World Health Organization

DRAFT WORKING DOCUMENT FOR COMMENTS:

Points to consider when including Health-Based Exposure Limits (HBELs) in cleaning validation

Please send your comments to **Dr Valeria Gigante**, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (gigantev@who.int), with a copy to Ms Claire Vogel (vogelc@who.int) before **21 September 2020**. Please use our attached Comments Table for this purpose.

Our working documents are sent out electronically and they will also be placed on the WHO Medicines website (http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en/) for comments under the "*Current projects*" link. If you wish to receive all our draft guidelines, please send your email address to jonessi@who.int and your name will be added to our electronic mailing list.

SCHEDULE FOR DRAFT WORKING DOCUMENT QAS/20.849/Rev.1

Points to consider when including Health-Based Exposure Limits (HBELs) in cleaning validation

Description of Activity	Date
During the Fifty-third Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP), the WHO Secretariat was recommended to revise Appendix 3, *Cleaning Validation* of Annex 3, *Good manufacturing practices: guidelines on validation* (WHO Technical Report Series, No. 1025, 2019).	October 2018
The update of Appendix 3, *Cleaning Validation*, was further discussed during the informal consultation on Good Practices for Health Products Manufacture and Inspection.	July 2019
Following a recommendation by the ECSPP, the WHO Secretariat was recommended to develop a *Points to consider* document on cleaning validation introducing the possibility of using HBEL-based approaches to setting safe cleaning limits and establishing a common understanding on which to develop guidelines that are appropriate for all stakeholders.	October 2019
Preparation of first draft working document.	April – May 2020
Mailing of working document to the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations (EAP) inviting comments and posting of the working document on the WHO website for public consultation	May – June 2020
Consolidation of comments received and review of feedback. Preparation of working document for discussion.	July – August 2020
Discussion of the feedback received on the working document with a working group of inspectors during virtual meetings in lieu of the planned Consultation on Good Practices For Health Products Manufacture and Inspection.	12 -13 August 2020
Preparation of working document for next round of public consultation.	August 2020
Mailing of revised working document inviting comments, including to the EAP, and posting the working document on the WHO website for a second round of public consultation.	17 August – 21 September 2020

Consolidation of comments received and review of feedback. Preparation of working document for discussion.	September 2020
Presentation to the Fifty-fourth meeting of the ECSPP.	12-16 October 2020
Any other follow-up action as required.	

46

47

Points to consider when including Health-Based Exposure Limits (HBELs) in cleaning validation

1. Introduction and background

The World Health Organization (WHO) has published the guideline entitled *Good manufacturing practices for pharmaceutical products: main principles* in the WHO Technical Report Series, No. 986, Annex 2, 2014 *(1)*.

The WHO *Supplementary guidelines on good manufacturing practice: validation* were published in 2006 and were supported by seven appendices. The main text *(2)* and its appendixes *(3, 4, 6, 7, 8, 9)* were revised between 2006 and 2019. Appendix 3, relating to cleaning validation *(5)*, was not updated at that time. Its revision, however, was discussed during an informal consultation held in Geneva, Switzerland, in July 2019. The outcome of the discussion was presented to the WHO Expert Committee on Specifications for Pharmaceutical Products (ECSPP) meeting in October 2019. The ECSPP acknowledged the importance of harmonization in regulatory expectations with regards to cleaning validation approaches. The Expert Committee recommended a "Points to consider" document be prepared in order to describe the current approaches used in cleaning validation and highlighting the complexities involved in order to establish a common understanding. A revision of the relevant appendix would then be considered by the Expert Committee thereafter.

Many manufacturers produce products in multi-product facilities where there is a risk of contamination and cross-contamination. Some of the main principles of good manufacturing practices (GMP) include the prevention of mix-ups and the prevention of contamination and cross-contamination. It is therefore important that manufacturers identify all risks for contamination and cross-contamination and identify and implement the appropriate controls to mitigate these risks.

These controls may include, for example, technical and organizational measures, dedicated facilities, closed systems, cleaning and cleaning validation.

It is strongly recommended that manufacturers review their existing technical and organizational measures, suitability of cleaning procedures and appropriateness of existing cleaning validation studies.

Technical controls, such as the design of the premises and utilities (e.g. heating, ventilation and air-conditioning {heating, ventilation and air conditioning (HVAC)}, water and gas), should be appropriate

for the range of products manufactured (e.g. pharmacological classification, activities and properties). Effective controls should be implemented to prevent cross-contamination when air is re-circulated through the HVAC system.

Organizational controls, such as dedicated areas and utilities, dedicated equipment, procedural control, and campaign production, should be considered where appropriate as a means to reduce the risk of cross-contamination.

It should be noted that the above examples are described in more detail in other documents. The focus of this document is on Health-Based Exposure Limits (HBELs) setting in cleaning validation

2. Scope

This document provides points to consider for a risk and science-based approach when considering HBELs, based on pharmacological and toxicological data, in cleaning validation.

This document further provides points to consider when reviewing the current status and approaches to cleaning validation in multiproduct facilities.

The principles described in this document may be applied in facilities where active pharmaceutical ingredients (APIs), investigational medical products (IMP), vaccines, human and veterinary medical products are manufactured. The principles may also be considered, where appropriate, in facilities where medical devices are manufactured.

This document should be read in conjunction with the main GMP text and supplementary texts on validation *(1-9)*.

3. Glossary

adjustment factor (safety factors). A series of modifying or safety factors are applied to take into account the fact that data from toxicological studies of differing types and durations in differing species have been used.

cleanability. The ability of a cleaning procedure to effectively remove material, cleaning agent residue and microbial contamination

cleaning validation. Documented evidence to establish that cleaning procedures are removing residues to predetermined levels of acceptability, taking into consideration factors such as batch size, dosing, toxicology and equipment size.

contamination. The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or on to a starting material or an intermediate or pharmaceutical product during handling, production, sampling, packaging, repackaging, storage or transport.

cross-contamination. Contamination of a starting material, intermediate product or finished product with another starting material or product during production.

Health Based Exposure Limits (HBELs)

See definition of Permitted Daily Exposure (PDE)

margin of safety. The margin of safety is the difference between the cleaning acceptance limit based on HBEL and the process residue data.

maximum safe carryover (MSC). The maximum amount of carryover of a residual process residue (API, cleaning agent, degradant, and so forth) into the next product manufactured without presenting an appreciable health risk to patients..

maximum safe surface residue (MSSR). The MSSR is the maximum amount of process residue that can remain on equipment surfaces and still be safe to patients. The MSSR is mathematically calculated dividing the Maximum Safe Carryover (MSC) by the total area of contact (MSC/Total).

permitted daily exposure (PDE). PDE represents 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.

point of departure. The dose at which a significant adverse effect is first observed, or the lowest-observed-adverse-effect level (LOAEL).

verification. The application of procedures to provide evidence through chemical analysis (e.g. after a batch or campaign) to show that the residues of the previous product and cleaning agents, where applicable, have been reduced below the scientifically set maximum allowable or maximum safe carryover level.

4. Historical approach

For details on the historical approaches in cleaning validation, see the WHO Technical Report Series, No. 1019, Annexure 3, Appendix 3, 2019 *(5).*

The acceptance criteria for cleaning validation recommended in historical GMP texts did not account for HBELs.

A limit based on HBELs should still be established. Historically established limits may be used as alert limits when these are more stringent than HBELs .

Where the historical approach cannot be satisfactorily justified, and in view of the risks of contamination and cross-contamination, the new approaches, as described below, should be prioritized and implemented.

5. New approaches

Historical cleaning validation approaches often merely showed that using a defined cleaning procedure achieved an objective of meeting historical limits. In many instances, no development work or cleanability studies were done nor was consideration given to toxicological data for establishing limits for cleaning residues.

Manufacturers should ensure that their cleaning procedures are appropriately developed and that their cleaning validation provides scientific evidence that residues of identified products that can be

manufactured in shared facilities are removed to safe levels, providing a high margin of safety to patients. Control measures should be implemented to mitigate the risks of contamination and cross-contamination.

This approach should include at least the following points (which are further described in the text below):

- risk assessment to identify hazards, analyse risks, and to identify risk controls;
- cleaning procedure development studies including cleanability studies, where applicable (e.g. new products or cleaning procedures);
- determination of technical and organizational controls;
- HBELs setting;
- selection of appropriate analytical procedures; and
- cleaning process control strategy.

Manufacturers should describe and implement their policy and approaches, including the points mentioned above, in a document such as a master plan.

Genotoxic and carcinogenic substances, degradants and other contaminants should be identified and their risks evaluated. Appropriate action should be taken where required *(11).*

5.1 Documentation

Risk management principles, as described by WHO and other guidelines on quality risk management (*10*), should be applied to assist in identifying and assessing risks. The appropriate controls should be identified and implemented to mitigate contamination and cross-contamination.

The policy and approaches in cleaning and cleaning validation require that good scientific practices should be applied (including the use of appropriate equipment and methods). This should be described in a cleaning validation master plan. Development studies, cleaning and cleaning validation should be performed in accordance with predefined, authorized standard operating procedures, protocols and reports, as appropriate. Records should be kept.

The design and layout of documents, and the reporting of data and information, should be in compliance with the principles of good documentation practices *(12)* and should also meet data integrity requirements *(12)*.

5.2 Equipment

Cleaning validation should cover direct product contact surfaces. Non-contact surfaces should be included in cleaning validation where these have been identified as areas of risk.

Authorized drawings of equipment should be current, accurate and available. Equipment surface area calculations should be documented and justified. The source data for these calculations should be available. The calculated values should be used in the calculations in cleaning validation.

All equipment and components, including those that are difficult to clean (for example, sieves, screens, filters and bags (such as centrifuge bags) should be considered in cleaning validation and calculations. Where the need is identified, dedicated equipment and or components should be used.

5.3 Cleaning agents

Cleaning agents (including solvents and detergents used in cleaning processes) should be selected with care. They should be appropriate for their intended use. The selection of the relevant cleaning agent should be scientifically justified.

There should be proof of effectiveness and appropriateness of the selected cleaning agent.

Other points to consider include the concentration in which these are used, their composition and removal of their residues to an acceptable level.

When cleaning agents are used in cleaning processes, these should be included in cleaning process development studies and cleaning validation.

5.4 Sampling

Historically, cleaning validation included different methods being applied to determine whether or not there was any residue remaining on surface areas after cleaning. The focus was mainly on product contact surface areas.

A combination of at least two or three methods should normally be used. These include, for example, swab samples, rinse samples and visual inspection. Visual inspection should always be performed. Swab sampling is the preferred other method to be used. Rinse samples should be taken for areas which are inaccessible for swab sampling.

Appropriate sampling procedures, swab material and sampling techniques should be selected and used to collect swab and rinse samples. The detail should be clearly described in procedures and protocols. The number of swabs, location of swabbing, swab area, rinse sample volume and the manner in which the samples are collected should be scientifically justified.

Swab and rinse sample methods should be validated. Recovery studies for swab and rinse sampling should be performed.

Where microbiological sampling is carried out, the microbiological method should also be validated.

The manner in which collected samples are stored (if required) and prepared for analysis should be appropriate, described in detail and included in the cleaning validation.

5.5 Cleanability studies

Before a new cleaning procedure is validated and adopted for routine use, a cleanability study should be performed in order to determine the appropriateness of the procedure for removing for example product residue, cleaning agents and microorganisms. For cleaning procedures that have already been validated where the data show that the cleaning procedure is effective and consistent, or where risk assessment indicated that cleanability studies may not be required, this may be considered acceptable.

5.6 Risk management

Risk management should be implemented with a focus on the identification, evaluation, assessment and control of risks to mitigate the risk of contamination and cross-contamination.

These controls should include technical and organization controls in order to deliver a validated cleaning process *(10).*

5.7 Guidance for Health-Based Exposure Limits (HBELs) setting

Manufacturers should establish, document and implement a company-wide policy on HBELs setting for shared facilities.

The appropriateness of the production and control of various APIs or various products in shared facilities should be evaluated on the basis of scientific data and information.

This is applicable to legacy products as well as when new products are planned to be introduced into a facility, for example, through a change control procedure.

Procedures should be established and implemented describing how the scientific and toxicological data and information are obtained and considered and how HBELs are established.

Data and information should be gathered by a person with appropriate qualifications and experience in the field of toxicology and/or pharmacology. The data and information should be presented in a report. The data and information presented should be free from bias.

Where this service is outsourced by the manufacturer, appropriate measures should be put in place in order to ensure that the data obtained are reliable. GMP requirements, such as vendor qualification, agreements and other related aspects, should be considered.

Note: The HBEL value for the same substance sometimes differs when it is determined by different individuals. The reason for the difference between the values should be clarified and investigated.

The report for each substance should include scientific detail and information, as applicable, such as:

- substance identification
- chemical structure
- clinical indication
- mode of action
- route of administration *(Note: Where more than one route of administration is available, it may be necessary to calculate separate HBELs)*
- preclinical/nonclinical data, for example, of acute and repetitive dose studies
  - genotoxicity data
  - reproductive toxicity data
  - carcinogenicity data
  - data relating to highly sensitizing potential
- clinical data
- pharmacodynamics and pharmacokinetics
- identification of the critical effect(s)
- point of departure for the HBEL calculation(s)
- adjustment factors
- justification of the selected lead rationale (if calculations with different points of departure were made).

The report should be reviewed for its completeness and appropriateness by the manufacturer's designated internal personnel or by an appointed external persons. The person should have in-depth knowledge, appropriate qualifications and experience in the field of toxicology. A summary document may be prepared for each relevant substance and should contain information on the PDE value, and toxicity *(13).*

The scientific report and calculated PDE value should be used when defining the cleaning validation control measures.

Note: If no NOAEL is obtained, the lowest-observed-adverse-effect level (LOAEL) may be used. Alternative approaches to the NOAEL, such as the benchmark dose, may also be used. The use of other approaches to determine HBELs could be considered acceptable if adequately and scientifically justified (13).

Manufacturers should periodically consider new data and information on HBELs. Appropriate action, such as the updating of PDE reports, should be taken where required.

5.8 Acceptance criteria

The limits established in cleaning validation should be justified.

Some manufacturers have specified acceptance criteria based on carryover limits or limits reflected in some GMP guidelines. These limits may no longer be acceptable as HBELs and related toxicity data were not included in the determination of such acceptance criteria.

Criteria such as Maximum Safe Carryover (MSC)/Maximum Allowable Carryover (MACO) and Maximum Safe Surface Residue (MSSR) values should be calculated. Calculations and data should be available and comply with data integrity principles. The calculation should include values of PDE, maximum daily dose, batch size and total shared equipment surface areas.

MSSR should be calculated and presented, for example, in table form listing preceding and following product values. The cleanability value obtained should be considered in determining the acceptability of the procedure(s) and whether other controls including separate, dedicated facilities are required. (See Annex 1 as an example.)

The margin of safety (the distance between the analytical data and the HBEL base limit) should be identified.

5.9 Analytical procedures

Samples obtained in cleaning validation should be analyzed by using procedures that are validated for their intended use. The procedures should be developed in accordance with the principles of Analytical Quality by Design.

Specific methods, such as High-performance Liquid Chromatography (HPLC), should be used where appropriate. Non-specific methods including UV spectrophotometry should only be used where specific methods cannot be employed and their use can be justified, for example, based on the outcome of risk assessment.

Testing for total organic carbon (TOC) may be used where indicated and where justified.

Where analytical procedures were developed and validated off-site, the scope and extent of validation when these are transferred to the site, should be defined and justified. This includes procedures that are transferred from research and development laboratories to site laboratories. Analytical procedures should be able to quantify or detect residue levels at the maximum safe surface residue level. (For analytical procedure validation, see reference *6*.)

Manufacturers should ensure that the procedures remain in a validated state.

5.10 Data integrity

Data, information and results pertaining to, for example, HBELs, PDE reports, results obtained from cleaning validation and calculations, should be scientific and should be in compliance with the principles as contained in data integrity guidelines (*12*).

5.11 Cleaning validation and cleaning verification

Cleaning validation

The cleaning procedure should be validated *(5)*.

Cleaning validation should include proof of, for example, the applicability of the procedure to clean equipment that:

- had been kept in an unclean state for a period of time (dirty equipment hold time);
- are used after a product is planned (e.g. change from one product to another product);
- are used in a campaign, where multiple batches of a product are produced one after the other; and/or
- are stored in a clean state for defined periods of time (clean equipment hold time).

HBEL should be considered when establishing carryover limits in cleaning validation.

Cleaning verification

The company should describe the policy and approach to cleaning verification. Cleaning verification is where the effectiveness of the validated cleaning procedure is routinely verified. The approach may

include swab or rinse samples. The results obtained from testing on a routine basis should be reviewed and subjected to statistical trending.

5.12 Visually clean

Visually clean is an important criterion in cleaning validation. It should be one of the acceptance criteria used on a routine basis. Personnel responsible for visual inspection should be appropriately trained. Training records should be kept.

Where visual inspection is used as a quantitative method, then Visible Residue Limits (VRLs) should be determined. The process to determine the limit should be appropriately described in procedures and protocols covering, for example, concentrations, method of spiking, surface areas, material of construction and other conditions such as light (LUX level) and angles.

5.13 Cleaning process capability

The cleaning procedure should remain in a validated state. It is recommended that cleaning verification results and calculated process capability data be used to support this. For example, the results from cleaning verification sample analysis could be statistically trended. The capability of the cleaning process is then calculated by using an appropriate statistical process.

Data should be presented, for example, in graph form, and the capability of the process in relation to control limits and the margin of safety should be presented and discussed as part of continuous improvement over the life cycle.

5.14 Personnel

Personnel should be trained on the procedures and principles of cleaning and cleaning validation, including contamination and cross-contamination control, HBELs setting, equipment disassembly, visual inspection, sampling, testing and statistical calculations, as appropriate and based on their responsibilities.

5.15 Quality metrics and performance indicators

Aspects of cleaning validation and cleaning verification should be considered in quality metrics, with performance indicators identified and monitored.

5.16 Life cycle

Cleaning procedures, cleaning validation and cleaning verification should be included in the life cycle approach described by the company.

References

1. Guidelines on good manufacturing practices for pharmaceutical products: main principle. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, forty-eighth report. Geneva: World Health Organization; 2014: Annex 2 (WHO Technical Report Series, No. 986; https://www.who.int/medicines/areas/quality_safety/quality_assurance/TRS986annex2.pdf?ua=1, accessed 12 August 2020).
2. Good Manufacturing Practices: Guidelines on Validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fifty-third report. Geneva: World Health Organization; 2019: Annex 3 (WHO Technical Report Series, No. 1019; https://www.who.int/medicines/areas/quality_safety/quality_assurance/WHO_TRS_1019_Annex3.pdf?ua=1, accessed 12 August 2020).
3. Guidelines on heating ventilation and air-conditioning systems for non-sterile pharmaceutical products and Part 2: interpretation of guidelines on heating ventilation and air-conditioning systems for non-sterile pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. Geneva: World Health Organization; 2019: Annex 2 (WHO Technical Report Series, No. 1019; https://www.who.int/medicines/areas/quality_safety/quality_assurance/WHO_TRS_1019_Annex3.pdf?ua=1, accessed 12 August 2020).
4. Good manufacturing practices: guidelines on validation. Appendix 4. Validation of water systems for pharmaceutical use. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fortieth report. Geneva: World Health Organization; 2006: Annex 3 (WHO Technical Report Series, No. 937; https://www.who.int/medicines/areas/quality_safety/quality_assurance/WHO_TRS_1019_Annex3.pdf?ua=1, accessed 12 August 2020).
5. Good manufacturing practices: guidelines on validation. Appendix 3. Cleaning validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. Geneva: World Health Organization; 2019: Annex 3 (WHO Technical Report Series, No. 1019; https://www.who.int/medicines/areas/quality_safety/quality_assurance/WHO_TRS_1019_Annex3.pdf?ua=1, accessed 12 August 2020).
6. Good manufacturing practices: guidelines on validation. Appendix 4. Analytical procedure validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. Geneva: World Health Organization; 2019: Annex 3 (WHO Technical Report Series,

No. 1019; https://www.who.int/medicines/areas/quality_safety/quality_assurance/WHO_TRS_1019_Annex3.pdf?ua=1, accessed 12 August 2020).

7. Good manufacturing practices: guidelines on validation. Appendix 5. Validation of computerized systems. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. Geneva: World Health Organization; 2019: Annex 3 (WHO Technical Report Series, No. 1019; https://www.who.int/medicines/areas/quality_safety/quality_assurance/WHO_TRS_1019_Annex3.pdf?ua=1, accessed 12 August 2020).

8. Good manufacturing practices: guidelines on validation. Appendix 6. Guidelines on qualification. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. Geneva: World Health Organization; 2019: Annex 3 (WHO Technical Report Series, No. 1019; https://www.who.int/medicines/areas/quality_safety/quality_assurance/WHO_TRS_1019_Annex3.pdf?ua=1, accessed 12 August 2020).

9. Guidelines on good manufacturing practices: validation, Appendix 7: non-sterile process validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. Geneva: World Health Organization; 2015: Annex 3 (WHO Technical Report Series, No. 992; https://www.who.int/medicines/areas/quality_safety/quality_assurance/Annex3-TRS992.pdf, accessed 12 August 2020).

10. WHO guidelines on quality risk management. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-seventh report. Geneva: World Health Organization; 2013: Annex 2 (WHO Technical Report Series, No. 981; http://digicollection.org/whoqapharm/documents/s20093en/s20093en.pdf, accessed 12 August 2020).

11. ICH M7 Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk.

12. Guidance on good data and record management practices. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. Geneva: World Health Organization; 2016: Annex 5 (WHO Technical Report Series, No. 996; https://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf, accessed 12 August 2020).

13. Guideline on data integrity. Draft for comments. Geneva: World Health Organization; 2019 (working document QAS/19.819; https://www.who.int/medicines/areas/quality_safety/quality_assurance/QAS19_819_rev1_guideline_on_data_integrity.pdf?ua=1, accessed 12 August 2020).
14. Guideline on setting health-based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities, European Medicines Agency, November 2014.
15. Guideline on setting health-based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities. EMA, 2014 (EMA/CHMP/CVMP/ SWP/169430/2012).
16. ISPE Baseline, Pharmaceutical Engineering Guide, Volume 7 – Risk-based manufacture of pharmaceutical products, International Society for Pharmaceutical Engineering (ISPE), Second edition, July 2017.
17. Guideline on setting health-based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities and Questions and answers on implementation of risk-based prevention of cross-contamination in production. European Medicines Agency, 2018.
18. ASTM E3219-20. Standard Guide for Derivation of Health-Based Exposure Limits (HBELs)
19. ASTM E3106. Standard Guide for Science-Based and Risk-Based Cleaning Process Development and Validation.

Further reading

- Comparison of Permitted Daily Exposure with 0.001 Minimal Daily Dose for Cleaning Validation. May 02, 2017. Ester Lovsin Barle, Camille Jandard, Markus Schwind, Gregor Tuschl, Claudia Sehner, David G. Dolan. Pharmaceutical Technology. Volume 41, Issue 5, pages 42–53.
- Questions and answers on implementation of risk-based prevention of cross-contamination in production and Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities. EMA, 2018 (EMA/CHMP/CVMP/SWP/246844/2018).
- ICH Topic Q3A (R2). Note for guidance on impurities testing: Impurities in new drug substances (www.ich.org).

Annex 1. Using Health-Based Exposure Limit (HBEL) to assess risk in cleaning validation*

Permitted Daily Exposure (PDE)

The Permitted Daily Exposure (PDE) can be calculated based on the data and information obtained. For example:

$$PDE = \frac{NOAEL \times weight\ adjustment}{F1 \times F2 \times F3 \times F4 \times F5}$$

Where NOAEL is no-observed adverse effect level, and

F represents various adjustment factors. The value selected for each factor should be justified.

The PDE is derived by dividing the NOAEL for the critical effect by various adjustment factors (also referred to as safety-, uncertainty-, assessment- or modifying factors) to account for various uncertainties and to allow extrapolation to a reliable and robust no-effect level in the human or target animal population. F1 to F5 are addressing the following sources of uncertainty:

- F1: A factor (values between 2 and 12) to account for extrapolation between species;
- F2: A factor of 10 to account for variability between individuals;
- F3: A factor 10 to account for repeat-dose toxicity studies of short duration, i.e., less than 4-weeks;
- F4: A factor (1-10) that may be applied in cases of severe toxicity, e.g. non-genotoxic carcinogenicity, neurotoxicity or teratogenicity;
- F5: A variable factor that may be applied if the no-effect level was not established. When only an LOEL is available, a factor of up to 10 could be used depending on the severity of the toxicity.

The use of additional modifying factors to address residual uncertainties not covered by the above factors may be accepted provided they are well supported with literature data and an adequate discussion is provided to support their use (Ref: EMA document).

If no NOAEL is obtained, the lowest-observed-adverse-effect level (LOAEL) may be used.

Calculating MSC and MSSR

MSC and MSSR can be calculated by using HBELs, to determine the risks associated with cleaning validation.

It can also give an indication of the acceptability, or not, of manufacturing specified products in shared facilities. For example:

Step 1. Calculate MSC

$$\text{MSC a (g)} = \frac{\text{PDE a (ug)} \times \text{Batch size b (kg)}}{\text{Maximum Daily Dose b (mg)}}$$

Where a = product a
b = product b or subsequent product

Step 2. Tabulate the data

API	PDE ug/day	MDD mg/day	Batch size Kg	Equipment surface (m2)
1				
2				
3				
4				
5				

Step 3. Calculate MSSR (mg/m2)

$$\text{MSSR} = \frac{\text{MSC a (g)} \times 1000}{\text{Surface for b (m2)}}$$

Step 4. Tabulate the data for MSSR and identify where there is a risk, based on the MSSR that are not met when considering the cleanability of the procedure.

MSSR		Following product b					
		1	2	3	4	5	6
Pre-Ce-ding Product a	1						
	2						
	3						
	4						
	5						
	6						

* Barle, E.L. Using Health-Based Exposure Limits to assess risk in cleaning validation. Pharmaceutical Technology.

***