World Health Organization

DRAFT WORKING DOCUMENT FOR COMMENTS:

WHO good practices for research and development facilities of pharmaceutical products

Please send your comments to **Dr Steve Estevão Cordeiro**, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (estevaos@who.int), with a copy to Ms Sinéad Jones (jonessi@who.int) before **31 August 2021**. Please use the "Table of Comments" document for this purpose.

Our working documents are sent out electronically and they will also be placed on the WHO Medicines website (https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/pharmaceuticals/current-projects) for comments under the "*Working documents in public consultation*" link. If you wish to receive our draft guidelines, please send your email address to jonessi@who.int and your name will be added to our electronic mailing list.

41 SCHEDULE FOR DRAFT WORKING DOCUMENT QAS/20.865:

42 # WHO good practices for research and development
43 # facilities of pharmaceutical products

Description of Activity	Date
Following a recommendation by WHO Prepublication Inspection Team, the Fifty-fifth Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) recommended that the WHO Secretariat should develop a new guidance on Good practices in research and development.	October 2020
Preparation of first draft working document.	October 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	November 2020
Consolidation of comments received and review of feedback. Preparation of working document for discussion.	January 2021
Discussion of the feedback received on the working document in a virtual meeting with an expert working group	February-March 2021
Preparation of working document for next round of public consultation.	March 2021
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.	April 2021
Consolidation of comments received and review of feedback. Preparation of working document for discussion.	June 2021
Discussion of comments in the virtual meeting on *Good practices for health product manufacture and inspection*	28 June- 2 July 2021
Preparation of working document for next round of public consultation.	July 2021
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.	July – August 2021
Consolidation of comments received and review of feedback. Preparation of working document for discussion in the ECSPP.	September – October 2021

Presentation to the Fifty-sixth meeting of the ECSPP.	TBD
Any other follow-up action as required.	

44

45

WHO good practices for research and development facilities of pharmaceutical products

Background

In view of the need for the development of health products, including the research and development for the treatment of COVID-19 therapies, the World Health Organization (WHO) Prequalification Inspection Services Team (PQT INS) raised the urgency for the development of life cycle appropriate good practices text to address the manufacturing of developmental batches, pilot batches and the sequential stability data that are submitted in product applications (dossiers) for marketing authorization and the prequalification of medical products.

There is currently no other specific WHO guideline which addresses this matter. The data collected from these batches influence the following aspects of the product:

- stability;
- process validation; and
- analytical method development and validation.

1. Introduction
2. Scope
3. Glossary
4. Quality management
5. Quality risk management
6. Sanitation and hygiene
7. Qualification and validation
8. Outsourced activities
9. Self-inspection and quality audits
10. Personnel
11. Training
12. Premises
13. Equipment and instruments
14. Materials

15. Documentation
16. Processing and process design
17. Quality control
18. Stability studies
19. Analytical procedure development
20. Technology transfer
21. Life cycle approach
22. Cleaning procedure development, cleaning verification and cleaning validation

Abbreviations
References
Further reading

1. Introduction

1.1. With an ever increasing awareness of the risks in pharmaceutical production and control and the life cycle approaches being followed, greater emphasis is being placed on ensuring that the research and development of products are appropriately controlled and documented.

1.2. Consequently, it is necessary that manufacturers of pharmaceutical products submit all relevant data and information related to the their development, including the facilities used, the experimental designs employed in the validations of manufacturing processes and quality control procedures, to the regulators for review to ensure that the facilities, quality systems, data and information meet the appropriate standards and good practices (GxP).

1.3. This document intends to provide guidance on good manufacturing practices (GMP) to research and development facilities. It further aims to ensure that the correct systems are followed, ensuring appropriateness, reliability and the quality of products, processes, procedures and data. This further helps to help ensure that products meet the requirements for safety, efficacy and quality that they purport to possess.

1.4 In addition to product development, other activities, including the production of pilot scale batches; process validation; cleaning procedure development; cleaning validation studies; as well as stability studies, are often undertaken in such facilities.

1.5 The World Health Organization (WHO) document entitled *Good manufacturing practices for investigational pharmaceutical products for clinical trials in humans (1)* specifically addresses the requirements and recommendations for products used in clinical trials. Other WHO guidelines address specific requirements and recommendations, including but not limited to, data integrity, stability testing, analytical method validation, cleaning validation and the technology transfer (TOT) (see References and Further reading sections).

1.6 This document should be read in conjunction with other WHO GMP guidelines, as referenced in the document *(2-9)*. Other documents of interest are also listed under the section “Further reading”.

2. Scope

2.1. This guideline is specifically applicable to research and development facilities of pharmaceutical products procedures, processes and data that are intended for transfer and submission for approval in marketing authorization applications, process validation, TOT *(10)*-related activities, validation *(7)*, quality control laboratory activities (*11)* such as stability testing and development, and validation of cleaning procedures (see Figure 1 and section 4 below).

2.2. The main focus of this document is to provide for GxP in the production and control of pre-clinical and not for human use batches, manufactured in pharmaceutical formulation and development facilities, where these are directly supporting; for example, shelf life claims, animal studies or validation activities. The principles described in this document may be applied in facilities where other products, such biopharmaceutical products, vaccines and medical devices, are manufactured.

2.3. This guide excludes whole cells, whole blood and plasma, blood and plasma derivatives (plasma fractionation), medicinal gases, radiopharmaceuticals and gene therapy products.

2.4. The GxP outlined below are to be considered general guides and they may be adapted to meet individual needs. The equivalence of alternative approaches, however, should be demonstrated.

2.5. In this guide, the term “should” indicates recommendations that are expected to apply unless shown to be inapplicable or replaced by an alternative demonstrated to provide an acceptable level of control.

2.6. This guide, as a whole, does not cover safety aspects for the personnel engaged in the research and development nor the aspects of protection of the environment. These controls are inherent responsibilities of the manufacturer and are governed by national laws.

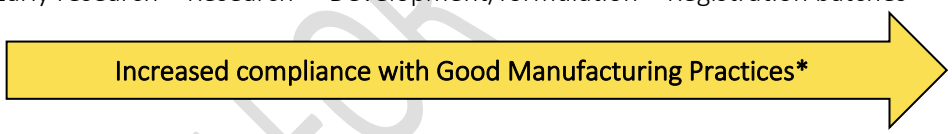
2.7. This guide is not intended to define registration requirements or modify pharmacopoeial requirements or other guideline recommendations. For details on process development, it is recommended that other guidelines, such as those published by The International Council for

Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), be read in conjunction with this document.

2.8. This guide does not affect the ability of the responsible regulatory agency to establish specific registration or filing requirements. All commitments in registration and filing documents must be met. This document provides information to consider for a risk- and science-based approach in the research and development of pharmaceutical products.

2.9. Due to the nature of development work, and an increasing expectation for compliance with standards in manufacture, the guidance in this document would normally be applied based on risk assessment, in an increasing manner, from development to commercial batch manufacturing. The stringency of GMP in research and development should increase as the process proceeds from early development work to the final steps of development and formulation, stability testing, process validation and cleaning validation.

Figure 1. Application of this guide



*The principles described in this guideline are applied, based on risk management principles, in an increased manner from early research to development to registration batches

3. Glossary

The definitions given below apply to the terms used in this guideline. They may have different meanings in other contexts.

batch (or lot). A defined quantity of starting material, packaging material or product processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the

capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

batch records. All documents associated with the manufacture of a batch of bulk product or finished product. They provide a history of each batch of product and of all circumstances pertinent to the quality of the final product.

bulk product. Any product that has completed all processing stages up to, but not including, final packaging.

calibration. The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

cleaning verification. The act of demonstrating that cleaning was done to an acceptable level; for example, between two batches.

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

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

finished product. A finished dosage form that has undergone all stages of manufacture, including packaging in its final container and labelling.

in-process control. Checks performed during production in order to monitor and, if necessary, to adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

intermediate product. A partly processed product that must undergo further manufacturing steps before it becomes a bulk product.

manufacture/manufacturing. Includes all operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release, storage, distribution and related controls.

manufacturer. A company that carries out operations such as production, packaging, repackaging, labelling and relabelling of pharmaceuticals.

marketing authorization (product licence, registration certificate). A legal document issued by the competent medicines regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labelling and shelf life.

master formula. A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

master record. A document or set of documents that serve as a basis for the batch documentation (blank batch record).

packaging. All operations, including filling and labelling, that a bulk product has to undergo in order to become a finished product. The filling of a sterile product under aseptic conditions, or a product intended to be terminally sterilized, would not normally be regarded as part of packaging.

packaging material. Any material, including printed material, employed in the packaging of a pharmaceutical, but excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

pharmaceutical product. Any material or product intended for human or veterinary use presented in its finished dosage form or as a starting material for use in such a dosage form that is subject to control by pharmaceutical legislation in the exporting state and/or the importing state.

production. All operations involved in the preparation of a pharmaceutical product, from receipt of materials through processing, packaging and repackaging, labelling and relabelling, to completion of the finished product.

quality audit. An examination and assessment of all or part of a quality system with the specific purpose of improving it. A quality audit is usually conducted by outside or independent specialists or a team designated by the management for this purpose. Such audits may also be extended to suppliers and contractors.

quality risk management. A systematic process for the assessment, control, communication and review of risks.

specification. A list of detailed requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

standard operating procedure (SOP). An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material (e.g. equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

starting material. Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

validation. The action of proving, in accordance with the principles of GMP, that any procedure, process, equipment, material, activity or system actually leads to the expected results.

4. Quality management

4.1 There should be a quality management system encompassing adequate resources, a written organizational structure and procedures to follow.

4.2 All parts of the quality system should be adequately resourced and maintained, including with sufficient competent personnel, suitable premises, equipment and facilities. The necessary resources should include, for example:

a) a sufficient number of appropriately qualified, trained personnel;
b) adequate premises and space;
c) suitable equipment and services;
d) appropriate materials, containers and labels; and
e) suitable storage and transport.

4.3 Roles, responsibilities and authorities should be defined, communicated and implemented.

4.4 The quality system should facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities.

4.5 Initial research, as well as development activities, should be defined and documented. Development activities, including initial research, should be adequately documented. Controls should be commensurate with the stage of product development (i.e. for testing options or at a final stage for further use where the guideline on *Good manufacturing practices for investigational pharmaceutical products for clinical trials in humans* applies).

4.6 The quality system should ensure, as applicable and according to the stage of research and development, that:

a) managerial responsibilities are clearly specified in job descriptions;
b) personnel are trained;
c) instructions and procedures are written in clear and unambiguous language, and followed;
d) procedures are correctly carried out;

e) records are made (manually and/or by recording instruments) during production and testing;
f) records are maintained;
g) there is a system for quality risk management (QRM) which is applied, as appropriate;
h) arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;
i) all necessary controls on starting materials, intermediate products, bulk products and other in-process controls are carried out;
j) calibrations and validations are carried out where appropriate;
k) the product and process knowledge is managed;
l) products are designed and developed in accordance with applicable GxP;
m) development procedures should be documented;
n) cleaning procedures are developed, verified and validated, where appropriate;
o) stability testing is done following written procedures and protocols; and
p) data meet ALCOA+ requirements, where applicable.

4.7 There should be periodic management review with the involvement of senior management.

5. Quality risk management

5.1 A system of quality risk management (QRM) should be implemented. The system should ensure that risks are identified based on scientific knowledge and experience. The appropriate controls should be identified and implemented to mitigate risks.

5.2 The level of effort, formality and documentation of the QRM process is commensurate with the level of risk and the stage from research to development, to commercial batch manufacturing and control (see Figure 1).

5.3 Systems should be in place to manage and minimize the risks inherent in research and development in order to ensure the ultimate quality, safety and efficacy of products and the reliability of data.

6. Sanitation and hygiene

6.1 Procedures should be implemented to maintain sanitation and hygiene. The scope of sanitation and hygiene covers personnel, premises, equipment and apparatus, production materials and containers, and products for cleaning and disinfection.

6.2 Potential sources of contamination should be identified and controlled.

7. Qualification and validation

7.1 Where qualification and validation are performed, the scope and extent should be appropriate using a risk-based approach.

7.2 The qualification and validation policy and approach should be defined and documented, for example, in a validation master plan.

7.3 Where qualification and validation is carried out, the responsibility of performing validation should be clearly defined.

7.4 Where process validation, cleaning validation and analytical procedure validation is done as a part of development, procedures and protocols should be followed. Reports should be available and retained.

8. Outsourced activities

8.1 Outsourced activities should be correctly defined, agreed and controlled through a written agreement.

8.2 All responsibilities and arrangements for activities, such as quality control (QC) testing and technology transfer, should be clearly described.

The contract giver

8.3 The contract giver is responsible for assessing the suitability and competence of the contract acceptor to successfully carry out the work or tests required and for approval of the contract activities.

8.4 The contract giver should provide the contract acceptor with all the information necessary to carry out the contracted operations correctly.

8.5 The contract giver should ensure that the contract acceptor is fully aware of any hazards associated with the product, work or tests.

8.6 The contract giver should review and assess the records and results related to the outsourced activities.

8.7 The contract giver is responsible for ensuring that the contract accepter understands that its activities may be subject to inspection by the competent authorities.

The contract accepter

8.8 The contract accepter must have adequate premises, equipment, knowledge, experience and competent, trained personnel to satisfactorily carry out the work ordered by the contract giver.

8.9 The contract accepter should not pass to a third party any of the work entrusted under the contract without the contract giver's prior evaluation and approval of the arrangements.

8.10 The contract accepter should agree to a period of time for retention of documents and data prior to archival or returning to the contract giver.

The agreement

8.11 The technical aspects of the agreement should be drawn up by competent persons suitably knowledgeable in the field of law, research, development and GMP.

8.12 The agreement should define the roles and responsibilities of all parties.

8.13 The agreement should permit the contract giver to audit the facilities and activities of the contract accepter.

9. Self-inspection and quality audits

9.1 There should be a written self-inspection programme.

9.2 Self-inspections should be performed routinely and may be, in addition, performed on special occasions.

9.3 The team responsible for self-inspection should consist of personnel with the appropriate knowledge and experience, free from bias.

9.4 Self-inspections should cover at least the following items:

a) personnel;
b) premises including personnel facilities;
c) maintenance of buildings and equipment;
d) storage of starting materials and finished products;
e) equipment;
f) production and in-process controls;
g) QC;
h) documentation;
i) data and data integrity;
j) sanitation and hygiene;
k) qualification and validation;
l) calibration of instruments or measurement systems;
m) control of labels; and
n) results of previous self-inspections and any corrective steps taken.

9.5 The outcome of the self-inspection should be documented. Corrective actions and preventive actions should be identified and implemented within a defined timeline. There should be an effective follow-up programme.

9.6 Self-inspections may be supplemented by quality audits.

10. Personnel

10.1 Individual responsibilities should be clearly defined and understood by the persons concerned and recorded as written descriptions.

10.2 All personnel should be aware of the principles of this guideline and other applicable GxP.

10.3 Steps should be taken to prevent unauthorized people from entering storage, production and QC areas.

10.4 Smoking, eating, drinking, chewing and keeping plants, food, drink, smoking material and personal medicines should not be permitted in any area where they might adversely influence product quality.

10.5 The appropriate protective garments should be worn, based on operation performed and risk.

10.6 Personnel who are ill should not engage in the manufacture of pharmaceutical products.

11. Training

11.1 Training should be provided in accordance with a written programme that covers topics such as the theory and practice of GMP and the duties assigned to them. The appropriate task-related training should be further provided based on technical requirements and activities undertaken.

11.2 The effectiveness of training should be assessed.

11.3 Training and assessment records should be kept.

11.4 Where appropriate, specific training should be given on the handling and segregation of highly active, toxic, infectious or sensitizing materials and the need for separate, dedicated facilities where these are required.

12. Premises

12.1 Premises should be located, designed, constructed, adapted and maintained to suit the operations to be carried out.

12.2 The layout and design should aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt and, in general, any adverse effect on the products and activities.

12.3 Measures should be taken to avoid cross-contamination and to facilitate cleaning.

12.4 The premises should be cleaned according to detailed procedures. Records should be maintained.

12.5 The electrical supply, lighting, temperature, humidity and ventilation should be appropriate.

12.6 Toilets, rest and refreshment rooms should be separate from production and control areas.

12.7 Storage areas should be of sufficient capacity with proper separation and segregation between materials.

12.8 Storage areas should be clean and dry, designed or adapted to ensure the required storage conditions are maintained. Conditions should be controlled, monitored and recorded, where appropriate.

12.9 Certain materials, such as highly active, radioactive materials and narcotics, should be stored in safe and secure areas.

12.10 Materials identified for testing should be sampled and analysed.

12.11 The stages in production, including weighing, compounding, and packaging, should be done in a manner to prevent contamination, cross-contamination and mix-ups.

12.12 QC areas should be separated from production areas. They should be designed to suit the operations to be carried out in them. There should be sufficient space, instruments, equipment and the appropriate reference materials, solvents and reagents

12.13 Poisons or pesticides should not be stored or used in product manufacturing areas.

13. Equipment and instruments

13.1 The equipment and instruments should be located, designed, constructed, adapted and maintained to suit the operations to be carried out. They should allow for effective cleaning and maintenance in order to avoid cross-contamination and a build-up of dust or dirt.

13.2 Pipework, instruments and devices should be adequately marked.

13.3 Measuring equipment should be available for production and control operations and, where necessary, should be calibrated, verified and serviced on a scheduled basis. Records should be maintained.

13.4 The equipment and instruments should be thoroughly cleaned on a scheduled basis.

13.5 Defective equipment and instruments should be removed from operational areas or be clearly labelled as defective in order to prevent use.

14. Materials

14.1 Materials should be purchased from approved suppliers.

14.2 Where so identified, materials should be quarantined immediately after receipt, sampled and tested.

14.3 Materials within their shelf life should be used.

14.4 Materials should be stored under the appropriate conditions as specified on their labels and in an orderly fashion to permit segregation.

14.5 The dispensing of materials for the production of a batch should be recorded. Materials should be accurately weighed or measured into clean and properly labelled containers.

14.6 No materials used for operations, such as cleaning, the lubrication of equipment and pest control, should come into direct contact with the product. Where possible, such materials should be of a suitable grade (e.g. food grade) to minimize health risks.

14.7 All materials, including water, should be suitable for its intended use.

14.8 Packaging and printed materials should be stored in secure conditions so as to exclude the possibility of unauthorized access.

14.9 Intermediate and bulk products should be kept under appropriate conditions.

14.10 Finished products should be stored under suitable conditions and appropriately segregated.

14.11 Rejected materials and products should be clearly marked as such. They should be handled in an appropriate and timely manner. Whatever action is taken should be approved by authorized personnel and recorded.

14.12 Toxic substances and flammable materials should be stored in suitably designed, separate, enclosed containers and, as required, by national legislation.

14.13 All waste materials should be stored in a safe manner and disposed of at regular intervals to avoid accumulation.

15. Documentation

15.1 Documentation includes procedures for materials and methods of production and control. The design and use of documents depend upon the research and development facility.

15.2 Documents should be designed, prepared, reviewed and authorized for use.

15.3 Standard operating procedures (SOP) should be reviewed periodically and kept up-to-date. Superseded documents should be retained for a defined period of time.

15.4 Entries of data and information should be clear and legible and meet ALCOA+ principles, as described above.

15.5 GxP data (including records for storage) may be recorded by electronic data-processing systems or by photographic or other reliable means. Batch production and control records should be protected throughout the defined period of retention.

15.6 Labels should be clear, unambiguous and in the company's agreed format.

15.7 There should be appropriately authorized and dated specifications, including tests on identity, purity and quality, for starting materials and for finished products, as appropriate.

15.8 Pharmacopoeias, reference standards, reference spectra and other reference materials should be available, where applicable.

15.9 Specifications should contain appropriate information such as the designated name; internal code reference; and qualitative and quantitative requirements with acceptance criteria. Other data may be added to the specification.

15.10 The packaging material should be examined for compliance with the specification, as appropriate.

15.11 Specifications for intermediate and bulk products should be available where the need has been identified, as appropriate.

15.12 Specifications for finished products should be available and include the required information, where available.

15.13 A master formula or batch recipe, containing the relevant information, should be available for the product and batch size.

15.14 Packaging instructions should exist for the products to be packed.

15.15 A batch processing record should be kept for each batch processed.

15.16 During processing, detailed information should be recorded at the time each action is taken. Upon completion, the record should be dated and signed by the person responsible in accordance with data integrity expectations.

15.17 A batch packaging record should be kept for each batch packed.

15.18 SOP and corresponding records, where required, should be available. These include, but are not limited to, for example:

a) equipment assembly and cleaning;
b) personnel training, clothing and hygiene;
c) maintenance;
d) sampling;
e) analytical apparatus and instrument calibration;
f) testing;
g) rejection; and
h) pest control.

15.19 Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues and labels or documents not required for the current operation.

16. Processing and process design

Processing

Note: For more details on specific aspects relating to process development, see ICH Q 8 *(12)* and ICH Q11 *(13).*

16.1 The selection of the starting materials and manufacturing process should be carefully considered in order to ensure that the intended product will meet the intended standards of safety, efficacy and quality in a consistent manner.

16.2 Knowledge management and risk assessment principles should be applied. Quality attributes, critical quality attributes, process parameters and critical process parameters should be defined and documented once sufficient data are available.

16.3 The design of experiments should cover identified variables.

Process design

Note: For details on process validation, see WHO Technical Report Series, No. 1019, Annex 3, Appendix 7, 2019 *(14)* as well as EU *(15)* and FDA Guidelines *(16).*

16.4 Process design is usually initiated by research and development facilities. This stage of process validation is also referred to as “process design”. (In a traditional or historical approach, this was often referred to as “prospective validation”.)

16.5 Product development activities provide key inputs to the process design stage. Laboratory or pilot-scale models designed to be representative of the commercial process can be used to estimate variability.

16.6 Process design should normally cover the design of experiments, process development, the manufacture of products for use in clinical trials, pilot-scale batches and technology transfer.

16.7 Process design should be verified during product development. Process design should cover aspects for the selection of materials; expected production variation; selection of production technology/process and qualification of the unitary processes that form the manufacturing process as a whole; selection of in-process controls; tests; inspection; and its suitability for the control strategy.

16.8 Where the validation data are intended to be used in applications for marketing authorizations, all batch data, results and related information should be clear, detailed and in compliance with ALCOA+.

17. Quality control

17.1 There should be adequate resources available to ensure that all the quality control (QC) arrangements are effectively and reliably carried out.

17.2 Activities and responsibilities of the QC unit include:

a) sampling and testing (e.g. starting materials, packaging materials, intermediate products, bulk products and finished products);
b) performing the necessary qualification and validation;
c) evaluating, maintaining and storing reference materials;
d) ensuring that stability programme and testing is done; and
e) conducting environmental monitoring.

17.3 The appropriate records should be kept, demonstrating that all the required activities were performed.

17.4 Sufficient samples of materials and products should be retained for a defined period of time.

17.5 The appropriate reference standards should be used. Standards should be stored in an appropriate way.

17.6 Whenever official reference standards exist, these should preferably be used.

17.7 Where secondary and working standards are established and used, these should be tested at regular intervals to ensure that they are fit for their intended use.

17.8 Reference standards should be appropriately labelled with at least the following information:

a) name of the material;
b) batch or lot number and control number;
c) date of preparation;
d) shelf life;
e) potency; and
f) storage conditions.

18. Stability studies

Note: See guideline on stability testing of active pharmaceutical ingredients and finished pharmaceutical products , WHO Technical Report Series, No. 1010, Annex 10, 2018 *(17).*

18.1 Where stability determination is initiated by research and development organizations, a written programme should be developed and implemented to include elements such as:

a) a complete description of the medicine involved in the study;
b) the complete set of testing procedure, parameters and limits;
c) attributes such as potency or assay, degradation products and physical characteristics;
d) evidence that these tests indicate stability;
e) the testing schedule for each medicine;
f) provision for special storage conditions; and
g) provision for adequate sample retention.

18.2 Sampling should be done in accordance with written procedures.

18.3 Sample preparation and testing procedures should be detailed and followed. Any deviations from the procedures should be clearly documented.

18.4 The results and data generated should be documented and include the evaluation and the conclusions of the study.

18.5 Where stability data are intended to be used in applications for marketing authorizations, all batch data, results and related information should be clear, detailed and in compliance with ALCOA+.

18.6 Records should be maintained for a defined period of time.

19. Analytical procedure development

19.1 Analytical procedures developed by research and development organizations should be appropriately recorded.

19.2 Analytical procedures developed by research and development facilities should be documented in sufficient detail to facilitate their successful transfer, when required.

19.3 Analytical procedures should be appropriately validated as fit for purpose.

Note: For details on analytical procedure validation, see WHO Technical Report Series, No. 1019, Annex 3, Appendix 4, 2019 *(18).*

20. Technology transfer

Note: For details on technology transfer, see WHO Technical Report Series, No. 961, Annex 7, 2011 (update in progress) *(10).*

20.1 Development work, including programmes, procedures, protocols, specifications, process design and validation from research and development facilities, may be transferred to production and QC sites.

20.2 Data and information relating to equipment, instruments, manufacturing and testing should be in an appropriate level of detail, traceable and available.

20.3 Authorized procedures should be followed when transferring technology from research and development organizations to production and QC facilities.

21. Life cycle approach

21.1 Industry should implement policies and procedures that will encourage science-based and risk-based approaches in product research and development.

21.2 Continual improvement should be encouraged across the entire product life cycle.

21.3 Knowledge gained from the commercial manufacturing of a product, as well as knowledge gained from other products, can be used to further improve process understanding and process performance.

21.4 New technologies and the review and interpretation of statistical evaluation of results from process design, validation and other processes, as well as other applicable data and information, should be considered in order to encourage continual improvement during the process development stage of the life cycle of the product.

21.5 Where appropriate, these should be shared and transferred to commercial manufacturing facilities.

22. Cleaning procedure development, cleaning verification and cleaning validation

Note: For details on cleaning validation, see WHO Technical Report Series, No. 1019, Annex 3, Appendix 3 *(19*), 2019 and the WHO Points to consider when including HBELs in cleaning validation, TRS 1033, Annex 2, 2021 *(20).*

22.1 Research and development facilities are often involved in the development and validation of cleaning procedures. QRM principles should be applied in cleaning procedure development and cleaning validation.

22.2 The development of cleaning procedures should include cleanability.

22.3 Where preparatory work for cleaning validation is done in research and development facilities with a view of technology transfer, the commercial manufacturing sites consideration should be given for inclusion of Health Based Exposure Limits (HBELs) in the approach.

22.4 The sampling of procedures should include swab and rinse samples. Maximum Safe Residue, Maximum Safe Surface Residue and Visible Residue Limits should be considered in the new cleaning validation approach.

22.5 The development of the analytical procedures to be used in the testing for residues should be appropriately documented. The procedures should be validated.

22.6 The procedures for sampling and testing, and the results obtained, should meet ALCOA+ principles. The data and information should be retained over the life cycle of the product.

22.7 Procedures and protocols should be followed for the TOT to commercial manufacturing sites.

22.8 Records should be maintained.

Abbreviations

ALCOA+	attributable, legible, contemporaneous, original and accurate, complete, consistent, enduring, and available
GMP	Good manufacturing practices
GxP	Good practices
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
QC	Quality control
QRM	Quality risk management

838 TOT Transfer of technology
839

840 References

841

842 1. WHO good manufacturing practices for investigational pharmaceutical products for clinical
843 trials in humans. In: WHO Expert Committee on Specifications for Pharmaceutical
844 Preparations: thirty-fourth report. Geneva: World Health Organization; 1996: Annex 7 (WHO
845 Technical Report Series, No. 863 {*under revision: working document QAS/20.863*}).
846 2. WHO good manufacturing practices for active pharmaceutical ingredients. In: WHO Expert
847 Committee on Specifications for Pharmaceutical Preparations: forty-fourth report. Geneva:
848 World Health Organization; 2010: Annex 2 (WHO Technical Report Series, No. 957).
849 3. WHO good manufacturing practices for pharmaceutical products: main principles. In: WHO
850 Expert Committee on Specifications for Pharmaceutical Preparations: forty-eight report.
851 Geneva: World Health Organization; 2014: Annex 2 (WHO Technical Report Series, No. 986).
852 4. WHO good manufacturing practices: water for pharmaceutical use. In: WHO Expert
853 Committee on Specifications for Pharmaceutical Preparations: forty--six report. Geneva:
854 World Health Organization; 2012: Annex 2 (WHO Technical Report Series, No. 970).
855 5. WHO guidelines for sampling of pharmaceutical products and related materials. In: WHO
856 Expert Committee on Specifications for Pharmaceutical Preparations: thirty-ninth report.
857 Geneva: World Health Organization; 2005: Annex 4 (WHO Technical Report Series, No. 929).
858 6. WHO guidelines on heating, ventilation and air-conditioning systems for non-sterile
859 pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical
860 Preparations:. fifty-second report. Geneva: World Health Organization; 2018: Annex 8 (WHO
861 Technical Report Series, No. 1010).
862 7. WHO supplementary guidelines on good manufacturing practices: validation. In: WHO Expert
863 Committee on Specifications for Pharmaceutical Preparations: fortieth report. Geneva: World
864 Health Organization; 2006: Annex 4 (WHO Technical Report Series, No. 937).
865 8. WHO good practices for pharmaceutical products containing hazardous substances. In: WHO
866 Expert Committee on Specifications for Pharmaceutical Preparations: forty-fourth report.
867 Geneva: World Health Organization; 2010: Annex 2 (WHO Technical Report Series, No. 957).
868 9. WHO good manufacturing practices for sterile pharmaceutical products. In: WHO Expert
869 Committee on Specifications for Pharmaceutical Preparations: forty-fifth report. Geneva:

World Health Organization; 2011: Annex 6 (WHO Technical Report Series, No. 961 {*under revision: consultation closed*}).

10. WHO guidelines on transfer of technology in pharmaceutical manufacturing. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fifth report. Geneva: World Health Organization; 2011: Annex 7 (WHO Technical Report Series, No. 961 {*under revision: working document QAS/QAS20.869*}).
11. WHO good practices for pharmaceutical quality control laboratories. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fourth report. Geneva: World Health Organization; 2010: Annex 1 (WHO Technical Report Series, No. 957).
12. ICH harmonised tripartite guideline. Pharmaceutical Development Q8. Geneva: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceutical for Human Use; 2009).
13. ICH harmonised tripartite guideline. Quality risk management Q9. Geneva: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceutical for Human Use; 2005.
14. WHO 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).
15. EMA Guideline on process validation for finished products - information and data to be provided in regulatory submissions. (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.1) Committee for Medicinal Products for Human Use (CHMP) and Committee for Medicinal Products for Veterinary Use (CVMP), 2016.
16. FDA Guidance for Industry Process Validation: General Principles and Practices, January 2011.
17. WHO stability testing of active pharmaceutical ingredients and finished pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-second report. Geneva: World Health Organization; 2018: Annex 10 (WHO Technical Report Series, No. 1010).
18. 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).

19. 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).
20. Points to consider when including Health-Based Exposure Limits (HBELs) in cleaning validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fifth report. Geneva: World Health Organization; 2021: Annex 2 (WHO Technical Report Series, No. 1025).

Further reading

- WHO model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fifth report. Geneva: World Health Organization; 2011: Annex 9 (WHO Technical Report Series, No. 961).
- WHO general guidelines for the establishment, maintenance and distribution of chemical reference substances. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-first report. Geneva: World Health Organization; 2007: Annex 3 (WHO Technical Report Series, No. 943).
- WHO good practices for pharmaceutical microbiology laboratories. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fifth report. Geneva: World Health Organization; 2011: Annex 2 (WHO Technical Report Series, No. 961).
- 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).
- WHO guidelines on variation to a prequalified product. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-seventh report. Geneva: World Health Organization; 2013: Annex 3 (WHO Technical Report Series, No. 981).
- WHO guidelines for drafting a site master file. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fifth report. Geneva: World Health Organization; 2011: Annex 14 (WHO Technical Report Series, No. 961).

- WHO general guidance on hold-time studies. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. Geneva: World Health Organization; 2015: Annex 4 (WHO Technical Report Series, No. 992).
- WHO technical supplements to model guidance for storage and transport of time- and temperature-sensitive pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. Geneva: World Health Organization; 2015: Annex 5 (WHO Technical Report Series, No. 992).
- WHO recommendations for quality requirements when plant–derived artemisinin is used as a starting material in the production of antimalarial active pharmaceutical ingredients. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. Geneva: World Health Organization: 2015: Annex 6 (WHO Technical Report Series, No. 992).
- 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).
- WHO general guidance on variations to multisource pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: Fiftieth report. Geneva: World Health Organization; 2016: (WHO Technical Report Series, No. 996).
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) ICH Q10, Pharmaceutical Quality System, 2008.
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) ICH Q11, Development and Manufacture of Drug Substances, 2018.
- ISPE. Good Practice Guide. Technology Transfer. Third edition, 2018.
- Pharmaceutical industry, the discovery, development, and manufacture of drugs and medications (pharmaceuticals) by public and private organizations. J. W. Dailey. 2003.
- 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).

***