Doris Borchert, PhD, Michael Hiob, PhD, Jens Hrach, PhD

# GMP Series

## A Pharma Guide to Cleaning Validation

### How to meet Agency Expectations and Establish Accepted Limits

Maas & Peither
GMP PUBLISHING

PDF Download

Excerpt from the GMP Compliance Adviser

German National Library Cataloguing in Publication Data
A catalogue record for this book is available from the German National Library at http://dnb.ddb.de



First edition, 06/2018

Published by
Maas & Peither AG – GMP Publishing
Karlstraße 2
79650 Schopfheim (Germany)
Phone: +49 7622 66686 70
Fax: +49 7622 66686 77
www.gmp-publishing.com
service@gmp-publishing.com

ISBN: 978-3-95807-099-8

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# Official requirements and agency expectations

*Michael Hiob, PhD*

**Here you will find answers to the following questions:**
- Which regulatory requirements apply to cleaning validations?
- How is the life cycle approach transferred to cleaning validations?
- What does a cleaning instruction regulate?
- What is the meaning of "hygienic design"?
- How is the risk evaluation of the cleaning process, equipment and products carried out?
- What must be observed during manual and automatic cleaning processes?
- How are the limits for cleaning validations defined?
- What sampling methods are permitted?
- How is the effectiveness of the cleaning process monitored?
- How are cleaning validations documented?

## 1 Principles

A number of different GMP regulations underline the need for effective cleaning processes. The cleaning processes should take the physicochemical properties of residues, the cleanability of the equipment and the impact of the manufacturing process and its environment into account.

A **cleaning validation** should provide documented evidence that when a defined cleaning process is used to clean a machine, there is a high degree of probability that residues from the previously manufactured product and cleaning agent residues are below the defined limits.

In so doing, a cleaning validation contributes in many ways to the safety of the
- manufactured products,
- personnel working in Production and
- the environment.

### 1.1 Life cycle concept

Annex 15 of the EU GMP Guidelines states that the manufacturer has to monitor the critical aspects of facilities, products and processes for the entire life cycle (Annex 15, Section 1.1). This requirement also applies to cleaning processes.

The life cycle approach to cleaning validation means that after validation, the state of control of the process is monitored on an ongoing basis (*ongoing process verification*). **Ongoing process verification** is more than just a simple revalidation of individual test batches. It requires a control system that delivers data continuously on the effectiveness of the cleaning process. In the case of automatic cleaning processes that are controlled and monitored using Process Analytical Technology (PAT), ongoing process verification is possible from the outset. Traditional validation is therefore not required.

The life cycle of cleaning validations can be divided into three phases (see figure 1).

The cleaning process is developed during the **design phase** (see chapter 5 *Design phase*). The equipment and surfaces to be cleaned during the cleaning process are also determined at this time. If the quality by design approach to development outlined in the ICH Q8 Guideline is taken, a control strategy for controlling and verifying the cleaning process must be designed. This control strategy is meant to ensure that the results are reproducible and comply with the specifications. If it is developed at an early stage, i.e. during the design phase, control and verification can be moved directly to routine

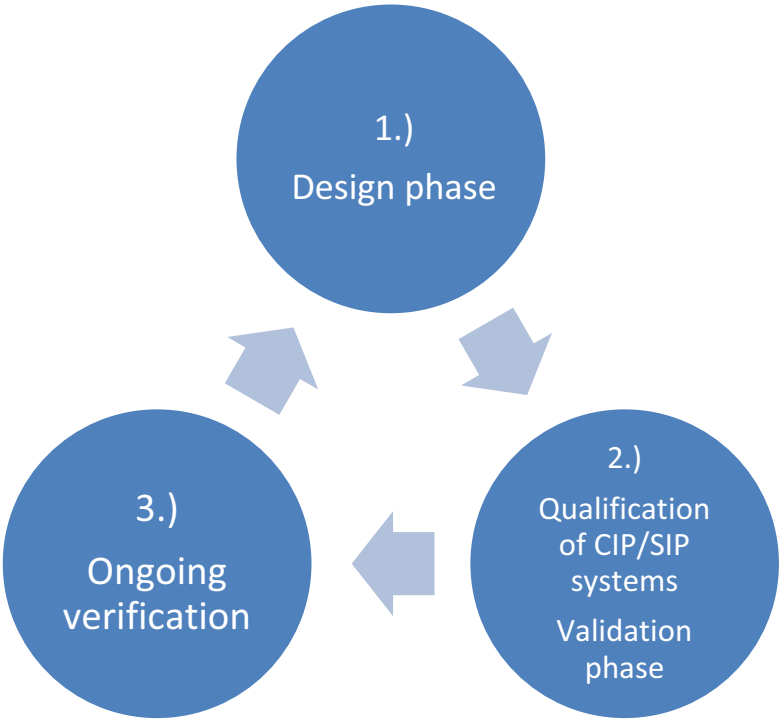


*Figure 1 The life cycle of the cleaning validation*

cleaning. A classic batch-related cleaning validation is then no longer required because it is continuously and prospectively ensured that the cleaning process is achieving the desired result. In all other cases where a functioning control strategy has not been established in advance, the suitability of the cleaning process must be proven in the traditional way using a predetermined number of batches.

Sufficient data should be collected during the **validation phase** (chapter 6 *Validation phase*) to prove the safety of the cleaning process. A challengeconcept should be used to show that the cleaning process also functions under unfavourable, but real conditions.

In the case of (semi-) automated processes, the cleaning validation includes the qualification of the cleaning systems.

**Ongoing verification** of the cleaning result (see chapter 7 *Ongoing verification/revalidation*) begins after the initial validation. The scope and time intervals of the individual validation activities depend on the respective cleaning process and relevant equipment, and their definition is risk-based.

## 1.2 Quality risk management

The revised version of Annex 15 not only stipulates that a life cycle approach be taken, it also demands the use of quality risk management (Annex 15, Section 1.7). Carrying out a risk analysis before selecting the products and equipment to be cleaned during the cleaning validation was common practice before the revision of Annex 15; it is now mandatory.

In principle, every cleaning process must be validated. When specifying the scope of validation, similar equipment can be pooled into **groups** – provided they are cleaned using the same process. The selection of equipment for the cleaning validation is risk-based, e.g. based on specific constructive characteristics.

Products can also be **grouped**, and the selection of products to be used during the cleaning validation is also risk-based. The cleanability and pharmacological and toxicological properties of the active ingredients are taken into account (see also chapter 6.2 *Group formation*).

A cleaning validation focuses primarily on the surfaces that come into contact with the product. Depending on how the process is conducted, however, additional external factors that influence the cleaning result can be taken into consideration. During the initial risk analysis, it is important to take a

required information must often be collected from different sources (e.g. the cleaning agent supplier, the equipment manufacturer, the contract giver in the case of contract manufacturing), evaluated, and distributed to different recipients (e.g. external service providers, points of service within the company). Coordinated methods of communication and a harmonised change control procedure between the parties concerned are essential prerequisites for successful information management.

# 2 Regulatory aspects

## 2.1 European requirements

Article 8 (2) of *Commission Directive 2003/94/EC* stipulates that the premises and manufacturing equipment must be laid out, designed and operated in such a way as to minimise the risk of error and permit effective cleaning and maintenance. Contamination, cross-contamination and other influences that negatively affect the quality of the product should be prevented.

The EU Directive is implemented in the *EU GMP Guidelines*. Chapter 3 *Premises and Equipment* and Chapter 5 *Production* cover various aspects of cleaning and cleaning validation. They contain the following requirements:

- The layout and design of the premises and equipment must permit effective cleaning and prevent cross-contamination (Chapter 3 General).
- Where starting and primary packaging materials are exposed to the environment, walls, floors and ceilings should be smooth and not shed particulate matter and should permit easy and effective cleaning and, if necessary, disinfection (Chapter 3.9).
- Open channels, gutters, etc. should be avoided where possible, but if necessary, they should be easy to clean and disinfect (Chapter 3.11).
- In cases where dust is generated, actions must be taken to prevent cross-contamination and facilitate cleaning (Chapter 3.14).
- The equipment used during cleaning should not be a source of contamination (Chapter 3.37).
- Effective and reproducible cleaning processes should be used to prevent cross-contamination (Chapter 5.19).
- A quality risk management system that also covers the cleaning processes should be used to control cross-contamination (Chapter 5.20).
- The outcome of the quality risk management process should be used to determine the technical and organisational measures required to control the risk of cross-contamination during manufacture, maintenance and cleaning. The cleaning processes themselves must not represent a contamination risk (Chapter 5.21).

The requirements for the cleaning validation process are specified in Annex 15 *Qualification and validation* of the EU GMP Guidelines. The following is of particular importance:

- All validation activities (including cleaning validation) must be planned and should follow a life cycle approach .(Chapter 1.1)
- They should only be carried out by suitably trained personnel who follow approved procedures (Chapter 1.2).
- The key elements of the validation (and of the cleaning validation) should be described in a validation master plan (Chapter 1.4).
- A quality risk management approach should be taken (Chapter 1.7).
- All of the analytical test methods used during the cleaning validation must be validated (Chapter 9.1).
- The cleaning validation should confirm the effectiveness of the cleaning processes used on surfaces that comes in contact with the product. *Simulating agents* can be used instead of starting materials if scientifically justified (Chapter 10.1).

[...]

# 3 Cleaning process requirements

## 3.1 Principles

Cleaning processes should remove residues from surfaces that come in contact with the product to prevent the cross-contamination of subsequent products. At the same time, measures must be put in place to maintain the cleaning status over a specific period of time.

The cleaning process and cleaning agent used must not put the medicinal product or manufacturing equipment at risk. This applies, for example, to cleaning agent residues, to residual humidity after cleaning or to the integrity of surfaces that have contact with the product.

Residues adhere to surfaces because of adhesive effects such as van der Waals forces, electrostatic attraction or mechanical bonding caused by the roughness of the surface material. The cleaning process is meant to overcome these adhesive forces, e.g. by mechanical effect, soaking/dissolving, emulsifying, by oxidation of the residues or the formation of salts, which makes it easier to dissolve the residues in water so that they can be rinsed off.

The success and efficiency of the cleaning process depends on the following parameters being controlled by the respective method:

- amount and/or concentration of the cleaning agent
- mechanical measures
- cleaning time and temperature and
- the number of rinsing cycles required

Written cleaning instructions must be created for all components that come in contact with the product.

When creating cleaning instructions, the **aspects** in figure 3 must be taken into account.

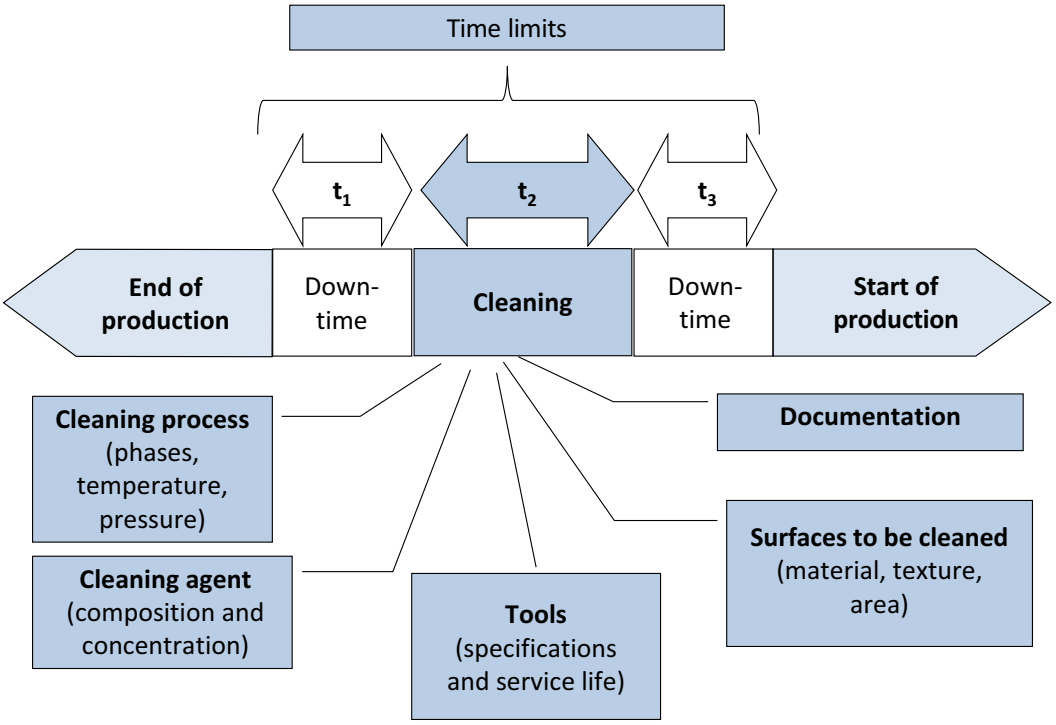


*Figure 3 Determination of cleaning instructions*

When the key elements of the cleaning process have been established, the details must be outlined in a cleaning instruction. The regulatory **content** shown in figure 4 must be kept in mind.

| **Regulatory content of cleaning instructions** |
|---|
| • responsibilities for the implementation and monitoring of cleaning<br>• components and surfaces to be cleaned<br>• application areas of the cleaning process (defined products or product groups)<br>• instructions on cleaning between similar or different products<br>• name of cleaning agent and aids (e.g. brushes, fibre materials, pumps) including information about when/how often they must be replaced<br>• time, duration and sequence of cleaning and rinsing<br>• type and duration of drying after cleaning<br>• information about process control (e.g. temperature control)<br>• instructions on checking the cleaning efficiency<br>• instructions on labelling cleaned devices and devices that have not been cleaned<br>• measures for protecting against external influences after cleaning (e.g. covering using hoods)<br>• maximum permitted hold times: from the end of production to the start of cleaning and/or from the end of cleaning to the start of production<br>• instructions on additional cleaning that may be required<br>• safety instructions, e.g. on handling inflammable solvents or hot water<br>• instructions about documentation (e.g. in the form of a cleaning record or a system log book) |

*Figure 4 Regulatory content of cleaning instructions*

Cleaning instructions must be related to specific equipment or groups of equipment and to specific products or product groups.

The responsible staff members must receive training on the cleaning instructions. The effectiveness of the training, especially in the case of manual cleaning processes, must be regularly checked on site.

The instructions and documentation must be available on site. They should be regularly checked for deviations and trends and to ensure they are up to date. It should be clear from the equipment documentation,

- which product was previously manufactured on the equipment
- when the equipment was cleaned
- until when the cleaned equipment can be used before it needs to be cleaned again.

A **log book** should be kept for important or critical pieces of equipment in which all validations, calibrations, maintenance work, cleaning work and repairs are entered with the date and name of the persons who carried out these activities.

An effective cleaning process must be able to remove product residues or their degradation products, residual cleaning agents and microbiological contamination until a specific limit is reached. Other potential sources of contamination such as lubricants, packaging material remnants, cleaning material remnants (e.g. brush hairs, textile fibres) and every type of airborne contaminant (dust particles) must also be considered. The rationale for setting **limits** for the transfer of product residues, cleaning agents and microbial contamination should be logical and based on the materials involved. The limits should be achievable and verifiable.

A cleaning process interacts with

- the physicochemical properties of starting materials, including their impurities from the supply chain
- the design of the manufacturing equipment
- the climatic, particulate and microbiological environmental conditions
- the technical equipment used for cleaning and
- the personnel that carry out and monitor the cleaning process

These interactions influence the effectiveness of the cleaning process. Knowing and mastering them is essential if the cleaning process is to be validated.

## 3.2 Manual cleaning processes

Manual cleaning processes depend strongly on the persons who carry them out. The process instructions should describe cleaning in as much detail as possible to minimise variations between the individual persons. Regular instruction on critical aspects of cleaning are mandatory for manual cleaning processes.

For more complex cleaning processes, it is particularly important that the process is divided into individual stages (e.g. pre-rinsing, cleaning, 2x rinsing, drying). Each stage should have a defined and verifiable objective and/or result. The next stage should only begin when the previous cleaning stage has been successfully completed. The effectiveness of each stage should be considered during the cleaning validation. This can be achieved by installing suitable in-process controls. The impact of each cleaning stage on the final result should be known and should be controllable.

Manual cleaning can be carried out where

[...]

# 4 Risk management

## 4.1 Principles

Annex 15 stipulates that all validation activities (including the cleaning validation) must be risk-based. This does not only apply to the risk analysis of the cleaning process. A holistic approach must be taken during which all the factors are evaluated that can affect the cleaning status of the equipment. Monitoring residue limits alone no longer meets the current standards.

To facilitate a holistic approach, a risk management concept must be established to ensure that all of the risks involved in the life cycle of the cleaning process can be identified, evaluated and controlled (see figure 6). These risks also include indirect contamination through the ventilation system or cross-contamination through personnel. Not all of these risks are tested during the subsequent cleaning validation, but it is important to consider all of the factors that could affect the cleaning status of the equipment at the beginning. A fishbone diagram (Ishikawa analysis) can be used to do this. A decision must then be made on the measures that can be taken to cover the risks that are not examined during the cleaning validation. In the above-mentioned example, this affects the qualification of the ventilation system, change management and personnel training.

This type of approach requires close cooperation between all participants across the individual life-cycle phases. Overlapping risk management activities, e.g. cooperation with R&D departments or contract manufacturers, must be coordinated. Information concerning the risk management process must be shared with all of the participants. A functioning information and change management system that includes all of the stakeholders (e.g. active ingredient manufacturers, contractors , suppliers of cleaning agents, equipment manufacturers) is essential so that risks and changes to risks can be contemporaneously recorded.

The following chapters only contain a general description of the risk management process for the cleaning validation because cleaning processes and their focus differ greatly.

**Deviations** during the cleaning validation are normally caused by decisions that were made during the development of the equipment or cleaning process. A holistic risk management system must cover the entire life cycle of a machine or cleaning process from development to decommissioning. It also includes additional risks, e.g. those of a technical (health and safety, environmental protection) or economic nature.

The planning and reporting systems in the different operational areas must be networked to facilitate a comprehensive risk analysis. Test results (e.g. quality controls, stability testing, environmental monitoring) must be processed in such a way that they allow conclusions to be drawn and risk evaluations to be carried out. Previous evaluations (e.g. product quality reviews, self-inspection reports, failure statistics, management reviews) should be included in the risk evaluation.

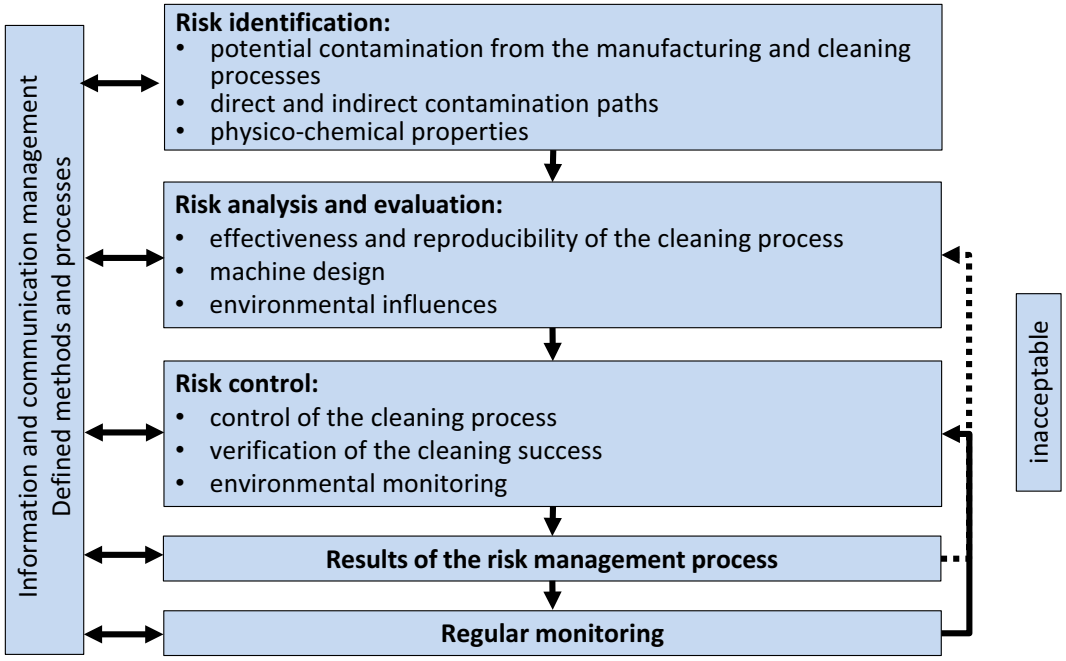


*Figure 6 Risk management system of the cleaning process*

## 4.2 Risk identification

The first step in a risk management process is the identification of risks. Logically speaking, risks that are not recognised cannot be evaluated and controlled.

During risk identification, the question of what sort of contaminants could get into the product (potential contamination) and how (potential paths of contamination) is asked.

### Potential contamination

Risks related to the cleaning process include all circumstances that may affect the results and reproducibility of the cleaning process and directly affect the safety of the medicinal product. If the cleaning process is to be controlled effectively, it is important that the causes of risk and/or sources of interference are recognised so that preventive actions can be taken.

Risks and sources of interference include design-related weaknesses, the effectiveness of the monitoring and control devices in place, or product attributes that complicate the cleaning process (see figure 7).

The aim of the cleaning process is the reduction of contaminants to a level below a defined acceptance level. Whether a contaminant is considered relevant depends on its identity and amount. During the risk identification

**a)** potential contaminants that could cause cross-contamination must be recognised and

**b)** the probability of these contaminants exceeding the defined limits must be determined.

The quality of potential contaminants depends on the nature of the processed substances (active substances and excipients) and other substances from the manufacturing environment (e.g. lubricants, dust, filter and seal abrasion). The degree of contamination and the risk of cross-contamination can be influenced, in particular, by the way in which the process is carried out (e.g. multi-purpose equipment versus dedicated equipment or containment versus open process).

| Contamination risks |
|---|
| Risks that result from the **design of the equipment** include, for example,<br>• places that are difficult to access<br>• adsorbent surface materials<br>• seals<br>• gaps<br>• dead legs<br>• built-in components |
| Risks that result from the **cleaning process** include, for example,<br>• reproducibility in the case of manual processes<br>• pump control in the case of automatic processes<br>• blocked spray nozzles<br>• inappropriate spray patterns<br>• pressure and temperature monitoring |
| Risks that result from the **product** include, for example,<br>• highly potent active substances<br>• adhesion phenomena<br>• excipients that stain or smell excessively<br>• incrustation tendency |

*Figure 7 Contamination risks*

## Contamination paths

In addition to identifying potential contaminants, the way in which the contaminant gets into the medicinal product must be also be identified. *Direct* cross-contamination is caused by surfaces that come in contact with the product (e.g. insufficient cleaning) or the process environment (e.g. through the ventilation and air-conditioning equipment). *Indirect* cross-contamination is spread from other areas to the equipment (e.g. pallet trucks, conveyor belts, tools). It is not possible to evaluate the effectiveness and reproducibility of cleaning processes if environmental influences are ignored. The EMA *Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities* states:

"(…) *accidental cross-contamination can result from the uncontrolled release of dust, gases, vapours, aerosols, genetic material or organisms from active substances, other starting materials, and other products being processed concurrently, as well as from residues on equipment, and from operators' clothing.*"

Not all of these aspects can be addressed individually during the cleaning validation. Aspects that are not related to the process such as the ambient air quality, for example, are examined on other occasions, e.g. during the qualification of the air conditioning and ventilation system.

## Physicochemical properties

The physicochemical behaviour of contaminants is another important factor during risk identification.

- *solubility of active ingredients* and their degradation products in the cleaning media:
  If the active ingredient is supplied by a number of different manufacturers, different crystal modifications and impurity profiles with different solubilities are possible.
- *Solubility of the cleaning agents* in water:
  Solubility should be so good that a defined rinsing time ensures that the maximum acceptable daily intake (ADI) is not reached. A list of ingredients and $LD_{50}$ values is useful when evaluating the toxicological risk of the cleaning agent. The manufacturer of the cleaning agent should name at least one analytically determinable lead substance and an appropriate analytic method.
- The *tendency of the product to form encrustations:* This can lead to poorer cleanability. For this reason, extended hold times prior to cleaning should also be examined during the cleaning validation.

# Establishment of limits

*Doris Borchert, PhD, Jens Hrach, PhD*

**Here you will find answers to the following questions:**
- What is the significance of the EMA demanding that limit values should be calculated based on scientific evidence?
- How are scientifically based limit values calculated?
- What significance does the new PDE approach have for established cleaning processes and for validations that have already been completed?
- How are the permitted residual levels in a sample calculated?
- What limit values apply to the microbiological state?

## 1 Paradigm shift in the establishment of limits for the validation of cleaning processes

*Jens Hrach, PhD*

Requirements for the establishment of limit values first appeared in the FDA Guide to Inspections of Validation of Cleaning Processes in 1993: "The firm's rationale for the residue limits established should be logical based on the manufacturer's knowledge of the materials involved and be practical, achievable, and verifiable. It is important to define the sensitivity of the analytical methods in order to set reasonable limits. Some limits that have been mentioned by industry representatives […] include analytical detection levels such as 10 PPM, biological activity levels such as 1/1000 of the normal therapeutic dose, and organoleptic levels such as no visible residue".

The following three established acceptance criteria were used routinely in the years that followed:
- The 1/1000 of the dose criterion: no more than 0.1% of the normal therapeutic dose of any product will appear in the maximum daily dose of the following product.
- The 10-ppm criterion: No more than 10 ppm of any product will appear in another product.
- The *visually clean* criterion: after cleaning, residues may not be visible on the production equipment. The visibility limit for many substances is approximately 4 µg/cm$^2$.

PIC/S PI 006-3 recommended that the strictest of these criteria should be used in a worst-case scenario.

These acceptance criteria became the subject of criticism because they are based on assumptions that have no scientific basis. The substance-specific properties are not taken into account in the case of the 10-ppm and "visually clean" criteria, because the limitation is based purely on quantity. In the case of the 1/1000 of the dose criterion, the therapeutic dose is taken into consideration; however, it says nothing about other potential effects of the active ingredient. As the number of newly developed highly active substances increased, the calls for a new scientifically based approach to the establishment of limit values for cleaning validations became louder.

The first *Concept Paper* called "Dealing with the Need for Updated GMP Guidance Concerning Dedicated Manufacturing Facilities in the Manufacture of Certain Medicinal Products" published by the EU Commission and the EMA in 2005 had already pointed out the need for science-based risk analysis to be the basis for the establishment of limit values for cleaning validations. However, it took an additional 10 years for this subject to be included in the final EMA guideline.

In 2010, the ISPE (International Society for Pharmaceutical Engineering) published its recommendations on establishing limit values, the so-called Risk-MaPP ("Risk-Based Manufacture of Pharmaceutical Products – A Guide to Managing Risks Associated with Cross-Contamination").

With the revision of the requirements in the EU GMP Guidelines (Chapter 3, Chapter 5 and Annex 15) and the introduction of the so-called *PDE guideline* of the EMA ("Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities"), the previously valid and officially accepted acceptance criteria became obsolete and have been gradually replaced by the **PDE value** (*Permitted Daily Exposure*).

The PIC/S (Pharmaceutical Inspection Cooperation Scheme) has aligned its **GMP Guide PE 009** with the revised Annex 15 of the EU GMP Guidelines for validation and qualification. This document is the equivalent of the EU GMP Guidelines for the countries that belong to the PIC/S.

It is expected that the PIC/S document on qualification and validation (PIC/S PI 006) will be revised to reflect the new requirements.

## 1.1 Current statutory requirements

What exactly do the regulations say and what does this mean for the establishment of limit values for use during the cleaning validation?

Section 3 of **Chapter 3 "Premises and Equipment"** of the EU GMP Guidelines states that dedicated facilities are required for medicinal products when

[...]

## 2 The PDE Guideline of the EMA

*Jens Hrach, PhD*

The official title of the EMA Guideline that became effective in June 2015 is "Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities", and this describes its content appropriately.

The document describes the method used for determining a health-based exposure limit (PDE) for cross-contaminants using an assessment of toxicological and pharmacological data from both clinical and non-clinical areas. A deviation from this method for safely determining limit values is certainly permitted, but only if adequate justification is provided.

In reality, it will be difficult to come up with a solid argument against this general demand for a scientifically based substance-specific determination of limit values. The document offers those experts

who are responsible for risk assessment the option of selecting a suitable method for determining a PDE.

## 2.1 How to determine the PDE – principles of a risk assessment

The **PDE** is defined in the EMA Guideline as "a substance-specific dose that is unlikely to cause an adverse effect if an individual is exposed at or below this dose every day for a lifetime." The PDE (Permitted Daily Exposure) can be used synonymously with the ADI (Acceptable Daily Intake).

The general idea of **risk assessment** includes:
- the determination of the potential damaging effect of a substance by analysing the relevant data
- the identification of the *"critical effect"*
- the identification of *dose descriptors* for the critical effects and their use as the starting point of the risk assessment (*reference value*),
- the deduction of a limit value by offsetting the reference value using safety factors.

The terminology used in the above-mentioned regulations is not without its problems. Production staff now has to deal with technical terms from the area of pre-clinical and clinical development or risk assessment: uncertainty is preprogrammed. To facilitate a better understanding of the requirements, the key points above are explained in more detail. This can only be done here on a general level that can be understood by non-professionals. It does not, however, enable an inexperienced person to carry out the respective assessment themselves. The PDE guideline stipulates that the persons carrying out the assessment have to provide a signed CV to prove that they are qualified.

During the risk assessment, an assessment of the relationship between exposure to a substance and the occurrence of an adverse reaction is carried out. The risk can be described as follows:

*risk = damaging effect of a substance (toxicity) x exposure*

A great white shark is a good example of this. A great white shark is a very dangerous animal; the damaging effect of its teeth is enormous. The probability of being bitten in countries such as Germany, Austria or Switzerland (= exposure) is very slight. Therefore, there is no risk.

This can be transferred to cleaning validation: the damaging effect of a substance (toxicity) is an intrinsic constant property, i.e. a substance will always have an identical effect as long as the dose remains the same (this is a key assumption of the risk assessment).

To minimise the risk – depending on the specific damaging effect – exposure to the cross-contaminants must be reduced because it is the only variable that can be influenced. It must be reduced to such an extent that the risk to patients' health caused by daily and unintentional intake over a lifetime through the next product is practically 0, as required by the definition of PDE.

To achieve this, the damaging effect of the substance must first of all be determined. Unfortunately, a human long-term limit value for medicinal products is practically never available directly; it must be calculated using the trial data available. The question is: what data is available, how can it be accessed and how is it handled?

Pre-clinical development knows many different toxicological and pharmacological endpoints that are tested in a targeted way during separate studies. Possible study types include:
- pharmacokinetic testing
- sub-chronic and chronic testing with repeat dosing
- reproductive toxicity/mutagenicity testing
- carcinogenicity studies
- effects on the organic system and CNS

These are just a few of the possible endpoints, and the number of possible study types is much larger.

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Doris Borchert has been working as an editor for Maas & Peither GMP Publishing since 2008. She is responsible for reviewing expert articles. Prior to this, she worked in the pharmaceutical industry for 15 years in quality assurance, process technology and production and was actively involved in many audits and inspections.

After graduating in Pharmacology and receiving a PhD in Pharmaceutical Technology, she started her professional career at Gödecke AG in Freiburg (later Pfizer GmbH) where she developed an FDA-compliant cleaning validation concept for a newly built solids factory. Other areas of activity included the qualification of facilities and laboratory equipment and the development of a quality assurance system. After moving to process technology, she worked as Project Manager, responsible for product transfers and the validation of NDA approvals. As a member of an international co-development team, she worked on current issues such as quality by design, Six Sigma and Right First Time. She was also responsible for optimising the process used during the manufacture of solid dosage forms. Doris Borchert has been using her expertise to support the editorial department of Maas & Peither GMP Publishing since 2008.

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He was Head of the Qualification/Validation expert group for more than ten years and is co-author of the aide mémoire "Inspektion von Qualifizierung und Validierung in pharmazeutischer Herstellung und Qualitätskontrolle" (Inspection of qualification and validation in pharmaceutical manufacture and quality control). He is also involved in a number of international organisations, including the European Medicines Agency (EMA).

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Jens Hrach received his PhD in Biology from Heidelberg University in collaboration with the Merck KGaA Institute of Toxicology. He then began his professional career as a Toxicologist at Forim GmbH, a subsidiary of Dr. Knoell Consult. He spent several years there evaluating toxicological studies, the risk evaluation of pharmacological active ingredients and deriving limit values in the area of safety in the workplace (calculation of OEL). In 2012, he was awarded the status of European Registered Toxicologist (DGPT). He was certified as Pharmacovigilance Manager in 2013.

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