Annex 2

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.

Some of the main principles of good manufacturing practices (GMP) include the prevention of mix-ups and the prevention of contamination and cross-contamination. Multi-product facilities in particular, have a potential risk of cross-contamination. It is therefore important that manufacturers identify all risks relating to 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 [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.

Measures to prevent cross-contamination and their effectiveness should be reviewed periodically in accordance with authorized procedures.

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). Numerical factor used in a quantitative risk assessment to represent or allow for the extrapolation, uncertainty, or variability of an observed exposure concentration and its associated health outcome in a particular laboratory species or exposed population to an exposure concentration for the target population (for example, from animals to human patients and short-term exposure to chronic exposure) that would be associated with the same delivered dose. Adjustment factors can also be used when dealing with clinical data, e.g. when a study population is not representative of the general population (*10*).

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

Cleaning validation. The collection and evaluation of data, from the cleaning process design stage through cleaning at commercial scale, which establishes scientific evidence that a cleaning process is capable of consistently delivering clean equipment, taking into consideration factors such as batch size, dosing, toxicology and equipment size.

Contamination. The presence of undesired foreign entities of a chemical, microbiological or physical nature in or on equipment, 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.

Health Based Exposure Limits (HBELs). *See definition of Permitted Daily Exposure (PDE)*

Margin of safety. The margin of safety is the ratio 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 by dividing the Maximum Safe Carryover (MSC) by the total area of shared contact (MSC/Total Product Contact Surface Area).

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 (of the HBEL calculation). The dose-response point that marks the beginning of a low-dose extrapolation to derive an HBEL. This point can be a No Observed Adverse Effect Level (NOAEL) or No Observed Effect Level (NOEL), Lowest Observed Adverse Effect Level (LOAEL) or Lowest Observed Effect Level (LOEL), or Benchmark Dose Level (BMDL) for an observed effect [the highest dose at which no unwanted/adverse effect is observed (NOEL/NOAEL), or, if unavailable, the dose at which a significant adverse effect is first observed (LOEL/LOAEL)].

Verification. Evidence that the equipment is clean (i.e. that residues are reduced from prior operations to levels no higher than those that are predetermined and specified as acceptable). Appropriate methods should be used and, depending upon the circumstances, may include visual inspection, analytical and microbial (as applicable) testing of swab and/or rinse samples.

4. Historical approach in cleaning validation

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 cleaning limit based on HBELs should be calculated and compared against an existing cleaning limit. Historically established cleaning limits may be used when these are more stringent than HBELs. Any alert and action limits should not be based on historically established cleaning limits, but should be based on a statistical analysis if existing data (i.e. statistical process control).

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 approach using HBELs in cleaning validation

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 pharmacological and 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 levels considered as safe for patients. Control measures should be implemented to mitigate the risks of contamination and cross-contamination.

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

- risk assessment to identify cross-contamination 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 (if relevant) 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 (*12*), 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 maintained and available.

The design and layout of documents, and the reporting of data and information, should be in compliance with the principles of good documentation practices (*13*) and should also meet data integrity requirements (*14*).

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 shared 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 based on cleaning process development studies including cleanability studies. They should be appropriate for their intended use.

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.

5.4 Sampling

Historically, cleaning validation has focused mainly on product contact surface areas.

A combination of at least two or three methods should normally be used. These include swab samples, rinse samples and visual inspection. Visual inspection should always be performed where possible and safe to do so. Sampling should be carried out by swabbing whenever possible. Rinse samples should be taken for areas which are inaccessible for swab sampling. The sampling materials and method should not influence the result.

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 for commercial product manufacturing and verified for IMPs. Recovery should be shown to be possible from all product contact materials sampled in the equipment with all the sampling methods used.

Where microbiological sampling is carried out, a compendial or validated method should be used.

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.

Measures should include technical and organizational controls in order to deliver a verified or validated cleaning process (*12*).

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 products already produced in a facility 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 and critically evaluated by a qualified expert. A qualified expert is an individual with relevant qualifications including educational background (e.g. toxicology, pharmacology or related health fields), certifications (e.g. (e.g. Diplomate of the American Board of Toxicology (DABT), European Registered Toxicologist (ERT) and with adequate experience in the practice of deriving HBELs, such as occupational exposure limits (OELs), PDEs for residual solvents, elemental impurities, and product contamination/nonconformances. The data and evaluation should be presented in a report that is peer-reviewed by another qualified expert (*10*, *15*). 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 there is more than one route of administration, separate HBELs should be derived for each route*)
- preclinical/nonclinical data, for example, of acute and repeat-dose toxicity data
  - genotoxicity data
  - carcinogenicity data
  - reproductive and developmental toxicity data
  - immunotoxicity and sensitization data
- 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 person. The person should have in-depth knowledge, appropriate qualifications and experience (see above). A summary document may be prepared from the report, for each relevant substance, which contains the key pharmacological/toxicological characteristics of the compound, the effect that drives the HBEL ("lead effect"), the basis of the rationale that has been used to set the HBEL and the HBEL itself including the route/s of exposure for which the HBEL(s) is/are valid (*15*, *16*, *17*, *18*, *19*).

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

Note: If no NOAEL is obtained, the 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 (16, 17).

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

Note: therapeutic macromolecules and peptides are known to degrade and denature when exposed to pH extremes and/or heat, and may become pharmacologically inactive. The cleaning of biopharmaceutical manufacturing equipment is typically performed under conditions which expose equipment surfaces to pH extremes and/or heat, which would lead to the degradation and inactivation of protein-based products. In view of this, the determination of health-based exposure limits using PDE limits of the active and intact product may not be required.

Where other potential routes of cross-contamination exist, the risks posed should be considered on a case-by-case basis.

5.8 Acceptance criteria

The limits established in cleaning validation should be scientifically justified.

Historically, some manufacturers have specified acceptance criteria where HBELs and related toxicity data were not included in the determination of such acceptance criteria.

Criteria such as Maximum Safe Carryover (MSC) 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, sample areas, sample dilution volumes and recovery factors.

MSC and 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 (*for example of IMPs see EudraLex Volume 4 Part 1 Chapter 3.6, Annex 15, Annex 13*).

The margin of safety 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. UV spectrophotometric methods and testing for total organic carbon (TOC) may be used where indicated and where justified. Non-specific methods 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.

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 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 (*14*).

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).

HBELs 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 and should include the same sampling and testing procedures used in cleaning validation. The results obtained from testing on a routine basis should be reviewed and subjected to statistical trending if possible.

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 and qualified and 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. The acceptability of visual inspection should be determined by comparing the VRL of that compound to the MSSR with an appropriate safety margin.

5.13 Cleaning process capability

The cleaning procedure should remain in a validated state. It is recommended that Process Capability (Cpk) be calculated and Statistical Process Control (SPC) be used to support cleaning verification results and data. For example, the results from cleaning verification sample analysis could be statistically trended. The capability (Cpk) of the cleaning process is then calculated using an appropriate statistical technique.

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 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/docs/default-source/medicines/norms-and-standards/guidelines/production/fr-trs986annex2gmp-main-principles.pdf, 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/expert_committee/trs_1019/en/, accessed 2 February 2021).

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/docs/default-source/medicines/norms-and-standards/guidelines/production/trs1010-annex8-who-gmp-heating-ventilation-airconditioning-part2.pdf, accessed 2 February 2021).

4. Good manufacturing practices: guidelines on validation. Appendix 2. 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 1019,; https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/production/trs1019-annex3-gmp-validation.pdf, accessed 2 February 2021).

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/docs/default-source/medicines/norms-and-standards/guidelines/production/trs1019-annex3-gmp-validation.pdf, accessed 2 February 2021).

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/docs/default-source/medicines/norms-and-standards/guidelines/production/trs1019-annex3-gmp-validation.pdf, accessed 2 February 2021).

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/docs/default-source/medicines/norms-and-standards/guidelines/production/trs1019-annex3-gmp-validation.pdf, accessed 2 February 2021).

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/docs/default-source/medicines/norms-and-standards/guidelines/production/trs1019-annex3-gmp-validation.pdf, accessed 2 February 2021).

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/docs/default-source/medicines/norms-and-standards/guidelines/production/trs1019-annex3-gmp-validation.pdf, accessed 2 February 2021).

10. ASTM E3219-20. Standard Guide for the Derivation of Health Based Exposure Limits (HBELs). West Conshohocken, PA: American Society for Testing Materials (ASTM) International.

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

12. 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; https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/production/trs981-annex2-who-quality-risk-management.pdf, accessed 2 February 2021).
13. 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/docs/default-source/medicines/norms-and-standards/guidelines/regulatory-standards/trs966-annex05-who-record-management-practices.pdf, accessed 2 February 2021).
14. Guideline on data integrity. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: Fifty-fifth report. Geneva: World Health Organization; 2021: Annex 4 (WHO Technical Report Series, No.xxx, website etc) Geneva: World Health Organization; 2019 (working document QAS/19.819; https://www.who.int/docs/default-source/medicines/norms-and-standards/current-projects/qas19-819-rev1-guideline-on-data-integrity.pdf, accessed 2 February 2021).
15. PIC/S. (2020). AIDE-MEMOIRE: Inspection of Health Based Exposure Limit (HBEL) Assessments and Use in Quality Risk Management (PI 052-1): Pharmaceutical Inspection Convention, Pharmaceutical Inspection Co-Operation Scheme.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. 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/CHMP/CVMP/SWP/246844/2018). European Medicines Agency, 2018.
17. ASTM E3106. Standard Guide for Science-Based and Risk-Based Cleaning Process Development and Validation.
18. ISPE Baseline, Pharmaceutical Engineering Guide, Volume 7 – Risk-based manufacture of pharmaceutical products, International Society for Pharmaceutical Engineering (ISPE), Second edition, July 2017.

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.
- ICH Topic Q3A (R2). Note for guidance on impurities testing: Impurities in new drug substances (www.ich.org).
- Regulatory Toxicology and Pharmacology. ADE Supplement, Volume 79, Supplement 1, Pages S1-S94 (15 August 2016) (https://www.sciencedirect.com/journal/regulatory-toxicology-and pharmacology/vol/79/suppl/S1, accessed 25 September 2020).
- Sehner C, Schwind M, Tuschl G, Lovsin Barle E. What to consider for a good quality PDE document? Pharm Dev Technol. 2019;24(7):803-811. doi:10.1080/10837450.2019.1592188

Appendix 1

Using Health-Based Exposure Limits (HBELs) 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:

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

Where NOAEL is no-observed adverse effect level, and

F represents various adjustment factors. The value selected for each factor should be justified. All adjustment factors should ideally be compound-specific. Default values should only be used where no compound-specific data are available.

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. (*Note: The values for the factors cited below are defaults and should only be used in the absence of compound-specific information*).

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.

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

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 (*17*).

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

Calculating Maximum Safe Carryover (MSC) and Maximum Safe Surface Residue (MSSR)

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

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	Shared Equipment surface (m2)
1				
2				
3				
4				
5				

Step 3. Calculate MSSR (mg/m2)

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

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 or the Visual Residue Limit of the compound / product.

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