DRAFT WORKING DOCUMENT FOR COMMENTS:

Good practices for research and development facilities

Please send your comments to Dr Sabine Kopp, Team Lead, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (kopps@who.int), with a copy to Ms Claire Vogel (vogelc@who.int) before 6 January 2021. Please use the attached “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 all our draft guidelines, please send your email address to jonessi@who.int and your name will be added to our electronic mailing list.

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**Good practices for research and development facilities**

<table>
<thead>
<tr>
<th>Description of Activity</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
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<tr>
<td>Preparation of first draft working document.</td>
<td>October 2020</td>
</tr>
<tr>
<td>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</td>
<td>November 2020</td>
</tr>
<tr>
<td>Consolidation of comments received and review of feedback. Preparation of working document for discussion.</td>
<td>January 2021</td>
</tr>
<tr>
<td>Discussion of the feedback received on the working document in a virtual meeting with an expert working group</td>
<td>February-March 2021</td>
</tr>
<tr>
<td>Preparation of working document for next round of public consultation.</td>
<td>March 2021</td>
</tr>
<tr>
<td>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.</td>
<td>April 2021</td>
</tr>
<tr>
<td>Consolidation of comments received and review of feedback. Preparation of working document for discussion.</td>
<td>June – July 2021</td>
</tr>
<tr>
<td>Discussion of the feedback received on the working document in a virtual meeting with an expert working group</td>
<td>August 2021</td>
</tr>
<tr>
<td>Presentation to the Fifty-sixth meeting of the ECSPP.</td>
<td>October 2021</td>
</tr>
<tr>
<td>Any other follow-up action as required.</td>
<td></td>
</tr>
</tbody>
</table>
Good practices for research and development facilities

1. Introduction and background
2. Scope
3. Quality management
4. Quality risk management
5. Sanitation and hygiene
6. Qualification and validation
7. Outsourced activities
8. Self-inspection and quality audits
9. Personnel
10. Training
11. Premises
12. Equipment and instruments
13. Materials
14. Documentation
15. Processing and process validation
16. Quality control
17. Stability studies
18. Analytical procedure development
19. Transfer of technology
20. Life cycle approach
21. Cleaning procedure development and cleaning validation

Glossary
Abbreviations
References
Further reading
1. Background

In view of the recent need for the unprecedented fast development of health products 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 good manufacturing practice (GMP) text to address the manufacturing of developmental batches, pilot batches and the sequential stability data that is submitted in product applications (dossiers) for marketing authorization and the prequalification of medical products.

There are currently no regulatory guidelines which address this matter, although the data collected from these batches influence the following aspects of the product:

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

2. Introduction

2.1. The modern era of the pharmaceutical industry, in particular focusing on chemical synthesis, began in the 19th century. The use of computerized systems in production and control is increasing rapidly. The ongoing evolution and advancement in the pharmaceutical industry is fundamental in the control and elimination of disease around the world.

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

2.3. Furthermore, as regulators request and review data and information such as the development data of products and processes, design of experiments, validation and stability results, it has become necessary to ensure that the facilities, quality systems, data and information meet the appropriate standards and good practices.
2.4. This document intends to provide guidance on 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. It further helps to help ensure that products meet the requirements for safety, efficacy and quality that they purport to possess.

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

2.6. The WHO document titled *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 stability testing, analytical method validation, cleaning validation and the transfer of technology (TOT). (*See the References and Further Reading sections*)

2.7. 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”.

3. **Scope**

3.1. This guideline is applicable to research and development facilities of products manufactured by chemical synthesis, extraction, cell culture or fermentation, by recovery from natural sources, or by any combination of these processes. It further covers development of procedures and processes intended for transfer and use 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*).
3.2. This guide excludes all vaccines, whole cells, whole blood and plasma, blood and plasma derivatives (plasma fractionation), medical gases, commercial products, radiopharmaceuticals and gene therapy products.

3.3. The good practices 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 proven.

3.4. 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.

3.5. 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.

3.6. 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.

3.7. 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 medical products.

3.8. The main focus of the document is on pharmaceutical formulation and development. The principles described in this document may however be applied in facilities where other products such as vaccines, veterinary products and biopharmaceutical products are developed. The principles may also be considered, where appropriate, in facilities where medical devices are manufactured.
Due to the nature of research 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 research to commercial batch manufacturing. The stringency of GMP in research and development should increase as the process proceeds from early research work to the final steps of development and formulation, stability testing, process validation and cleaning validation.

Figure 1. Application of this guide

Early research – Research – Development/formulation – Registration batches

Increased compliance with Good Manufacturing Practices*

*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

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. 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. All parts of the quality system should be adequately resourced and maintained, including with sufficient competent personnel, suitable premises, equipment and facilities.

4.6. Initial research, as well as development activities, should be defined and documented. The detail should be in accordance with risk assessment and the increasing scale of GMP requirements from early to final stages of development.

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

- managerial responsibilities are clearly specified in job descriptions;
- instructions and procedures are written in clear and unambiguous language;
- procedures are correctly carried out;
- records are made (manually and/or by recording instruments) during production and quality control;
- any significant deviations are recorded, investigated and the appropriate action taken;
- records are maintained;
- there is a system for quality risk management (QRM);
- arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;
- all necessary controls on starting materials, intermediate products, bulk products and other in-process controls are carried out;
- calibrations and validations are carried out where appropriate;
- the product and process knowledge is managed;
- products are designed and developed in accordance with applicable good practices (GxP);
- production and control operations are clearly specified in written form;
- continual improvement is facilitated through the implementation of quality improvements appropriate to the current level of process and product knowledge;
- product realization is achieved;
- cleaning procedures are developed and validated;
- stability testing is done following written procedures and protocols; and
- data meet ALCOA+ requirements.

4.8. 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.

5.4. Risk assessments should be periodically reviewed in light of improvements, current technology, scientific knowledge and experience.

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 eliminated.

7. **Qualification and validation**

7.1. Qualification and validation required should be identified based on risk assessment and, in addition, should be appropriate to the stage of research and development.
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. Qualification and validation should provide documentary evidence that specifications and other requirements are met. Protocols and reports should be made available, when required.

7.5. 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 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 his or her 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 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.

The agreement

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

8.11. The agreement should describe the handling of materials, such as samples and products, if they are out of specification or rejected.

8.12. The agreement should permit the contract giver to audit the facilities and activities of the contract acceptor.

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) quality control;
h) documentation;
i) sanitation and hygiene;
j) qualification and validation;
k) calibration of instruments or measurement systems;
l) control of labels; and
m) 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. 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 GxPs.

10.3. Steps should be taken to prevent unauthorized people from entering storage, production and quality control areas.
10.4. The heads of production and quality unit should be independent of each other.

10.5. 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.

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.

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 of highly active, toxic, infectious or sensitizing materials.

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. Where product dust is generated, measures should be taken to avoid cross-contamination and to facilitate cleaning.

12.4. Premises should be cleaned according to detailed written procedures. Records should be maintained.
12.5. 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. Animal houses should be well isolated from other areas, with a separate entrance (animal access) and air-handling facilities.

12.8. Storage areas should be of sufficient capacity with proper separation and segregation between materials, based on risk assessment.

12.9. 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.

12.10. Segregation should be provided for the storage of quarantined, released and rejected materials and products.

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

12.12. Materials identified for testing should be sampled in accordance with written procedures and analysed for compliance with their specifications.

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

12.14. Quality control (QC) laboratories 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.
13. Equipment and instruments

13.1. 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. Balances and other measuring equipment of an appropriate range and precision should be available for production and control operations and should be calibrated on a scheduled basis.

13.4. 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. Materials, identified through risk assessment, should be quarantined immediately after receipt, sampled and tested in accordance with specifications.

14.3. Materials released by the quality department and within their shelf life should be used.

14.4. Materials identified through risk assessment should be stored under the appropriate conditions as specified on their labels and in an orderly fashion to permit segregation, stock rotation and a first-expire, first-use rule.

14.5. The dispensing of materials for the production of a batch should be done according to a written procedure. 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. Water used should be suitable for its intended use.

14.8. Packaging 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.

14.11. Rejected materials and products should be clearly marked as such and stored separately in restricted areas. 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. 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 specifications and procedures for materials and methods of production and control. The design and use of documents depend upon the research and development facility. The scope and extent should be established based on risk assessment and the stage of research and development (see Figure 1).

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

15.3. Documents 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.

15.5. Data (and 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.

15.8. Pharmacopoeias, reference standards, reference spectra and other reference materials should be available in the QC laboratory.

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

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

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

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

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

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. It should be based on the relevant parts of the current specifications on record.
15.16. During processing, detailed information should be recorded at the time each action is taken and, after completion, the record should be dated and signed by the person responsible for the processing operations.

15.17. A batch packaging record should be kept for each batch or part batch processed.

15.18. Standard operating procedures (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) release and rejection; and

h) pest control.

15.19. Cross-contamination should be avoided by taking the appropriate technical or organizational measures.

15.20. 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, labels or documents not required for the current operation.

15.21. To prevent cross-contamination and mix-ups, different products should not be packaged in close proximity.
16. Processing and process validation


Processing

Note: For more details on specific aspects relating to process development, see ICH Q 11.

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.

16.3. The design of experiments should cover identified variables.

Process validation

16.4. Process validation is usually initiated by research and development organizations. During this stage, the 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. As 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. The QC unit should be independent from production.

17.2. There should be adequate resources available to ensure that all the QC arrangements are effectively and reliably carried out.

17.3. 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 standards for substances;

d) ensuring that stability programme and testing is done;

e) participating in environmental monitoring; and

f) participating in QRM programmes.

17.4. Appropriate records should be kept, demonstrating that all the required activities were performed.

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

17.6. Appropriate reference standards should be used. Standards should be stored in an appropriate way.
17.7. Whenever official reference standards exist, these should preferably be used.

17.8. 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.

17.9. 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


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 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. As the procedures are usually intended to be transferred to quality control units in manufacturing facilities of commercial batches, procedures and records should be sufficiently detailed to ensure that TOT will be successful.

19.3. Analytical procedures should be appropriately validated.


20. Transfer of technology

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

20.1. Development work, including programmes, procedures, protocols, specifications and validation from research and development organizations, may be transferred to production and quality control sites.
20.2. Data and information relating to equipment, instruments, manufacturing, and testing should be detailed, traceable and available.

20.3. Authorized procedures should be followed when transferring technology from research and development organizations to production and quality control 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 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 and cleaning validation

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. Health Based Exposure Limits (HBELs) should be considered in the approach to cleaning validation.

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. 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. Records should be maintained.
Glossary

The definitions given below apply to the terms used in this guide. 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.

**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.

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

TOT Transfer of technology

References


Further reading


