Cleaning validation in active ingredient production

Principles, risk analysis/risk assessment, regulatory requirements and acceptance criterion PDE value

Jörg Koppenhöfer
gempex GmbH, Mannheim

Correspondence: Jörg Koppenhöfer, gempex GmbH, Besselstr. 6, 68219 Mannheim,

Germany; e-mail: public-relation@gempex.com

■ SUMMARY

The requirements on the part of the authorities (including the EU, FDA) for the
for the production of active pharmaceutical ingredients have steadily increased in recent years. In this context
the need to clean plants for the production of active pharmaceutical ingredients in the chemical industry according to validated chemical industry to be carried out according to validated procedures. This is also promoted in the corresponding regulations, especially if the plants are operated as multi-product plants.
During cleaning validation, documented proof must be provided that a defined and described cleaning procedure leads to the desired success in a reproducible manner. As a result of a successfully performed validation, sampling and analytical checks after cleaning can be reduced to a necessary minimum in routine operation. With regard to the definition of acceptance criteria for residue determination after purification, the revision of the GMP Guideline (Chapters 3 and 5 as well as Annex 15) and the presentation of the EMA PDE Guideline have provided a new approach, which is briefly presented here. The aim of the following article is to present the systematic implementation of a cleaning validation project for multi-product active substance plants in the chemical industry and also to address new approaches with regard to the determination of acceptance criteria.

■ ABSTRACT

Cleaning Validation of multi-purpose equipment in API production / Principles, risk analysis/risk assessment, regulatory requirements and acceptance criterion PDE value

The regulatory requirements of authorities (FDA, local German authorities, ...) on manufacturing of APIs have steadily increased in the recent years. This has also consequences with view to cleaning of equipment used for API production. This is also required within relevant guidelines to perform cleaning of equipment according to validated cleaning procedures especially when the manufacturing equipment is used to produce different products (multi-product equipment).
facturing equipment is used to produce different products (multi-product equipment).
In the Cleaning Validation the documented evidence must be provided that a defined and described cleaning procedure meets the requirements reproducibly As a result of a successful validation routine sampling and the analytical monitoring can be reduced to a necessary minimum.
With regard to the establishment of limits (acceptance criteria) a new approach is given by revision of the GMP-Guide (Chapter 3 + 5 and annex 15) and the PDE-Guideline of EMA which is briefly presented here.
Objective of the following article is to present the methodical execution of a cleaning validation project with regard to multi-product manufacturing equipment in the chemical industry and the special considerations that have to be made. Some new developments in the establishment of limits will be given as well.

1. Guidelines

There are numerous references in the literature on the subject of "cleaning validation* * [1-4]. The necessity of cleaning validation is mentioned in many places, but concrete statements on how this is to be carried out are missing. z mostly. The PIC/S-document (PI 006-3) [1] is particularly particularly helpful. In this article there are frequent references to this document, as it contains the most detailed guidelines and is the guidelines and in particular makes reference to :

■ KEY WORDS

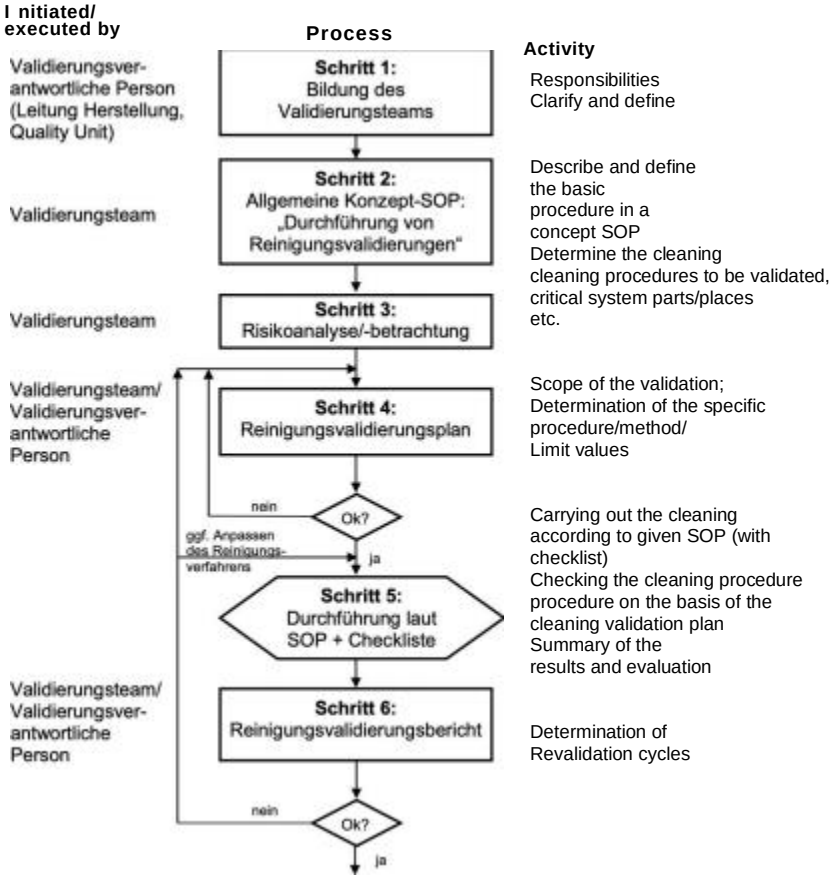
• Cleaning instructions/cleaning Cleaning checklist
- Risk analysis/risk assessment Cleaning" assessment
- Bracketing (equipment groups, product groups)
- Inspection and sampling plan
- Acceptance criteria (new PDE value)
- Assessment of validity Pharm. Ind. 81, No. 6,822-829 (2019)

- Aim of the cleaning validation
- Basic considerations and requirements for the cleaning procedures
- Requirements for documentation
- Requirements for equipment and personnel
- Requirements for the cleaning agents used
- Sampling, analytical methods and associated acceptance criteria

For the purpose of cleaning validation, statements can be found in the PIC/S document (PI 006-3), which are mentioned there in points 7.1.2; 7.1.3 and 7.1.4 [1]. In particular, it is emphasised in these passages that, in the case of a successful cleaning validation, sampling in routine operation should be dispensed with.

sampling in routine operation can be dispensed with. Further information can be found in Annex 15 of the EU GMP Guide [6]. However, the PIC/S document referred to here is the

the more detailed one.



2. Principle procedure of a Cleaning validation project

The process of a cleaning validation

The process of a cleaning validation project is basically divided into 6 steps. These steps are

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Figure 1: Process of a cleaning validation project (source of the figure: the author).

These steps are summarised in the flow chart shown in Fig. 1 and are described step by step in the following chapters 3 to 8.

3. Step 1: Validation team

3.1 Clarification of responsibilities

At the beginning of each cleaning validation project, the responsibilities are defined and the validation team is formed.

The first step is to clarify the question of product responsibility. According to the GMP guidelines/regulations, the management of the manufacturing/production and the management of the Quality Unit (QU) are responsible for the product. Both are responsible for ensuring that all GMP requirements - including those relating to cleaning of the production facility - are implemented in practice. The production management - together with the Quality Unit - is thus responsible for the entire validation. In active

In active substance plants, the task of managing the production is often assumed by the corresponding plant managers (see PI 006-3, point 2.7.1 [1]). These specifications are usually already made in the higher-level validation master plan.

3.2 Formation of the validation team

In order to manage the extensive tasks of a validation project, the formation of a so-called validation team has proven itself in practice. The production management, together with the quality unit management, determines the persons responsible for the special tasks of validation. For extensive projects, the appointment of a person for project coordination has proven to be successful in practice. In the validation team, the scope and the concrete implementation of the upcoming validation project are decided. All results from the validation are discussed and evaluated in the team. The validation team finally decides on the success of the validation project. In addition to the head of the validation team, the following are members of the team

of the production always include the head of the quality unit or their representatives. All team members have assigned roles and tasks (for examples, see the following text and PI 006-3, point 2.7.4 [1]).
In concrete terms, the following positions and responsibilities must be defined and documented for a cleaning validation project in the active substance area:
- Person responsible for the proper execution of the cleaning (e.g. plant foreman, management operator).
- Person responsible for the GMP-compliant documentation of the cleaning process (e.g. plant operator, operator).
- Person responsible for carrying out the samples and the analytical evaluation of the samples (e.g. laboratory staff).
- Person responsible for compiling the results and preparing the reports (e.g. project coordinator or validation coordinator).
- Person in charge of the quality assurance unit (e.g. QU representative)
These specifications are usually made in the superordinate validation master plan.

4.Step 2: Concept SOP "Perform cleaning validations

In a next step, the validation team must clarify whether a generally valid concept SOP for carrying out cleaning validations is available for the production site. This SOP must describe the basic procedure for cleaning validations and is usually coordinated with all persons concerned at the active substance plant in order to ensure a uniform procedure and to avoid misunderstandings. If such an SOP is not available, it must be drawn up and approved (see PI 006-3, point 4.1.1 [1]).

The concept SOP should describe the basic procedure in general terms. A flow chart such as the one shown in Fig. 1 can be helpful. Furthermore, all documents/forms/form templates that are mandatory for a cleaning validation and the required contents of these documents should be defined or created in the SOP.

Basically, specifications or information should be given on:

- Procedure of the cleaning validation process in general
- Structure, content and instructions for carrying out the risk analysis/risk assessment "cleaning".
- Structure and content of the cleaning validation plan
- Basic implementation of cleaning during validation Necessary documentation
- Structure and content of the cleaning validation report

5.Step 3: Carrying out the "cleaning" risk analysis/risk assessment

The risk analysis/risk assessment "Cleaning is the central document for defining the requirements for the cleaning of a specific installation. All critical points are collected and evaluated by the validation team. The following considerations should be made and documented：.

- Recording of the plant (parts of the plant)/equipment to be cleaned.
- Identify the products/contaminants handled in the plant/equipment.
- Recording of the cleaning procedures/steps used in the plant/equipment.
- Formation of product and equipment groups (bracke ting, worst-case consideration)
- final determination of the scope of validation

(see PI 006-3, points 2.5.6 and 7.3.4 [1]).

5.1 Recording of the plant/equipment to be cleaned

• A list is made of the entire plant/equipment and the cleanability requirements for each part of the plant are specified. The following points should be noted and documented： Is this a multi-product plant?

• - Is there a multi-product plant? For which products is the plant/equipment used?

• - Is the plant section operated in closed mode? Could

• Could contaminants enter the plant from the outside? - Where are the critical points for cleaning located?

• critical for cleaning (e.g. dead spaces, areas that are difficult to clean). The documentation can be done with the help of drawings (e.g. P&I diagram, construction drawings).

• - Which parts require very good cleaning? Are there CIP/SIP requirements?

• - Which cleaning media are used in each case?

•

5.2 Recording of products/contaminants handled in the plant/equipment

• All possible input materials, products, cleaning media and other substances that could enter the respective system parts are also recorded in a list (substance list). The following points must be observed and documented:

• - Which substances occur (input materials, degradation/decay products, by-products, media)?

• - Characteristic properties of the substances (e.g. toxicity, efficacy, solubility, pharmacological potency).

- Critical specifications (microbial, particulate requirements)
• - Which cleaning agents are used (are they possibly contaminants themselves and what properties do they have)?

5.3 Recording of the cleaning procedures/steps used for the plant/equipment

All cleaning steps or cleaning procedures of the entire plant are compiled and evaluated by the validation team. This is divided into critical and non-critical cleaning steps. Especially critical are the product changeover cleaning processes in multi-product plants. These must always be subjected to a cleaning validation.

5.4 Formation of product and equipment groups (worst-case considerations)/bracketing

In order to reduce the validation effort, it makes sense and is common practice, especially in the case of active substance plants, to make the following considerations/evaluations to increase efficiency and as a cost-saving measure and to document these in the risk analysis/risk assessment (bracketing) (see PI 006-3, point 7.3.5 [1]): Formation of equipment groups
Can the results of the validation of the corresponding cleaning process be transferred to other, similar plants (parts)?
This is possible if the cleaning process and the corresponding system geometry are almost identical (e.g. identical containers).
Formation of product groups
Is it possible to form product groups with similar properties when carrying out validation with regard to the properties of the contaminants to be cleaned?
The validation must then only be carried out for the contaminant with the worst properties (worst case). Very often, the solubility of the contaminant in the purification media used is used for this purpose. In certain cases, however, toxicity can also be decisive.
The documentation of the formation of product groups in the validation plan can be carried out, for example, on the basis of a list of substances according to Table 1.
For cleaning validation in the biotechnological production of active substances, the article by Münsch in Pharm Ind. 07/2018, p. 990 [11] provides a good insight.

5.5 Final determination of the Validation scope

Based on the results of the considerations in Chapters 5.1. to 5.4., the cleaning procedures/steps to be validated are finally derived on the basis of the critical systems/equipment and the critical protaminant occupancy and the result is documented in the risk analysis/risk assessment.

6. Step 4: Preparation of the cleaning validation plan

6.1 SOP on the cleaning procedure for the most critical substance or for critical plant parts/verification of the procedure

Before starting to draw up the cleaning validation plan, the SOP for cleaning the cleaning procedure to be validated must be available as a basic prerequisite. This must clearly define and describe how the cleaning is to be carried out. Validation is not possible until the cleaning procedure/step is clearly defined. Ideally, the cleaning procedure in question should be verified (test runs) before the cleaning validation is carried out. By dividing into product/apparatus groups, it is possible to sensibly reduce the relevant cleaning procedures (see chapter 5.4).

The documentation of the cleaning procedure with the activities to be carried out and the samples taken can be done, for example, using a cleaning checklist (see PI 006-3, point 7.4.4 [1]).

6.2 Preparation of the specific cleaning validation plan for each cleaning cleaning step

Depending on the results of the risk analysis/risk assessment, a cleaning validation plan is then drawn up by the validation team for each cleaning procedure/step defined there that is to be validated. This plan defines the scope of the cleaning validation for each individual process/step, describes the specific procedure and contains the testing and sampling plan as a core element. The validation plan is released in the validation team (see PI 006-3, pts. 7.4.1; 7.4.2 [1]).

In the testing and sampling plan, the critical points for cleaning defined in the risk analysis/risk assessment are described and a designated testing or sampling point is defined for this purpose (Tab. 2). Visual or analytical examinations can then be carried out at these inspection or sampling points.

6.3 Content of the cleaning validation plan

The content of the cleaning validation plan should be as follows (see PI 006-3, points 7.4.1; 7.10.1; 7.11.1 [1])

■ **Table 1**

Substance list for the formation of product families.

Contamination	Toxicity LD50 Rat	Solubility in Cleaning agent tion	Effective ciency	Active Substance content	Therapeutic dose	Cleanable quality (qualitative)	Comments
Intermediate products							
Input materials							
By-products							
Other substances							
Cleaning agents							

■ **Table 2**

Example testing and sampling plan (as part of the cleaning validation plan).

For plant/plant part :

Testing/sampling site/location	Test method	Comments	Acceptance criterion	Results	Signum
1: Container bottom	GC analysis	On preliminary product	< 0,1 % = 1000 ppm		
1: Container bottom	Evaporation residue	Final rinse	< 0,1 % = 1000 ppm		
2+3: Container dome	Visual	Dismantle manhole cover	visually clean		

- Description of the specific procedure for the validation (description of the procedure, the execution and the reference to the valid cleaning SOP).
- Description of the cleaning agents used
- Specification of the testing/sampling plan with:
- Place and time of sampling
-description of the test points (example see Tab. 2)
- Specification of the follow-up measures in case of deviations - Listing of the documentation to be prepared during validation
- Determination of the test methods/evaluation methods and the associated acceptance criteria for a successful validation. The following are usually considered as essential acceptance criteria: -10 ppm criterion (max. concentration of preliminary product

in the downstream product)

-1/1 OOO dose criterion (max. concentration for residues (product or cleaning agent) in the cleaning medium, depending on the lowest thepeutical dose and a safety margin)

-Visible Clean - no limit value, but part of the acceptance criterion for the validity of the procedure (see [9,10]).

-LD50 criterion (max. a fraction of the LD50 in a daily dose of the successor product).

- Permitted Daily Exposure (PDE) criterion max. concentration for residues depending on concrete scientific data, especially on toxicology (see Chapter 6.5).

The determination of the acceptance criteria depends on the individual case and should be scientifically justified. A visual inspection must always be carried out in any case. The analytical methods and procedures used must be validated and sufficiently sensitive to detect residues and contaminants.

Additional information on the content of a cleanliness validation plan can be found in the following articles [9,10].

6.4 Problems of the Swab test as a test method (practice)

The surface wipe test (swab test) is clearly described in the regulations as a suitable test method. It should be used in combination with the examination of the final rinse(s) in order to detect both soluble and insoluble impurities (see PI 006-3, point 7.8.2 [1]).

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In the field of active substances, however, it is in most cases problematic in practice to use the Swab test at all, especially since sampling and validation of the Swab test are difficult.

The test is often not technically feasible because in many cases the actual critical points are not accessible or are difficult to access (e.g. due to the dimensioning of the anchor). The test often cannot be carried out in a technically sensible manner, since in many cases the critical points are not accessible or are difficult to access (e.g. due to the dimensions of the plant). This raises the question of whether a swab test must and can be used in large active ingredient plants.

However, the determination of residues in the final rinse water cannot always be used in all cases, as the results of these tests are significantly influenced by the following factors,

$$PDE\backslash mg / d\sim\backslash = \frac{NOAEL[\hat{}\hat{}\sim i \bullet BW\backslash kg\backslash}{F\backslash.F2.F3.F4.F5}$$

NOAEL (No Observed Adverse Effect Level)

BW(body weight): Assumptions: EMA: 50 kg; FDA: 60 kg.

Fl to F5: Safety factors to compensate for risks.

Fl: Interspecies extrapolation: values from 1-12; differences human/animal,

z. e.g. rat: 12; dog: 2; human: 1

F2: Interindividual variability: human/human differences: usually set at 10.

F3: Study duration: values from 1-10, e.g. short-term, less than 4 weeks: use 10.

F4: Toxicological severity: values from 1-10; severity of effect: for high toxicity, use 10.

F5: Additional factor: values from 1-10; variable: if LOAEL (Lowest Observed Adverse Effect Level) is used instead of NOAEL: 10.

Figure 2: Formula for calculating the PDE value (source of the figure: EMA guideline [5] and ICH Q3C [7]).

whether any residues adhering to the walls of the equipment can actually be easily removed during cleaning and whether the residues dissolve well in the cleaning medium. Therefore, precise investigations are necessary with regard to the dissolving behaviour of the selected cleaning medium, whereby, for example, the parameters of solvent quantity, temperature and exposure time must also be taken into account. The results of these investigations must be incorporated into the development of the corresponding cleaning process.

In practice, an analysis of the final rinse using various analytical methods (e.g. evaporation residue, TOC, ...) in combination with visual controls (e.g. optical, endoscopic) has often proved successful in the field of active substances.

6.5 The PDE value as an acceptance criterion (practice)

The PDE value is clearly recommended in the newer regulations for the determination of acceptance criteria in the validation of the purification of medicinal products [5, 6]. This value should result in a limit value for which lifelong exposure does not represent any harm to the patient. Clinical and non-clinical studies in humans and animals are included, taking into account the most harmful effect (side effect), dosage, toxicology and other points. For the calculation, a "dose descriptor" is first defined:

•NOAEL (No Observed Adverse Effect Level)
Highest administered dose of a substance at which no significantly increased findings requiring treatment (no adverse effect) are detectable.

This is included in the following calculation formula (cf. Fig. 2).

Once all the above parameters have been determined and can be traced back to scientific considerations (e.g. toxicology), the PDE value can be calculated [5-8].

Evaluation of the PDE value from practice

The PDE value must be calculated according to the specifications of the new guidelines/regulations and stated in the documents for cleaning validation (risk assessment or plan). However, due to the many correction factors that are included in the calculation and the sometimes rather arbitrary assumption of many boundary conditions, it no longer represents the simplification and scientific improvement of the determination of acceptance criteria (limit values of residues) originally intended when it was introduced. Although the F4 factor, i.e. toxicology, is a very important variable, in practice the calculation often cannot be carried out meaningfully without fundamental knowledge of all the boundary conditions involved and the associated correction factors (e.g. duration of application). The use of expert knowledge is therefore absolutely necessary and urgently recommended. This approach poses serious problems for most active ingredient producers, since much of the data is often not (yet) known at the start of a cleaning validation project and cannot be determined ad hoc. Thus, a meaningful calculation is not possible, which in turn diminishes the scientific approach of this method.

In practice, however, it has so far been shown in many cases (approx. 85%) that the calculation according to the bis pharm 1/1 OOO dose criterion as the acceptance criterion, and thus there are no practical changes to the previously established procedure with regard to the acceptance criteria. Nevertheless, the PDE value should be calculated and documented according

to the rules (see [9], p. 1074 ff.).

7.Step 5: Carry out cleaning during validation

Based on the cleaning validation plan, the cleaning SOP or the cleaning checklist belonging to the instruction, the cleaning validation is carried out for each process to be validated. For this purpose, usually 3 cleaning runs are carried out in succession and documented. It must be ensured that the cleaning instructions (SOP/checklist) are always followed. Deviations are entered in the checklist and thus recorded. In this way, if acceptance criteria (deviations) are not met, appropriate measures can be taken. The deviations are assessed in the cleaning validation report (see chapter 8) and the resulting measures are specified.

A successfully completed cleaning instruction/checklist is the prerequisite for a successful cleaning validation run. This also includes the date and signature of the person carrying out the cleaning steps (see PI 006-3, points 7.4.5; 7.4.6; 7.8.1).

8.Step 6: Preparation of the Cleaning Validation Report

In a cleaning validation report, the results and deviations are finally compiled for each individual validation run (intermediate report) or for all 3 runs together (overall report). This can be done using tables/diagrams or similar tools. The preparation of interim reports is appropriate if there are longer periods between the individual validation runs due to the worst-case selection (e.g. half a year).

Deviations that might have occurred during the cleaning validation run are:

• - Cleaning was not carried out according to the specified SOP/checklist.

• - Samples were not taken at the designated places or were forgotten.

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The analytical results of the samples taken are outside the acceptance criteria specified in the validation plan.

- The documentation for carrying out the cleaning or evaluating the samples is incomplete (e.g. missing raw data).

These possible deviations are considered in the report, evaluated and, if necessary, concrete follow-up measures are determined. If this is an interim report, these follow-up measures may already apply to the next validation run. These measures could be：

- The personnel must be trained accordingly.
- The validation run carried out must be repeated due to technical problems.

If the following critical deviations occur, it is usually assumed that the entire validation must be repeated (all 3 runs) to prove the validity of the cleaning process.

- Reconsider/modify/adapt the acceptance criteria for a test method.

criteria for a test method

- Modification of the cleaning procedure (SOP) in important steps
- Revise/amend the cleaning validation plan with regard to procedure, critical points/acceptance criteria.

After the execution of the usually 3 successful cleaning runs, all essential results are summarised once again in an overall report and the cleaning procedure is assessed with regard to validity. This assessment is important and should be explicitly mentioned in the report. In addition, information is given on the trigger for a revalidation of the cleaning procedure. Revalidation is usually carried out, for example, in the event of serious plant modifications or changes to the cleaning process.

The validation report is released by the production management and the management of the quality unit (for the report see PI 006-3, points 7.4.3; 7.3.6; 7.3.8; 7.5.1 [1]).

9. Conclusion

The implementation of cleaning validation in the active substance sector, but also in the pharmaceutical sector, can be made particularly efficient and cost-saving if, in practice, apparatus groups and product families can be formed according to the above explanations (bracketing/worst-case consideration). These measures - combined with a structured approach - can considerably reduce the validation effort.

It is thus possible, e.g. by forming the ap- parate group "container" ， to clean an entire

It is also possible to conclude the cleaning validation of a single container in a container store by carrying out the cleaning validation of a single container in this store, if all containers do not differ significantly from each other in their design and in their product occupancy.

It is also feasible, e.g. by forming the product family "water soluble substances", to introduce and validate a single cleaning process for a particular plant that removes the most poorly water soluble substance handled in the plant. This eliminates the need to establish and validate many different cleaning procedures.

The procedure presented here for carrying out cleaning validations in the active substance area has already proven itself in practice in many places. The clearly structured and detailed planned procedure can increase the efficiency of the entire cleaning validation project enormously.

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