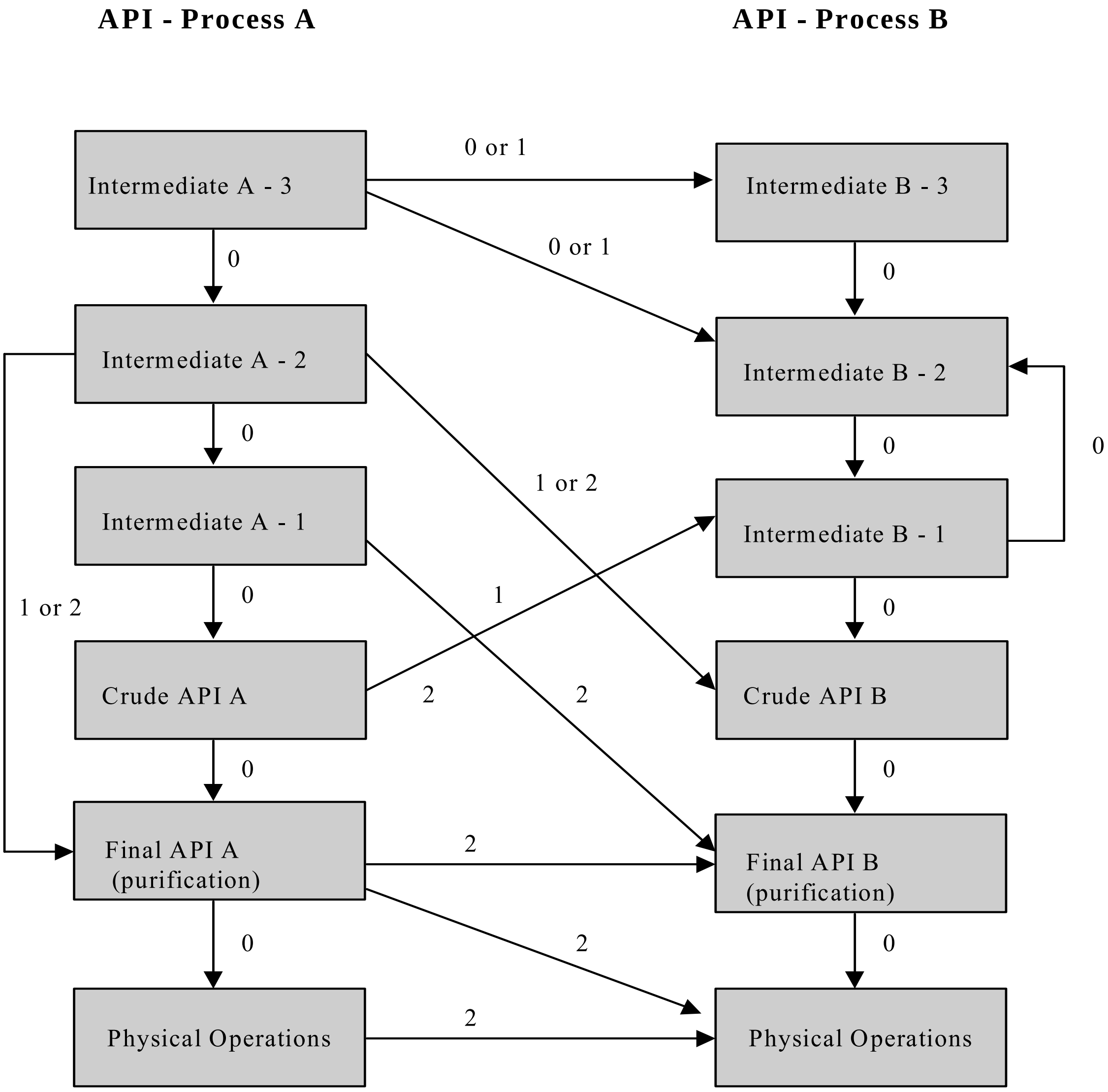
## 5.2 Procedure

The CEFIC – APIC Guide to Cleaning Validation recommends three levels of cleaning that 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.

| Level | Thoroughness of cleaning | Cleaning Validation |
|---|---|---|
| 2 | Carry over of the previous product is critical. Cleaning required until predetermined stringent carry over limits are met. | Essential. |
| 1 | Carry over of the previous product is less critical. Cleaning should reduce the potential carry over to a less stringent limit as required for level 2. | Increase from not required to necessary (lower acceptable carry over limits). |
| 0 | Only gross cleaning if carry over of the previous product is not critical. | Not required. |

A general approach how these levels could be established for typical product changeover situations in a multi-purpose API-plant is outlined in figure 1.

# 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 carry over of the previous product will decrease from early steps in the route of synthesis to the final API due the fact that early steps undergo further processing and/or purification and so the potential carry over will be reduced by further processing.

Principally two different product changeover scenarios exist which have a big impact on the cleaning level required:

1. Previous and following product **do** belong to the same synthetic chain (product changeover within process „A“ or within process „B“

2. Previous and following product **do not** belong to the same synthetic chain ( „A-x-“ to „B-x“; x = 0; 1; 2; 3 including crude and final API „A“ and „B“)

**If the product changeover is within the same synthetic chain (1.) there are two different situations possible:**

**Previous and following product is identical (in campaign cleaning).**
In this instance level 0 may be applied with no cleaning validation required. However potential degradants, accumulation of side products and microbiological growth should be considered. If applicable idle time (maximum period of time until complete and thorough cleaning of the equipment has to be done) for cleaning should be established.

In some instances e.g. at the physical steps no equipment cleaning at all may be performed between batch to batch changeover (dryer, blender, micronizer). Complete cleaning is done after finishing the campaign or after an idle time if established.

**Cleaning between different steps of the same synthetic chain.**

There are two different situations possible:

1. *The following product is the next step in the synthetic chain.*

There is a very low risk to effect the quality of the final API, because the previous product is the starting material of the following process 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. For this situation level 0 also applies.

*2. The following product is **<u>not</u>** the next step of the 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 harmless, level 1 may be acceptable.

**If the product changeover is <u>not</u> within the same synthetic chain (2.)** the level of cleaning required depends of 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:

- 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

Instead of the investigation of each individual cleaning situation similar situations could be grouped and classified using bracketing concepts (ref. section 6, page 20).

# 6.0 Bracketing and Worst Case Rating

## 6.1 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.

1. By means of a bracketing procedure the substances are grouped.
2. A worst case rating procedure is used to select the worst case in each group.
3. 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.

It is recommended that at formal „worst case rating project“ is carried out, including studies to support the "worst case rating". When finalized, the results of the worst case rating shall give the priority of the validation efforts of the program.

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 within the bracket, including those not individually tested.

## 6.2 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 multi purpose 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. The ideal with regard to cleaning validation (as will be discussed in 6.3, page 22) 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).

CleanCompany

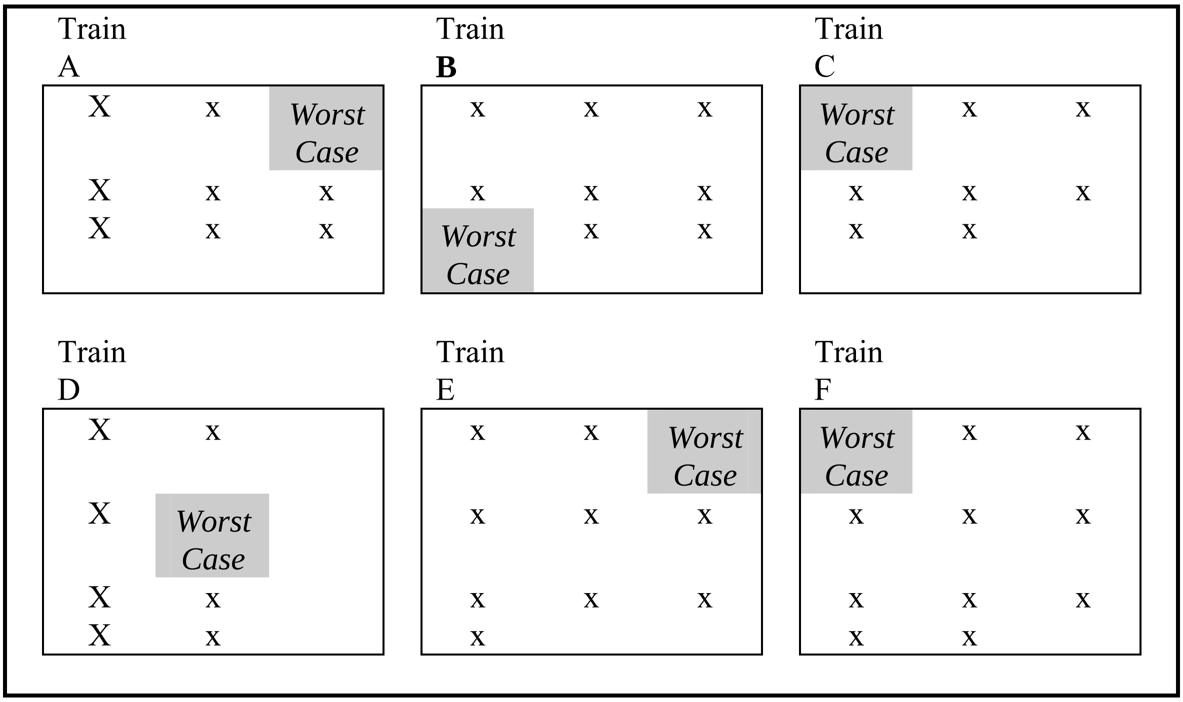


*Figure 1 CleanCompany's ideal example (1 train considered as 1 group) gives 6 worst cases.*

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 as well as low daily doses and/or low batch sizes (and the opposite).
- Produce in the same train substances with very low therapeutic doses (and the opposite).
- Produce in the same train non toxic substances.
- Produce in the same train substances with high solubility (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 therapeutic dose, 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 6.3 (page 22). More explanations on effects of different strategies will be evident from section 6.4 (page 23).

## 6.3 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.

For API, the cleaning procedures have often been developed for maximum efficiency with regard to less time required to clean out a specific substance. In many cases specific cleaning procedures exists for each product. 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.<br>- 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 CleanCompany 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 | substance - typeB. |
| Class III | acetone soluble substances. |
| Class IV | separate class for special substances. |

## 6.4 Investigations and Worst Case Rating (WCR)

A worst case rating study, 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) Highest toxicity
d) Lowest therapeutic dose
e) Lowest limit (based on therapeutic doses / tox data, batch sizes, surface areas etc.)
f) Other scientific rationales

In order to present documented evidence supporting the scientific rating for each criterion, investigations 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"). The descriptive terms for swab limits (based on therapeutic doses/tox data, batch sizes, surface areas etc.) could be chosen based on the possibility to normally detect the actual level by visual inspection.

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 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 there are no scientifically rationales.

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

### 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<br>- |

### c) Toxicity

An evaluation including classification of non-toxic and toxic substances as well as a rating according to the toxicities should be carried out. Possible rating numbers, with explanations, are presented in the table below. The descriptive terms are given in [2] - page 53 - *Casarett, Doull,s; Toxicology - The Basic Science of Poisons; Ed.2; 1980.*

| *Group* | *Included descriptive terms* | *Probable oral lethal dose for humans (mg/kg)* |
|---|---|---|
| 1 | Practically nontoxic<br>Slightly toxic | >15 000<br>5 000 - 15 000 |
| 2 | Moderately toxic | 500 - 5 000 |
| 3 | Very toxic | 50 - 500 |
| 4 | Extremely toxic | 5 - 50 |
| 5 | Supertoxic | <5 |

## d) Therapeutic Doses

An investigation of therapeutic doses is typically based on oral and 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* | *Included dose intervals (smallest therapeutic dose)* |
|---|---|
| 1 | >1000 mg |
| 2 | 100-1000 mg |
| 3 | 10-99 mg |
| 4 | 1-9 mg |
| 5 | <1 mg |

## e) Limits

Acceptance limits swabs for the substances should be calculated according to company procedures. From the acceptable amount (MACO) and the area in product contact, the swab limit can be calculated (see also 4.2.4, page 9):

$$\text{Limit} = \frac{\text{MACO}}{\text{Area in product contact}}$$

As evident from the description of how to calculate swab limits, the product combination and the area of the product contact surfaces have to be known. During this study, an evaluation of the combinations of substances in the different equipment classes could be carried out. If for example only one substance has a very low swab limit, it could be recommended to produce it in another train. Low swab limits usually results in very ambitious cleaning processes, and very low detection limits of the analytical methods.

| **Rating Group** | **Descriptive terms** | **Rationale** |
|---|---|---|

| | | |
|---|---|---|
| 1 | High limit | Most probably detectable on equipment by visual evaluation |
| 2 | Moderately high limit | Probably detectable on equipment by visual evaluation |
| 3 | Moderately low limit | Possibly detectable on equipment by visual evaluation |
| 4 | Low limit | Probably not detectable on equipment by visual evaluation |
| 5 | Very low limit | Impossibly detectable on equipment by visual evaluation |

### f) Other Scientific Rationales

Other scientific criteria than those suggested in section 6.4 a)-e) (page 23 – 26) can be used.

## 6.5 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 swab 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.
Choice of common, general residual limit

Evaluate if the lowest calculated limit is reasonable to apply on all substances. If that is the case, this swab 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.

Criteria for the validation of the cleaning processes:

1. For the substances with common, general swab limit, it is required that the substance with the lowest solubility 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 6.4 a)-f) (page 23 – 26) 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 four 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* | b): Solubility | c): Toxicity | d): Ther. dose | e): Swab limit | f): Other |
|---|---|---|---|---|---|---|---|
| Esubstance | III | 2.3 | 1 | 4 | 3 | 4 | NA |
| Fsubstance | IV | 2.2 | 1 | 2 | 4 | 4 | NA |
| Csubstance | III | 2.1 | 1 | 3 | 2 | 4 | NA |
| Lsubstance | III | 1.9 | 1 | 3 | 3 | 4 | NA |
| Osubstance | II | 2.8 | 2 | 2 | 3 | 4 | NA |
| Msubstance | II | 2.5 | 2 | 2 | 3 | 3 | NA |
| Psubtance | III | 2.2 | 1 | 2 | 3 | 4 | NA |
| Rsubstance | I | 1.6 | 2 | 3 | 3 | 4 | NA |
| Tsubstance | I | 1.8 | 1 | 2 | 3 | 4 | NA |

* Each figure is the mean value for different questions answered by operators and supervisors.

The lowest limit is 22 µg/dm$^2$ (Fsubstance), but the general limit was set to 40 µg/dm$^2$ since all the other substances have a limit above 42 µg/dm$^2$. Therefore, Fsubstance will be tested according to criterion no 2 (section 6.5 a, page 26). Substances with the lowest solubility in used solvents in each class will be tested (according to criterion no 1). In this case three substances will be tested at a limit of 40 µg/dm$^2$. The results from the rating is presented in the following figure.

| Criterion for validation | Class | Substance | Swab | Comments |
|---|---|---|---|---|

| | | | | **limit** | |
|---|---|---|---|---|---|
| 1. | General limit) | NA | Fsubstance | 22 μg/dm$^2$ | Tested due to lower limit than general limit |
| 2. | Worst Case in each class | I: | Rsubstance | 40 μg/dm$^2$ | |
| | | II: | Qsubstance | 40 μg/dm$^2$ | |
| | | III: | Esubstance | 40 μg/dm$^2$ | |
| | | IV: | NA | NA | Fsubstance only product, tested at low limit |

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 example for all the Trains within CleanCompany resulted in 20 worst cases to test. This is considerably less than 55 which would be the case without the rating. But it is more than 6 which should be the ideal case, and this is due to many cleaning classed identified instead of the ideal case with one class for each equipment train. However, the choice was to partly use cleaning methods effective for each product class.

The WCR 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 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 table 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.

# 7.0 Determination of The Amount of Residue

## 7.1 Introduction

This section provides a practical guidance how the amount of residue in cleaned equipment can be determined based on requirements from regulatory authorities [1] – page 53 -, actual requirements on analytical validation [2] – page 53 - and experience.

The section covers specific requirements on analytical and sampling methods validation for cleaning validation purposes. Further examples of sampling methods are given and a short recommendation on use of analytical methods. Several formulas for residue quantitation are proposed.

Whereas the acceptance limit ($M_{per}$) is a calculated figure (See section Acceptance Limits) and represents the specification for the equipment cleanliness, the amount of residue (M) in the equipment is the target value of the system[1] and must be determined by suitable methods. Principally the determination proceeds in two steps. These are the sampling and the quantitation of the contaminant in the sample.

Because the decision on acceptable cleanliness of the equipment bears potential risk for the product quality, it must be made based on correct and scientifically sound values for M (and $M_{per}$, see section Acceptance Limits). Therefore the method for determination of M must be suitably validated [1] – page 53. For suitable validation at least the specificity, sensitivity and recovery should be determined.

For validation, a surface similar to the equipment surface can be spiked with the expected contaminant, subsequently the contaminant can be recovered and analyzed by the methods to be validated. If possible both the sampling and the analytical method should be validated together (as a chain) at least for recovery and sensitivity (Limit of Quantitation - LOQ, or Limit of Detection - LOD).

## 7.2 Validation Requirements

### General

The requirements for analytical methods validation are defined in [2] – page 53. According to [2] – page 53 - there are four types of analytical methods with principally different validation requirements (Table 1). This list should be considered

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[1] The system is defined by: the equipment, the cleaning the sampling and the analytical methods and by the product to be cleaned out of the equipment.

typical for the analytical procedures cited but occasional exceptions should be dealt with on a case-by-case basis. It should be noted that robustness is not listed in the table but 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. The criteria can be documented in a written general policy or in a Validation Plan. However there should be one Validation Report per method validated, summarizing the specific results.

**Table 1: Requirements List**

| **Type of Analytical Procedure:** | **Identification** | **Testing for Impurities** | | **Assay** |
|---|---|---|---|---|
| | | **Quantitative** | **Limit** | |
| **Characteristic:** | | | | |
| Accuracy | - | + | - | + |
| Precision | | | | |
| Repeatability | - | + | - | + |
| Intermediate Precision | - | +1) | - | +1) |
| Specificity2) | + | + | + | + |
| Detection Limit | - | -3) | + | - |
| Quantitation Limit | - | + | - | - |
| Linearity | - | + | - | + |
| Range | - | + | - | + |

| | |
|---|---|
| - | Signifies that this characteristic is not normally evaluated. |
| + | Signifies that this characteristic is normally evaluated. |
| 1) | In cases where reproducibility has been performed, intermediate precision is not needed. |
| 2) | Lack of specificity of one analytical procedure could be compensated by other supporting analytical procedure(s). |
| 3) | May be needed in some cases. |

It is usual to employ the requirements for "Testing for Impurities" when validating cleaning validation analytical methods. The requirements for "Quantitative Testing for Impurities" can apply for example in cases, where a method should be suitable for several possible acceptance limits[2] and therefore quantitation of the residue over a certain range may be necessary. The requirements for "Limit Testing for Impurities"

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[2] 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 change overs.

can apply for example in cases, where the method should be suitable for one specific acceptance limit[3].

In the following some aspects of analytical methods validation specific to cleaning validation are emphasized. For further details refer to [2] – page 53.

According to [2] – page 53 - specificity is a basic requirement for all types of analytical methods. In 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 characterize the unknown impurities, develop and validate suitable analytical methods. However this can be an unacceptably time consuming task.

In this case a method which detects **all** potential impurities together can be suitable even, when it is not specific for each of the impurities. For example in a case, where it is sure that **only non volatile** impurities occur, the dry residue determination could be a suitable method (which is specific for the sum of non volatile impurities), provided the validation requirements according to Table 1 are satisfied (e.g. sensitivity). Then for the acceptance of the equipment for the following production it must be assumed that the whole 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 completion of a cleaning validation study an unspecific method (e.g. dry residue) may be used for the routine checks after cleaning of an equipment by the validated cleaning procedure. The precondition for this practice is, that during the validation study it was 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 the sampling and analytical methods together. This can be achieved for example by spiking of a surface equivalent (material, polish grade) to the equipment surface with different known amounts of the impurity. Subsequently the impurity is recovered and analyzed by the same sampling and analytical methods, which will be used for the cleaning validation study. The overall results of this procedure are then compared to criteria for detection or quantitation limits as defined in [2] – page 53. The limits may subsequently be validated by the analysis of samples known to be near at the limits.

The measured values below LOQ should be reported as = LOQ (worst case approach). For example if LOQ is 10 mg/l, the measured blank 7 mg/l and the measured residue amount 3 mg/l, the calculation should be: M = 10 - 10 = 0 mg/l (and not M = 3 - 7 = - 4 mg/l). Because the resulting 0 mg/l again are below LOQ, the reported value for this sample should be = LOQ = 10 mg/l. So for further

---

[3] E.g. the measured M must be compared with $M_{per} \leq 105$ g/Equipment.

calculations e.g. of the residue amount in the equipment 10 mg/l should be used (and not - 4 mg/l nor 0 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 = $M_{per}$) or lower. LOQ should never be higher than the specification ($M_{per}$).

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**

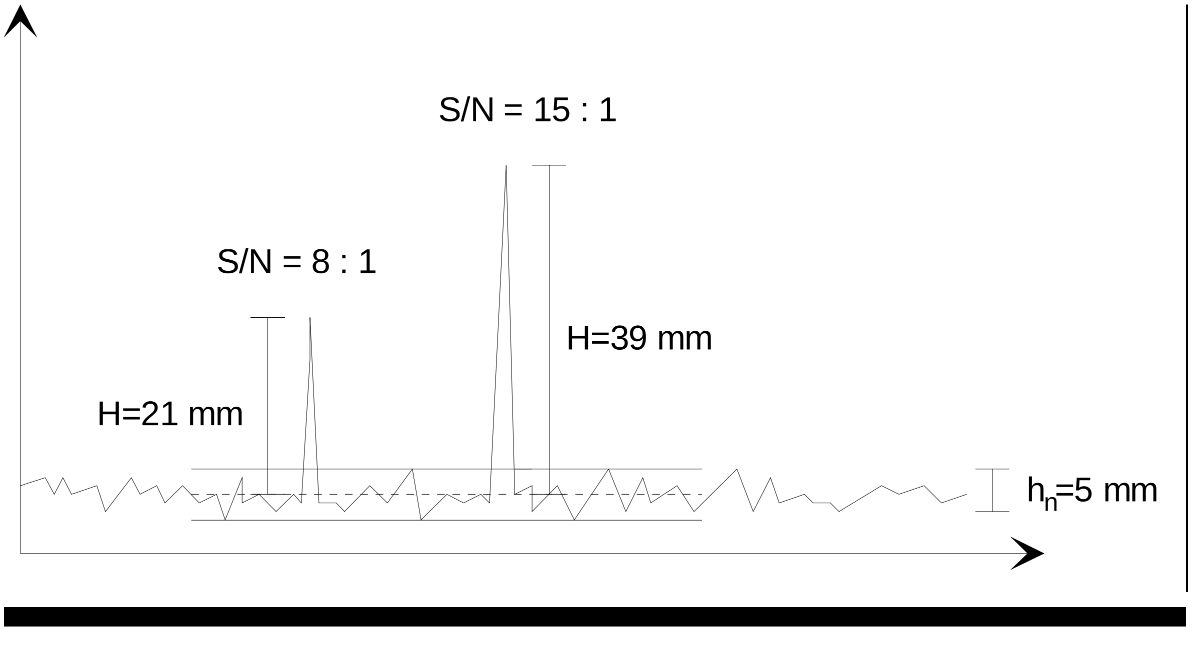
  This approach can only be applied to analytical procedures, which exhibit baseline noise (e.g. GC, HPLC). A signal-to-noise ratio (S/N) between 3 or 2:1 is generally considered acceptable for estimation the detection limit (LOD) and a typical ratio for acceptable quantitation limit is 10:1 (LOQ). The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

**Equation 1:** $S/N = (2 * H)/h_n$

H High of the peak from the mean baseline..

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

**Figure 1**



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

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

**Equation 2:** $\mathbf{LOD = (3.3 * \sigma)/S}$

**Equation 3:** $\mathbf{LOQ = (10 * \sigma)/S}$

| | |
|---|---|
| $\sigma$ | The standard deviation of the response. |
| S | The slope of the calibration curve. |

Where the $\sigma$ values may be obtained for example by analyzing an appropriate number of blank samples and calculating the standard deviation of these responses.

Alternatively a specific calibration curve can be studied using samples containing an analyte in the range of LOD or LOQ respectively. The residual standard deviation of a regression line or the standard deviation of y-intercepts of regression lines may be used as the standard deviation $\sigma$.

If possible, the recovery of impurity detection for cleaning validation should be determined for the sampling and analytical methods together This can be achieved for example by spiking of a surface equivalent (material, polish grade) to the equipment surface to be cleaned with different known amounts of the impurity. Subsequently the impurity is recovered and analyzed by the same sampling and analytical methods which will be used for the cleaning validation study. The overall measured results of this procedure are then compared to the actual amounts applied to the surface.
The recovery usually is determined during the accuracy determination and should be reported as % of the known applied amount of the impurity.

As example for quantitative impurity determination recoveries of ≥ 90 % are usually regarded acceptable. Therefore 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 (Equation 4) and recoveries of < 50 % should be omitted.

**Equation 4:** $\mathbf{M = M_{res} * 1/R}$

| | |
|---|---|
| M | True value for the amount of residue remaining in the equipment after cleaning. |
| $M_{res}$ | The measured amount of residue (sampling and then analytical measurement). |
| R | Recovery in % divided by 100 (for 75 %: 75/100 = 0.75). |

In Table 2 the requirements for the validation of “Quantitative Testing for Impurities“ according to [2] – page 53 - which were not addressed in the previous sections are summarized. Additionally “Acceptance Criteria“ are proposed. The proposed “Acceptance Criteria“ are examples only. Different “Acceptance Criteria“ may be established based on sound scientific rationale.

It is important to note, that the summarized requirements should be used for validation of “Quantitative Testing for Impurities“ during cleaning validation studies. According to section 0 validation of “Quantitative Testing for Impurities“ will be usually applied when it is foreseen to use the analytical method for several specifications of the residue amount in the equipment (= Acceptance Limit, = $M_{per}$). The lowest foreseen Acceptance Limit is referred as $M_{perMin}$, the highest as $M_{perMax}$ inTable 2. For one specific Acceptance Limit normally “Limit Testing for Impurities“ and corresponding validation of the analytical method is sufficient. If exceptionally for one specific Acceptance Limit the validation of “Quantitative Testing for Impurities“ will be used, then $M_{perMin} = M_{perMax} = M_{per}$.

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

**Table 2: Validation Requirements**

| **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) using 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 | |

| Experiments | Possible Acceptance Criteria |
|---|---|
| ***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 % wichever 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 |
| ***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 $M_{perMax}$ |

## 7.3 Sampling Methods

In the following some examples for sampling methods are presented. Depending on case-by-case considerations the most suitable method must be chosen. For all methods the sampling points must be fixed in a manner that the true contamination of the equipment will be reflected.

### Rinse, Wash Solvent Sampling

Usually the API equipment will be cleaned by several washing cycles (runs). Sometimes rinsing cycles/runs (e.g. to rinse out the washing solvent) may follow the washing cycles. 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 run of the routinely used cleaning procedure.

*Final rinse / final boil sampling*

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 washing or rinsing run (or any reaction) would not wash more than the same amount of residue out of the equipment as the analyzed solvent portion did.

The advantage of this sampling method is, that the whole equipment will be reached by the solvent, even difficult to reach locations which can not be disassembled (e.g. sealings, slots, condensers, piping). Therefore if appropriately designed this method will probably give the best picture of the amount of residue in the equipment.

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 Equation 5.

**Equation 5**: $M = V * (C - C_B)$

| | |
|---|---|
| $M$ | Amount of residue in the cleaned equipment in mg. |
| $V$ | Volume of the last rinse or wash solvent portion in l. |
| $C$ | 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. |

### Swab sampling

During swab sampling usually a small area of the cleaned equipment is swabbed with a pre-defined material and method (swab material, solvent, technique). Subsequently the swab is extracted and the extract examined by a suitable analytical method.

Then the quantified residue of the samples is 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.
- To choose the swabbing material such that its extractable materials do not interfere with the expected residue.
- To choose the sampling points such that they represent the worst case spots of the equipment.

The disadvantage of this sampling method for the often complex API equipment is, that difficult to reach areas (e.g. sealings, slots, condensers, piping) 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**:

$$M = (1 / WF) * (F_{tot} * \Sigma (M_i / F_i) / N) = (1 / WF) * (F_{tot} * \Sigma ((C_i - C_{Bi}) / F_i) / N$$

| | |
|---|---|
| $M$ | 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$^2$. |
| $M_i$ | 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). |

Exceptionally the first production batch (placebo batch) of the following product (or another placebo product) may be sampled and analyzed for impurities (for preceding product). As analytical methods usually chromatographic methods will be used (e.g. HPLC, GC, TLC).

### Stamps

In this exceptionally used sampling method, “coins“ (stamps) will be placed on appropriate sampling points in the equipment **during the manufacturing** of the previous product **and during cleaning**. After cleaning the contamination of the coins will be analyzed. The overall equipment contamination will be calculated by extrapolation of the coin's contamination to the whole equipment. For quantitation the coins may be first swabbed and the samples further analysed.

## 7.4 Analytical Methods

A sample isolated by any of the sampling methods (section 7.3, page 37) must further be analysed by a suitable analytical method (e.g. HPLC, GC, TLC, dry residue, TOC, UV, titration, conductivity, pH). The suitability of the method can be documented by appropriate validation as delineated in section 7.2 (page30).

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

# 8.0 Cleaning Validation Protocol

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.: ________________

## TABLE OF CONTENTS

### 8.1 Background

Equipment X is routinely cleaned after product Y (or group of products*) according to procedure XXX......

**If group of products describe rational for chosing this grouping strategy.*

Describe: Equipment.
Cleaning method.
Cleaning agents.

### 8.2 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.

### 8.3 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 must determine the number adequate for their operation.)*

In order for the cleaning procedure to be deemed valid all data generated during the study must be within the acceptance criteria detailed in section 8.7 (page 44) of this protocol.

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

*The equipment must 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 what ever system is in-place to ensure that equipment is not used).*

## 8.4 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* |

## 8.5 Sampling Procedure

Remove swab and rinse samples from the equipment as detailed in section 7.3 (page 37) of this guidance document.

**SWAB SAMPLES:**

See attached equipment sampling diagram (It is important to show clearly where the sampling locations are)

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 pertinent 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 validated 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.

All sampling details (swab and rinse) should be referenced in Table 1. Samples should then be sent to the QC department for analysis. Any relevant sample transfer conditions should be noted.

### 8.6 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

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.

## 8.7 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 (manu): _______ Date: _______

Verified (QA?): ______ Date: _______

- The swab / rinse sample acceptance criteria for product and cleaning agent residues 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 5 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).

Worst case sample residue values can be used to determine the worst case level of contamination on the equipment. (Alternatively, determine what the worst case swab level and use that as the limit.)

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.

## TABLE 1: SAMPLE REFERENCE TABLE

| **sample** | **to be tested for** | **area swabbed** | **total surface area (cm$^2$)** | **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** | **test for** | **sample volume** | **total volume of rinse** | **sample ref.** | **signed / date** |
| rinse sample 1 | Active | | | | |
| rinse sample 1 | Cleaning agent | | | | |

## 8.8 Deviations from protocol

Please indicate whether or not Planned/ Unplanned* deviations occurred during the completion of this Validation Protocol and give details of same.

Signed: _________________
Verified: ________________

*(*please delete as appropriate, If no deviations please delete both)*

# 9.0 Validation Questions

**Remarks:** **References given in this question and answer section refer to the Cleaning Validation Guideline of CEFIC APIC, published on September 6, 1999. (See [1] – page 53 - for reference.)**

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

***Advice:*** *Ref. Section 7.0 and 10.0*

*Companies must 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 may consider a periodic revalidation of cleaning methods, which are subject to variation (i.e. manual procedures etc.), as an additional precaution.*

**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 8.6*

*The answer to this question depends on individual situations. Typically, companies perform visual inspection and remove rinse samples as required.*

*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 litre 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 (chromato-graphic) technique. Start with a TLC-limit test (inexpensive and fast to validate, broad detection range – UV and specific derivatisation – 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 method 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.*

**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 not 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, 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.*

**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. Section 7.0 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 swap 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.*

# 10.0 References

**Bracketing and Worst Case Rating**

1. USP 24, The United States Pharmacopoeia, United States Pharmacopeial Convention, Inc., 12601 Twinbrook Parkway, Rockville, MD 20852.
2. Casarett and Doull; “Toxicology - The Basic Science of Poisons“; Macmillan Publishing Co, Inc. New York, Ed.2; 1980.
3. William E. Hall, Ph.D., Hall & Associates, Validation of Cleaning Processes for Bulk Pharmaceutical Chemical Processes, Journal of Validation Technology.

**Determination of the Amount of Residue**

1. PIC PH I/96, in “Pharm. Ind. 58, Nr. 4 (1996); Draft API GMP Guide, PIC, Geneva September ‘97; Guide to Inspections Validation of Cleaning Processes, FDA, 93; Draft Guidance for Industry Manufacturing, Processing, or Holding API, FDA, April 98.

2. Validation of Analytical Procedures: Q2A, Definitions and Terminology, ICH, October 1994; Q2B, Methodology, ICH, November 1996.

**Validation Questions**

1. Cleaning Validation in Active Pharmaceutical Ingredient Manufacturing Plants, CEFIC-APIC, September 6, 1999.

# 11.0 Glossary

| | |
|---|---|
| **$A_i$** | Area for the tested piece of equipment # i. |
| **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. |
| **$LD_{50}$** | Lethal Dose 50 in g/kg animal. The identification of the animal (mous 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"). |
| **$MACO_{ppm}$** | Maximum Allowable Carryover: acceptable transferred amount from the investigated product ("previous"). Calculated from general ppm limit. |
| **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. |
| **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 through 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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