World Health Organization

DRAFT WORKING DOCUMENT FOR COMMENTS:

Points to consider on the different approaches – including HBEL – to establish carryover limits in cleaning validation for identification of contamination risks when manufacturing in shared facilities

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 30 June 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

Points to consider on the different approaches – including HBEL – to establish carryover limits in cleaning validation for identification of contamination risks when manufacturing in shared facilities

Description of Activity	Date
During the Fifty-third Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP), the WHO Secretariat was recommended to revise the 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
Discussion of working document during the informal consultation on Good Practices for Health Products Manufacture and Inspection	June 2020
Revision of the working document based on comments received during the informal Consultation on Good Practices for Health Products Manufacture and Inspection.	July 2020
Mailing of revised working document to the EAP inviting comments and posting the working document on the WHO website for public consultation.	August – September 2020
Consolidation of comments received and review of feedback. Preparation of working document for discussion.	End of September 2020
Presentation to the Fifty-fourth meeting of the ECSPP.	12-16 October 2020

Any other follow-up action as required.	

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References

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. In 2019, the WHO *Good manufacturing practices: guidelines on validation* (*2*) were updated and republished. Some of the seven appendices were also individually updated between 2013 and 2019:

- Appendix 1. Validation of heating, ventilation and air conditioning systems *(3).*
- Appendix 2. Validation of water systems for pharmaceutical use (*4*).
- Appendix 3. Cleaning validation *(5).*
- Appendix 4. Analytical procedure validation *(6).*
- Appendix 5. Validation of computerized systems *(7).*
- Appendix 6. Guidelines on qualification *(8).*
- Appendix 7. Non-sterile process validation *(9).*

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

2. Scope

The scope of this document is to discuss the different possible approaches – including methods that account for pharmacological and toxicological data (Health-Based Exposure Limits {HBEL}) – that could be used when establishing safe Carryover limits when manufacturing in shared facilities.

This document further provides clarification on cleaning validation and presents points to consider when reviewing the current status and approaches to cleaning validation in multiproduct facilities. It reflects the current regulatory guidance and expectations. It further focuses on approaches where HBELs setting need to be considered in cleaning and cleaning validation approaches.

The principles should be applied in manufacturing facilities with active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs).

This document should be read in conjunction with the main GMP text and supplementary texts on validation *(1-10).*

3. Glossary

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.

margin of safety. The margin of safety is the distance between a calculated acceptance limit and the actual residues after cleaning. It indicates the probability that a patient has to be exposed to the API residues resulting from cleaning.

maximum safe Carryover (MSC). Mathematically calculated quantity of residue from a previous product when carried over into a different product that can represent potential harm to the patients.

maximum safe surface residue (MSSR). The maximum safe surface residue is mathematically calculated dividing the quantity of residue on a contact surface by the total area of contact (Maximum Safe Carryover/Total Equipment Surface Area).

verification. The application of methods, procedures, tests and other evaluations, in addition to monitoring, in order to determine compliance with GMP principles.

4. Traditional approach

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

One traditional approach is that cleaning validation is performed and the appropriateness of the cleaning procedure was based on acceptance criteria suggested in GMP texts. This approach may no longer be acceptable and justifiable as HBELs were not considered.

Where traditional acceptance limits are used, the decision should be discussed and justified as an alternative to new approaches in setting acceptance criteria.

In view of the risks of contamination and cross-contamination, the new approaches, as described below, should be implemented without delay.

5. New approaches

Traditional cleaning validation approaches were often based on verifying that a cleaning procedure was effective. However, in many instances, no development work or cleanability studies were performed for these cleaning procedures.

Manufacturers should ensure that their cleaning is effective and appropriate and that their cleaning validation provides scientific evidence that identified products can be manufactured in shared facilities – with control measures 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:

- cleanability studies;
- risk assessment and risk control;
- technical and organizational controls;
- HBELs setting;
- analytical procedures; and
- cleaning verification with proven capability through statistical evaluation.

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

It is strongly recommended that manufacturers review their existing technical and organizational measures, suitability of cleaning procedures and appropriateness of cleaning validation. Genotoxic and carcinogenic substances, degradants and other contaminants should be identified and the appropriate action should be taken in order to ensure that materials and products are not contaminated when produced in shared facilities.

5.1 Documentation

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

Procedures, protocols, reports and other related and supportive documentation should be prepared, used and maintained.

The policy and approaches in cleaning and cleaning validation may be described in a Cleaning Validation Master Plan. Experiments and validation should be performed in accordance with predefined, authorized standard operating procedures, protocols and reports.

The design and layout of documents, and the reporting of data and information, should be in compliance with the principles of good documentation practices *(11)* and should also meet data integrity requirements *(12)*.

5.2 Equipment

Consideration for cleaning validation should cover contact surfaces, as well as non-contact surfaces, where the latter have been identified as areas of risk.

Authorized drawings of equipment should be current, accurate and available. These should be used when equipment surface areas are calculated. Source data for these calculations should be available. The calculated values should be used in the calculations in cleaning validation.

Equipment and components that are difficult to clean, such as sieves, screens and bags, should also be included in the cleaning validation and calculations.

5.3 Detergents and solvents

Solvents and detergents used in cleaning processes should be selected with care. They should also be appropriate for their intended use. The selection of the relevant solvent and detergent should be justified.

There should be proof of effectiveness and appropriateness of the selected solvent and detergent.

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

The use of solvents and detergents should be included in cleanability studies.

5.4 Sampling

Traditionally, cleaning validation included the sampling of equipment and other areas in order to determine whether or not there was any residue remaining on the surfaces. The focus was mainly on contact surface areas. Non-contact surface areas were sometimes considered by some manufacturers.

A combination of at least two or three sampling methods should be used. These include a combination of swab samples, rinse samples and visual inspection.

The appropriate sampling procedures and techniques should be selected and used to collect samples. These should be clearly described in procedures and protocols. The location (swab sample) and the manner in which the samples are collected should be clearly described and be scientifically justifiable.

The manner in which a rinse sample is collected should be described in detail. The procedure should be clear and unambiguous.

The manner in which samples collected are prepared for analysis should be appropriate and described in detail.

5.5 Cleanability studies

Before a 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 material, product residue, cleaning agents and microorganisms.

The lowest concentration of a substance that can be removed by following the cleaning procedure should be established for different materials, intermediates and products on different materials of construction. The concentration can be expressed in mg/m2.

Cleanability studies should be described in authorised documents, such as protocols and procedures. The method should be scientific and may include spiking on coupons made from different materials of construction. The so-called beaker method, or other appropriate method, may be used.

Consideration should be given to all substances and different procedures where different processes or solvents are used, including different surface materials.

The results should be documented in authorized reports and used in further determinations, such as Maximum Safe Residue.

5.6 Risk assessment and risk control

Risk identification should be performed with a focus on the assessment of risks and defining and implementing controls to mitigate the risk of contamination and cross-contamination.

These should include technical and organization controls, including but not limited to, premises, equipment, utilities, containment, closed systems, cleaning and cleaning validation.

5.7 Technical and organizational controls

The appropriate technical and organizational controls should be defined and implemented.

Their appropriateness and effectiveness should be evaluated. *Note:* Cleaning and cleaning validation are considered additional and supplementary controls to technical and organizational controls.

Technical and organizational controls should be justifiable and clearly documented.

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).

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

5.8 Health Based Exposure Limits (HBELs) setting

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

APIs and products manufactured in shared facilities should be reviewed based on scientific evidence in order to determine whether production and control activities in shared facilities may be considered acceptable or whether dedicated facilities are required for the production and control of identified products.

This is applicable to legacy products as well as the introduction of new products introduced into a facility through a change control procedure.

Procedures should be established and implemented describing how scientific data and toxicological information on HBELs should be obtained.

Data and information should be gathered and presented in a report. The data should be free from bias. Where this service is outsourced, the 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.

The report should include scientific detail, including information on:

- chemical structure;
- hazard identification;
- mode of action;

- identification of critical effects;
- establishing NOAELs (no-observed-adverse-effect level);
- adjustment factors;
- pre-clinical, clinical and non-clinical data;
- pharmacokinetics and pharmacodynamics;
- expert assessment;
- identification of the critical effect;
- assignment of adjustment factors (AF);
- argumentation for the selected HBEL;
- routes of administration;
- point of departure (POD);
- justification for critical effect of POD; and
- justification for factor.

The Permitted Daily Exposure (PDE) should 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 event level, and
F represents various factors. The value selected should be justifiable.

The report should be reviewed by the manufacturer's in-house team for completeness and appropriateness. Team members should have the appropriate qualifications and experience in the field of toxicology. A summary report should be prepared for each product and contain information on the PDE value, genotoxicity and carcinogenicity *(13).*

These scientific reports should be used when considering the cleaning validation control measures.

Manufacturers should periodically review and update PDE reports. The appropriate action should be taken where such a report needs to be updated.

5.9 Acceptance criteria

Limits established in cleaning validation should be justifiable.

Manufacturers often specified acceptance limits based on historical GMP texts. These traditional limits may no longer be acceptable as HBELs (PDE) and cleanability studies were not performed in many cases.

Criteria such as Margin of safety, 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 equipment surface areas.

Maximum Safe Surface Residue (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.)

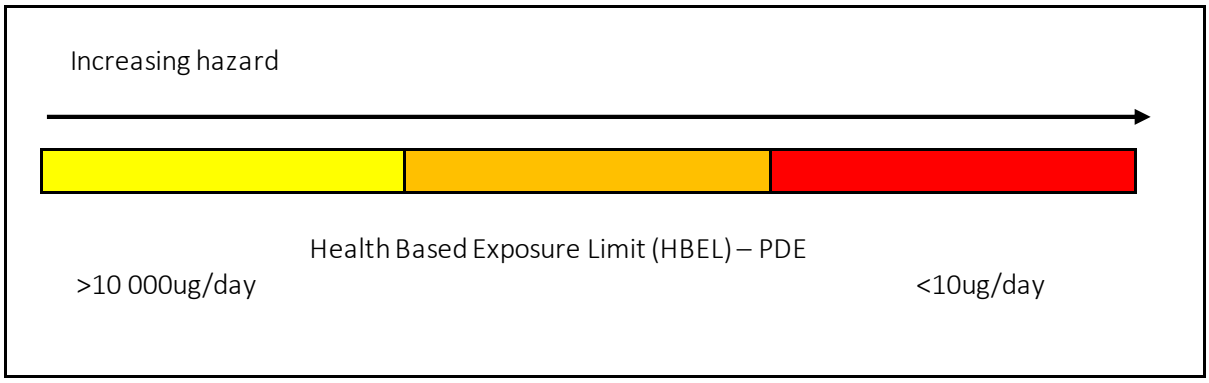
5.10 Grouping by therapeutic use

The risk associated with contamination and cross-contamination from one product to another product in one therapeutic group, and between products in different therapeutic groups in shared facilities, should be considered. For example, due to the risk, certain products should be manufactured in dedicated or segregated self-contained facilities, including certain antibiotics, certain hormones, certain cytotoxics and certain highly-active drugs – even though these are in the same therapeutic class.

The risk assessment should include, for example, PDE values, batch size, maximum daily dose of the next product, as well as other criteria associated with cleaning.

The higher the PDE value, the lower the risk. The products and therapeutic groups considered for manufacturing should be plotted based on an identified scale of risk (*14, 15*). An illustration is presented in figure 1 where hazard is plotted against risk

382 **Figure 1.** Increasing hazard and PDE values



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384 5.11 Analytical procedures

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386 Samples obtained in cleaning validation should be analyzed by using specific, validated
387 procedures. The procedures should be developed, validated and appropriate for their intended
388 use.

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390 Specific methods, such as HPLC, should be used where possible. Non-specific methods
391 including UV spectrophotometry should only be used where specific methods cannot be
392 employed.

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

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396 Analytical procedures validation should be done on-site. Where analytical procedures were
397 developed and validated off-site, the scope and extent of validation should be defined and
398 justified. This includes procedures that are transferred from research and development
399 laboratories to site laboratories. (For analytical procedure validation, see reference *6*).

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

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5.12 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*).

5.13 Cleaning validation and cleaning verification

The cleaning procedure should be validated after the cleaning procedure had been developed and the cleanability study had been done.

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 product change-over;
- 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).

Cleaning validation should include consideration of HBELs when the appropriate method used in establishing Carryover limits. Where HBELs are not used, scientific justification should be provided.

The company should describe the policy and approach to cleaning verification. The effectiveness of the validated cleaning procedure should be 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.

5.14 Visually clean

Visually clean is an important criterion in cleaning validation and should be one of the acceptance criteria used on a routine basis.

Visible residue limits (VRLs) should be determined. The process to determine the limit should be appropriately described in procedures and protocols including concentrations, method of spiking, surface areas, material of construction and other conditions such as light and angles.

VRLs should be quantitatively established for APIs, excipients, detergents and pharmaceutical products.

Visual Detection Index (VDI) may be calculated using MSSR.

5.15 Cleaning verification and process capability

The cleaning procedure should remain in a validated state. Cleaning verification and process capability may be used to provide data 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 through an appropriate statistical process.

The presentation of individual results and data used in the calculation, such as with a Central Processing Unit (Cpu) and acceptable daily exposure (ADE) base limit, should meet ALCOA principles.

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 discussed as part of continuous improvement.

5.16 Personnel

Personnel should be trained in the principles of cleaning validation, with an emphasis on contamination and cross-contamination control, HBELs setting, equipment disassembly, sampling, testing and statistical calculations.

5.17 Quality metrics and performance indicators

Aspects of HBELs setting, cleanability studies, cleaning validation and cleaning verification, as well as process capability, should be considered in quality metrics, with performance indicators identified and to be monitored.

5.18 Life cycle

HBEL reports, protocols, cleaning validation and cleaning verification should be included in a company policy and life cycle approach in preventing cross-contamination in shared facilities.

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; 2013: Annex 2 (WHO Technical Report Series, No. 986; https://www.who.int/medicines/areas/quality_safety/quality_assurance/TRS986annex2.pdf?ua=1, accessed 4 May 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; http://digicollection.org/whoqapharm/documents/s23430en/s23430en.pdf, accessed 5 May 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 4 May 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 4 May 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 4 May 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 4 May 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 4 May 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 4 May 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?ua=1, accessed 4 May 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; https://www.who.int/medicines/areas/quality_safety/quality_assurance/Annex2TRS-981.pdf, accessed 4 May 2020).

11. 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 4 May 2020).

12. 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_data_integrity.pdf?ua=1, accessed 4 February 2020).

13. 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.

14. ISPE Baseline, Pharmaceutical Engineering Guide, Volume 7 – Risk-based manufacture of pharmaceutical products, International Society for Pharmaceutical Engineering (ISPE), Second edition, July 2017.

15. 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. European Medicines Agency, 2018.

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