World Health Organization

DRAFT WORKING DOCUMENT FOR COMMENTS:

WHO good manufacturing practices for excipients used in pharmaceutical products

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Our working documents are sent out electronically and uploaded into PleaseReview™. The working documents are also placed on the WHO Medicines website (https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/pharmaceuticals/working-documents-public-consultation) under the "Working documents in public consultation". If you wish to receive all our draft guidelines, please send your full name, organization / affiliation, and email address to nsp@who.int and your name will be added to our electronic mailing list and review platform.

SCHEDULE FOR DRAFT WORKING DOCUMENT QAS/23.921:

WHO good manufacturing practices for pharmaceutical Excipients

Description of Activity	**Date**
Preparation of first draft working document.	December 2022
Review and finalization of the first draft working document with an informal drafting group.	February 2023
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.	March 2023
Consolidation of comments received and review of feedback. Preparation of working document for discussion.	May – June 2023
Discussion of the feedback received on the working document in a virtual meeting with an informal consultation group.	June – July 2023
Preparation of a working document for discussion and possible adoption by the ECSPP	August – September 2023
Presentation to the Fifty-seventh meeting of the ECSPP.	October 2023
Any other follow-up action as required.	

WHO good manufacturing practices for excipients used in pharmaceutical products

Background

The WHO guideline Good Manufacturing Practices: supplementary guidelines for the manufacture of pharmaceutical excipients, was published in the WHO Technical Report Series No 885, 1999.

As excipients are sometimes used in large quantities in pharmaceutical dosage forms, and may contain impurities, they can affect the quality of a finished pharmaceutical product.

The manufacturer of the finished pharmaceutical product is normally dependent on the manufacturer of the excipient to supply excipients meeting the required specification. An appropriately established and implemented quality management system evaluating and controlling risks in the production and quality control of such excipients is therefore required.

Some excipient manufacturers may be required to follow good manufacturing practices for excipients used in pharmaceutical products. Reports of pharmaceutical products which contain contaminated excipients, or excipients with impurities leading to the death of patients, have further highlighted the need for a revision of the original guideline. Furthermore, the concept of ongoing improvement, life cycle approach, better quality management systems, risk management and management review should be described in such a guideline, alongside the necessary good storage, good trade and good distribution practices to ensure their reliability throughout the supply chain.

The manufacturer of excipients used in pharmaceutical products should be able to identify risks associated with the production (including stages of manufacturing, route of synthesis) and quality control of its products. This includes, but is not limited to, the premises, equipment, utilities, storage and distribution. The manufacturer of such excipients should assess those risks, and identify appropriate measures to mitigate such risks. The effectiveness of the measures should be evaluated to ensure that they are appropriate.

This document provides information on good manufacturing practices that should be implemented to assist manufacturers to produce and control excipients used in pharmaceutical products that will meet their intended specifications, in a consistent manner. Risk assessment may be useful in determining which excipients should be manufactured in accordance with this guideline.

WHO good manufacturing practices for excipients used in pharmaceutical products

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1. Introduction and scope

1.1. The purpose of this document is to provide guidance for the production, control, storage and distribution of excipients used in pharmaceutical products, focusing on good manufacturing practices (GMP) under an appropriate system for managing quality. It is also intended to help ensure that such excipients meet the requirements for quality and purity that they purport or are represented to possess.

1.2. The document does not cover aspects of protection of the environment, nor safety aspects for the personnel engaged in the manufacture and control of materials and excipients.

1.3. Excipients are often used in large quantities in industrial chemistry, as well as the food and cosmetic industry. Specifications for excipients used in these applications may vary and may not always be appropriate for use in pharmaceutical products. It is the responsibility of the finished product manufacturer and of the applicant to ensure that the finished product is manufactured using excipients of a suitable grade conforming to its intended use.

1.4. Excipients are often used in significant quantities in the production of pharmaceutical products. They should be of appropriate quality as they could affect the quality of finished pharmaceutical products.

1.5. The manufacturer of the finished pharmaceutical product is highly dependent on the excipient manufacturer to provide materials that are homogeneous in chemical and physical characteristics, and of the desired quality.

1.6. In general, excipients are used as purchased, with no further refining or purification. Consequently, impurities present in the excipient will be carried over to the finished pharmaceutical product.

1.7. To achieve the objective of ensuring that excipients used in pharmaceutical products are of appropriate quality, an appropriate level of GMP should be established, implemented and maintained during their production, packaging, repackaging, labelling, quality control, release, storage, distribution and other related activities. Additional measures should be taken when manufacturing excipients for which scientific literature, information in the public domain or historical data indicate that they present higher risk because of potential formation of toxic impurities during the manufacturing process, or due to potential contamination during storage and distribution.

1.8. Specific analytical procedures should be used by the excipient manufacturer, where the excipient is intended to be used in a pharmaceutical product, to ensure that it is suitable for its intended use. Pharmacopoeia and regulatory requirements should be considered by the manufacturers as a reference for these analytical tests. Information in the public domain may also be considered. Risk management principles should be implemented in order to identify and mitigate risks.

1.9. A thorough knowledge and understanding of the processes and associated risks are required. This includes all unit operations and processing steps, key steps in the process, critical parameters (time, temperature, pressure, etc.), environment conditions, equipment used, contamination protection and monitoring points.

2. Glossary

The definitions given below apply to the terms used in this document. They have been aligned as much as possible with the terminology in related WHO guidelines and good practices (GxP) and included in the WHO Quality Assurance of Medicines Terminology Database - List of Terms and related guideline https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/mqa-terminology-sept-2020.pdf?sfvrsn=48461cfc_5, but may have different meanings in other contexts.

Acceptance criteria. Numerical limits, ranges or other suitable measures for acceptance of test results.

Batch (or lot). A specific quantity of material produced in a single process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defi ned fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval.

Batch number (or lot number). A unique combination of numbers, letters and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined.

Calibration. The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements.

Commingling / commingled. The blending of carry-over material from one grade of an excipient with another, usually due to a continuous process.

Computer system. A group of hardware components and associated software, designed and assembled to perform a specific function or group of functions.

Computerized system. A process or operation integrated with a computer system.

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

Critical. Describes a process step, process condition, test requirement or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the excipient meets its specification.

Cross-contamination. Contamination of a material or product with another material or product.

Deviation. Departure from an approved instruction or established standard.

Excipient for pharmaceutical use. Substances, other than the active ingredient, which have been appropriately evaluated for safety and are included in a drug delivery system to:

- aid in the processing of the drug delivery system during its manufacture;
- protect, support or enhance stability, bioavailability, or patient acceptability;
- assist in product identification; or
- enhance any other attribute of the overall safety and effectiveness of the drug during storage or use.

Expiry date (or expiration date). The date placed on the container or labels of an excipient designating the time during which the excipient is expected to remain within established shelf-life specifications if stored under defi ned conditions and after which it should not be used.

Finished pharmaceutical product (FPP). WHO: A product that has undergone all stages of production, including packaging in its final container and labelling. An FPP may contain one or more APIs.

Impurity. Any component present in the intermediate or product that is not the desired entity.

Impurity profile. A description of the identified and unidentified impurities present in an intermediate or product.

In-process control (or process control). Checks performed during production in order to monitor and, if appropriate, to adjust the process and/or to ensure that the intermediate or product conforms to its specifications.

Intermediate. A material produced during steps of the processing of an excipient for pharmaceutical use that undergoes further molecular change or purification before it becomes an excipient for pharmaceutical use. Intermediates may or may not be isolated.

Lot. See Batch.

Lot number. See Batch number.

Manufacture. All operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release, storage and distribution of excipient and related controls.

Material. A general term used to denote raw materials (starting materials, reagents, solvents), process aids, intermediates, APIs and packaging and labelling materials.

Model product. A product which simulates a group of similar products.

Mother liquor. A concentrated solution from which the product is obtained by evaporation, freezing, and/or crystallization. (Or: The residual liquid which remains after the crystallization or isolation processes. A mother liquor may contain unreacted materials, intermediates, levels of the excipient for pharmaceutical use and/or impurities. It may be used for further processing).

Packaging material. Any material intended to protect an intermediate or excipient for pharmaceutical use during storage and transport.

Procedure. A documented description of the operations to be performed, the precautions to be taken and measures to be applied, directly or indirectly related to the manufacture of an intermediate or excipient for pharmaceutical use.

Process aids. Materials, excluding solvents, used as an aid in the manufacture of an intermediate or excipient for pharmaceutical use that do not themselves participate in a chemical or biological reaction (e.g. filter aid or activated carbon).

Production. All operations involved in the preparation of a excipient for pharmaceutical use from receipt of materials through processing and packaging of the excipient for pharmaceutical use.

Qualification. Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.

Quality assurance (QA). The sum total of the organized arrangements made with the object of ensuring that all excipients for pharmaceutical use are of the quality required for their intended use and that quality systems are maintained.

Quality control (QC). Checking or testing that specifications are met.

Quality unit(s). An organizational unit independent of production which fulfils both quality assurance (QA) and quality control (QC) responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

Quarantine. The status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection.

Raw material. A general term used to denote starting materials, reagents and solvents intended for use in the production of intermediates or excipient for pharmaceutical use.

Reprocessing. Introducing an intermediate or excipient for pharmaceutical use, including one that does not conform to standards or specifications, back into the process and repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g. distillation, filtration, chromatography or milling) that are part of the established manufacturing process. Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process and not to be reprocessing.

Retest date. The date when a material should be re-examined to ensure that it is still suitable for use.

Reworking. Subjecting an intermediate or excipient for pharmaceutical use that does not conform to standards or specifications to one or more processing steps that are different from the established manufacturing process to obtain acceptable quality intermediate or excipient for pharmaceutical use (e.g. recrystallizing with a different solvent).

Signature (signed). See Signed.

Signed (signature). The record of the individual who performed a particular action or review. This record can be in the form of initials, full handwritten signature, personal seal or an authenticated and secure electronic signature.

Solvent. An inorganic or organic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of an intermediate or excipient for pharmaceutical use.

Specification. A list of tests, references to analytical procedures and appropriate acceptance criteria that are numerical limits, ranges or other criteria for the test described. It establishes the set of criteria to which a material should conform to be considered acceptable for its intended use. “Conformance to specification” means that the material, when tested according to the listed analytical procedures, will meet the listed acceptance criteria.

Validation. A documented programme that provides a high degree of assurance that a specific process, method or system will consistently produce a result meeting predetermined acceptance criteria.

Validation protocol. A written plan stating how validation will be conducted and defining acceptance criteria. For example, the protocol for a manufacturing process identifies processing equipment, critical process parameters and operating ranges, product characteristics, sampling, test data to be collected, number of validation runs and acceptable test results.

3. Quality management

3.1. Manufacturers involved in the production, control, storage and distribution of excipients for pharmaceutical use should establish, document, implement and maintain a comprehensively designed and clearly defined quality management system.

3.2. Senior management should assume responsibility for the quality management system, as well as the quality of the excipients for pharmaceutical use manufactured, controlled, released, stored and distributed.

3.3. The quality management system should encompass the quality policy, organizational structure, procedures, processes and resources. All parts of the quality management system should be adequately resourced and maintained.

3.4. The quality management system should cover all activities necessary to ensure that excipients for pharmaceutical use will meet their intended specifications, including quality and purity.

3.5. The quality management system should incorporate the principles of good practices (GxP) which should be applied to the life cycle stages of excipients for pharmaceutical use. This includes steps such as the receipt of raw materials, production, packaging, testing, release, storage and distribution.

3.6. All quality-related activities and procedures should be defined and documented manually or electronically.

3.7. All quality-related activities should be recorded at the time they are performed.

3.8. The quality management system should ensure that:

a) sufficient resources are available (e.g. equipment, personnel, materials);
b) excipients for pharmaceutical use are manufactured, controlled, stored and

distributed in accordance with the recommendations in this document and other associated guidelines such as good quality control laboratory practices and good storage and distribution practices, where appropriate;

c) managerial roles, responsibilities and authorities are clearly specified in job descriptions;

d) operations and other activities are clearly described in a written form such as standard operating procedures (SOPs) and work instructions;

e) arrangements are made for the manufacture, supply and use of the correct containers and labels;

f) all necessary controls are in place;

g) calibrations and validations are carried out where necessary;

h) the excipient for pharmaceutical use is correctly processed and checked according to the defined procedures and specifications;

i) deviations, suspected product defects, out-of-specification test results and any other non-conformances or incidents are reported, investigated and recorded. An appropriate level of root cause analysis is applied during such investigations and the most likely root cause(s) is/are identified;

j) proposed changes are evaluated and approved prior to implementation. After implementation of any change, an evaluation should be undertaken to confirm that the quality objectives were achieved and that there was no unintended adverse impact on product quality;

k) appropriate corrective actions and preventive actions (CAPAs) are identified and taken where required processes are in place to ensure the management of any outsourced activities that may impact product quality, purity and integrity;

l) excipients for pharmaceutical use are not released and supplied before it has been certified that each batch has been produced and controlled in accordance with product specifications, the recommendations in this document and any other regulations relevant to the production, control and release of these products;

m) there is a system for handling complaints, returns and recalls;

n) there is a system for self-inspection;

o) there is a system for product quality review.

3.9. The quality unit(s) should be independent of production. The responsibilities of the unit should be clearly defined and documented.

3.10. The person(s) authorized to release excipients for pharmaceutical use should have appropriate qualifications, and be specified.

Quality Risk Management

3.11. There should be a system for managing risks. The system for quality risk management should be comprehensive and should cover a systematic process for the assessment, control, communication and review of risks in the production, testing, storage and distribution of excipients for pharmaceutical use. Controls identified should be appropriate, ensure that risks are eliminated or mitigated, and ultimately protect the patient from receiving a pharmaceutical product containing the wrong, contaminated or unsuitable excipients for pharmaceutical use.

3.12. Risk assessments should be documented. Appropriate controls should be implemented and their effectiveness checked and documented at suitable intervals.

Note: See WHO guidelines on quality risk management(1)

Management review

3.13. There should be a system for regular management review. All elements of the quality management system should be included.

3.14. Management should ensure that the quality management system achieves its intended objectives and measure managing and performance in areas such as, but not limited to:

a) Self-inspections, inspections, quality audits and supplier's audits;
b) Complaints, returns and recalls;
c) Changes and deviations;
d) Rejected batches;

e) Quality control, out of specifications and out of trend results;
f) Maintenance;
g) Qualification and validation;
h) Corrective and preventive actions;
i) Risk management;

3.15. Key performance indicators should be identified and monitored with the view of continual improvement.

3.16. Records of meetings, discussions and actions should be maintained.

4. Complaints

4.1. There should be a written procedure describing the recording and investigation of complaints.

4.2. All decisions made and measures taken as a result of a complaint should be recorded.

4.3. Complaint records should include at least the following:

a) Date of receiving the complaint;
b) Name, address and other relevant details of complainant;
c) Details of the complaint including name of the excipient and batch number;
d) Details of the investigation and action taken;
e) Copy of the response provided;
f) Final decision based on the outcome of the investigation.

4.4. Where necessary, the appropriate corrective action and follow-up action should be taken after the investigation and evaluation of a complaint.

4.5. Where necessary, a recall of the batch or batches should be considered.

4.6. Records of complaints should be retained in order to evaluate trends.

5. Recalls

5.1. There should be a written, authorized procedure describing the managing of a recall of excipient for pharmaceutical use.

5.2. The recall procedure should indicate the responsibilities of personnel involved in the recall, how the recall should be initiated, who should be informed about the recall and how the recalled material should be handled.

5.3. The recall of an excipient for pharmaceutical use should be documented. Records should be kept.

6. Returns

6.1. There should be a written, authorized procedure describing the handling of returned excipients for pharmaceutical use.

6.2. The disposition of the returned product should be approved by the quality unit. The conditions under which the excipient for pharmaceutical use had been stored and shipped should be considered when deciding on the fate of the returned product. If the condition of the container itself casts doubt on the safety, quality or purity of the excipient, the product should be destroyed, unless scientific justification can be provided that proves that the product meets the appropriate predefined quality standards.

6.3. Where returned excipient containers are reused, all previous labelling should be removed. The containers should be appropriately cleaned and there should be no risk of contamination from one material to another.

7. Self-inspection, quality audits and supplier's audits and approvals

7.1. There should be written SOPs and programs for periodic self-inspections, quality audits and supplier audits.

7.2. Self-inspections should be performed routinely in accordance with a self-inspection program.

7.3. The team responsible for self-inspection should consist of personnel with the appropriate knowledge and experience. Team members may be from inside or outside the manufacturer, but members of the team should be free from bias.

7.4. Areas to be covered in self-inspections may include for example:

a) Premises;
b) Personnel;
c) Equipment;
d) Maintenance and calibration;
e) Storage conditions of materials and finished products;
f) Production and in-process controls;
g) Quality control;
h) Documentation, data generation and data integrity; and
i) Change control and deviations management;
j) Complaints management;
k) Qualification and validation.
l) Cleaning procedures

7.5. The excipient's end use should be considered during inspection of excipient

manufacturers. It is particularly important to know whether the excipient will be used in the preparation of a sterile dosage form. The excipient manufacturer is responsible for ensuring that excipients are pyrogen free if the manufacturer makes such a representation in specifications, labels or a drug master file.

7.6. Self-inspection should also ensure that appropriate measures are in place to prevent contamination of materials during storage and production.

7.7. The outcome of the self-inspection should be documented including corrective actions and preventive actions.

8. Personnel

8.1. There should be an adequate number of personnel with appropriate qualifications, training and/or experience to perform their respective activities.

8.2. Responsibilities should be specified in written job descriptions.

8.3. Training should be regularly conducted and should include for example, GMP and the particular operations of the employee. Assessment of understanding of training topics should be done and documented.

8.4. Records of training should be maintained.

9. Sanitation and hygiene

9.1. Excipients for pharmaceutical use should be protected from contamination. Documented risk assessment should identify controls to be implemented to ensure appropriate sanitation and hygiene actions are taken.

9.2. Written procedures should be followed for cleaning and sanitization, as appropriate, for example manufacturing areas, equipment, and utilities.

9.3. Personnel should practice good hygiene and health habits.

9.4. Personnel should wear clean clothing suitable for their activities. Additional personal protective equipment should be worn when necessary.

9.5. Personnel should avoid direct contact with starting materials and excipients for pharmaceutical use.

9.6. Smoking, eating, drinking, chewing and the storage of food should not be allowed in production and quality control areas.

9.7. Personnel with an infectious disease or who have open lesions on the exposed surface of the body should not engage in activities that could result in compromising the quality of excipient for pharmaceutical use.

9.8. Jewellery and mobile phones should only be used in authorized areas.

10. Documentation

10.1. Documents such as SOPs, specifications and others related to the production and control of excipients for pharmaceutical use should be prepared, reviewed, updated, approved and distributed according to written procedures.

10.2. The issuance, revision, withdrawal and retention of documents should be appropriately controlled.

10.3. Documents should be retained for a defined period of time.

10.4. Where documents require the entry of data, these entries should be clear, legible and indelible. Entries should be in compliance with good documentation practices and data integrity requirements.

10.5. Records should be made or completed when any action is taken and in such a way that all significant activities are traceable to the person making the entry including signatures and dates. Corrections made to incorrect entries should be dated and signed with a description of the reason for the change as appropriate.

10.6. Electronic documents and records should meet the requirements for good documentation practices, and computerized systems.

Standard operating procedures and records

10.7. SOPs and associated records should be available for at least, but not limited to:

a) equipment;
b) analytical apparatus and instruments;
c) Out of specifications
d) maintenance and calibration;
e) cleaning and sanitization;
f) personnel matters such as training, clothing and hygiene;
g) qualification and validation;
h) self-inspection
i) complaints;
j) recalls; and
k) returns.

10.8. The SOPs for sampling should specify the person(s) authorized to take samples and the sampling instructions.

10.9. The SOPs describing the details of the batch (lot) numbering system should ensure that each batch of excipient for pharmaceutical use is identified with a specific batch number.

10.10. Records of analysis should be maintained.

10.11. Written release and rejection procedures should be available, in particular for the release of the excipient for pharmaceutical use for sale.

10.12. Records should be maintained of the distribution of each batch of excipient for pharmaceutical use.

10.13. Records should be kept for major and critical equipment, as appropriate, of any qualifications, calibrations, maintenance, cleaning or repair operations, including the dates and the identities of the people who carried out these operations.

Specifications

10.14. Specifications should be established and maintained for starting materials, packaging materials, excipients for pharmaceutical use, and other related materials where necessary.

10.15. Quality attributes, acceptance limits and test procedures should be defined. Relevant pharmacopoeia monographs, when available, should be considered for use or to be used as a basis for the development of internal manufacturer's specifications.

10.16. A positive identification test uniquely applicable to the excipients should be established through analytical technology, such as infrared spectrophotometry and chromatography.

10.17. Appropriate limits for impurities should be specified. These limits should be based upon appropriate toxicological data, or limits described in national compendial requirements. Manufacturing processes should be adequately controlled so that the impurities do not exceed such established specifications.

10.18. Where excipients are extracted from or purified by the use of organic solvents, specifications should include tests and limits for residues of solvents and other reactants.

10.19. Container specifications should be established for all excipients to assure consistency in protecting the product during storage and transport, to maintain the stability of the product, and for protection against contamination, infestation, and handling.

Batch documentation

10.20. A master batch manufacturing document with instructions for each excipient for pharmaceutical use should be prepared and authorized (dated and signed)

10.21. A master batch manufacturing document should include for example:

a) the name of the excipient for pharmaceutical use being manufactured;
b) a complete list of materials (formula) and quantities;
c) the production location;
d) equipment to be used;
e) detailed production instructions, in process controls and flow chart if needed
f) where appropriate, precautions to be followed;
g) labelling and packaging materials and instructions;

10.22. A batch manufacturing record should be prepared for each batch of excipient for pharmaceutical use produced. It should contain detailed information relating to the production and control of the batch.

10.23. The batch manufacturing record should provide traceable information including for example:

a) the batch number;
b) dates and, when appropriate, times;
c) identification number of equipment used;
d) actual results from testing;
e) information regarding any sampling performed;
f) signatures of operators and supervisors;
g) records of packaging, packaging materials and labels;
h) records of any deviations that occurred;
i) results of release testing.

10.24. The manufacturer should demonstrate that:

a) the batch is homogeneous and compliant with its specification;
b) a capable process is used to assure batch to batch consistency;
c) a batch has not been commingled with material from other batches for the purpose of either hiding or diluting an adulterated substance;
d) samples have been taken, where required, in accordance with a sampling plan that ensures a representative sample was taken;
e) the batch has been analysed using scientifically established tests and procedures;
f) scientific data support the shelf life of the excipient for pharmaceutical use.

10.25. Where computerized systems are used in the production of a batch, the electronic data and records should comply with the guidelines on good practices for computerized systems. The system should be suitable for the intended use.

10.26. When computerised systems are in use, access and privileges, data integrity, audit trail, and back-up systems should be considered during risk assessment.

Labels

10.27. Excipients for pharmaceutical use should be labelled. Labels should be clear, unambiguous and in compliance with national or regional legislation as appropriate

10.28. Information on labels may include for example:

a) the name of the excipient;
b) the batch number assigned by the manufacturer;
c) the expiry or use-before date, if applicable;
d) any special storage conditions or handling precautions that may be necessary;
e) warnings and precautions;
f) the name and address of the manufacturer.

11. Premises

11.1. The premises where excipients for pharmaceutical use are manufactured should provide sufficient space for the production, quality control testing and storage operations.

11.2. The premises should be located, constructed, cleaned and maintained to suit the operations to be carried out.

11.3. The layout and design of the premises should aim to minimize the risk of errors, mix-ups, contamination and cross-contamination. In addition, it should allow for effective cleaning and maintenance without any adverse effect on the quality of the products.

11.4. Only authorized persons should have access to relevant areas.

11.5. Adequate lighting should be provided.

11.6. Separate, dedicated facilities should be used for the production of highly sensitizing and toxic materials, herbicides and pesticides

Note: The method used to achieve this separation will depend on the nature, extent and risk of the overall operation.

12. Equipment and utilities

12.1. Equipment and utilities should be selected, located, designed, constructed and maintained to suit the operations to be carried out.

12.2. The installation and use of equipment and utilities should aim to minimize the risk of errors and contamination, cross-contamination, build-up of dust or dirt and, in general, any adverse effect on the quality of products.

12.3. Written procedures should be established and followed for repairs, maintenance, and cleaning. These operations should not have any adverse effect on the quality of the excipient for pharmaceutical use. Records of these activities should be maintained.

12.4. Equipment and instruments identified as being part of the quality management system, should be appropriately controlled. This includes those used in production and quality control. The control programme should include standardization or calibration of reagents, instruments, apparatus, gauges and recording devices at defined, suitable intervals. Written procedures should contain specific instructions, schedules, acceptance limits. Records should be maintained.

12.5. Reagents, lubricants, instruments, apparatus, gauges and recording devices that can affect the quality of the product should not be used.

12.6. Computerized systems that may impact on the quality of the excipient for pharmaceutical use should be suitable for their intended use. These should be appropriately validated. Quality data should comply with the requirements for data integrity including but not limited to data management, audit trails, access and privileges for users.

12.7. An appropriate level of validation should be performed for computerized systems.

12.8. Equipment and utilities should be commissioned and qualified as appropriate.

12.9. Utilities such as heating, ventilation and air conditioning (HVAC), water, nitrogen and compressed air systems should be appropriate for their intended use, not have any negative impact on operations and the quality of the excipient for pharmaceutical use, and not be a source of contamination.

12.10. Where HVAC systems are used, air should be filtered to an appropriate level. The design should ensure that the risk of contamination or cross-contamination is minimized, that specified environmental conditions where required are achieved and maintained such as grade or class, temperature and relative humidity.

12.11. Water purification systems, where used, should be suitably designed, installed, maintained and operated. Water should be sampled, tested, and should meet the its relevant specification.

12.12. Compressed air and nitrogen generation systems should be designed and controlled in accordance with the outcomes of risk assessment.

12.13. Measuring and control devices, where so determined, should be calibrated at defined *intervals.*

13. Materials

13.1. Materials, including raw materials and packaging materials, should be sourced from approved suppliers.

13.2. A procedure for supplier approval should be followed. Records should be maintained.

13.3. Written procedures should be followed for the receiving, sampling, storage and testing of materials.

13.4. Materials should meet their agreed specifications. Materials that may have a negative impact on the quality of the excipient for pharmaceutical use should not be used.

13.5. Materials should be stored in accordance with their status and labelling requirements.

13.6. Specific tests, based on risk assessment of the material and pharmacopoeia requirements, should be done where applicable. Impurities should be identified and appropriately controlled.

13.7. A procedure for handling nonconforming products should be established covering the investigation, evaluation and treatment of nonconforming products. The disposition of

nonconforming materials, intermediates and finished products shall be approved by the quality unit and recorded.

13.8. Recovered or recycled materials such as solvents, should only be used if scientifically justifiable, and meeting their relevant specification. The process of recovery should follow written procedures and records should be maintained.

13.9. Blending or mixing of batches should be controlled and validated. Procedures and records should be maintained.

13.10. Materials used in batches of excipients for pharmaceutical use should be traceable.

13.11. Material from waste should be appropriately treated and discarded in a manner that will not have any negative effect on the environment.

13.12. A procedure for waste management should be followed. Records of waste treatment and disposal should be maintained.

14. Production

14.1. Raw materials for manufacturing of excipients for pharmaceutical use should be weighed or measured in appropriate areas, under appropriate conditions, using suitable devices.

14.2. This material to be used in production, should be kept in suitable containers bearing labels with required details such as the name of the material, traceable control number, weight or volume.

14.3. Equipment in production areas should be labelled for example with an asset or other unique identification number, calibration status if applicable.

14.4. Where appropriate, materials should not be kept for periods longer than the validated

hold time.

14.5. The extent, stringency and type of testing (e.g. in-process) as well as acceptance criteria should be defined. All tests and results should be fully documented as part of the batch record.

14.6. The sampling process should not increase the risk of contamination of the material. Samples should be handled with care and their integrity maintained.

14.7. Production operations should be conducted in a manner that will prevent contamination and cross-contamination.

14.8. Manufacturers should have written procedures and related documents for the production and control of excipients for pharmaceutical use.

14.9. Batches should be produced following written instructions as reflected in batch manufacturing documentation.

14.10. Manufacturing process should be described in detail, and risks associated with the production and control of the excipient for pharmaceutical use should be appropriately controlled. This include, but is not limited to requirements specified in the recognized pharmacopoeia, TSE/BSE, impurities, and others.

14.11. Batches should be produced on suitable equipment, in an appropriate environment, protected from possible contamination and cross-contamination.

14.12. In-process sampling and testing should be done in accordance with written instructions. Records should be maintained.

14.13. Batch manufacturing records should be kept. These records should, as appropriate, include relevant information such as the following:

a) name of the product;
b) batch number;

c) identification of the person(s) carrying out each significant step;
d) equipment used (e.g. reaction vessels, driers, centrifuges, filling manifold);
e) operations performed;
f) key parameters to be controlled
g) results of appropriate checks and quality control tests (including reference to the calibration status of the test equipment);
h) any deviation from instructions;
i) batch quantity and yield;
j) date of testing and certification statement;

14.14. Checks and maintenance operations should not affect the quality of the excipient for pharmaceutical use.

14.15. Changes and deviations in production should be managed through the relevant procedures.

14.16. Blending operations should be controlled to ensure homogeneity of the final batch. A blended batch should be assigned a unique batch number, and batches used in the blend should be traceable.

14.17. A sampling procedure should be followed to ensure that a sample collected from the blend is representative of the batch.

14.18. Each batch of product to be mixed should be produced in accordance with the batch manufacturing document, tested separately and meet the corresponding specifications. The mixed batch should be tested and should be in compliance with its specification. The expiry date of the mixed batch should be based on the production date of the earliest batch included in the mix.

14.19. Blending of batches to salvage out of specification batches or adulterated material is not an acceptable practice.

14.20. Where solvents and mother liquors are recovered, appropriate procedures should be

followed to ensure that they meet their specifications. Recovery procedures for reactants and intermediates are acceptable provided that the recovered materials meet suitable specifications.

14.21. Manufacturers should regularly review the capability of the process and ensure batch-to-batch consistency of the excipient for pharmaceutical use meeting its specification.

14.22. Written procedures should be followed for the receipt, identification, quarantine, sampling, examination and/or testing and release/rejection and handling of packaging and labelling materials. Records should be kept.

14.23. Packaging materials such as containers should provide adequate protection against deterioration or contamination of the excipient for pharmaceutical use. They should be clean and dry, should not be reactive, additive or absorptive.

14.24. Printed packaging material such as labels, should be in the prescribed format.

14.25. Access to printed packaging material storage areas should be controlled.

14.26. Stock should be reconciled at periodic intervals including receipt, issued, and returned quantities. Discrepancies found should be investigated.

14.27. Batch coded labels not used for the specified batch, obsolete and outdated labels should be destroyed.

14.28. Written procedures should be followed for packaging operations. Controls should be in place to prevent any mix-ups during packaging. These should include line opening and line closing checks, segregation between packaging lines, and verification of materials on the packaging line prior to the start of packaging.

Rework

14.29. Reworking should only be undertaken when the outcome of a risk assessment

indicates that this is acceptable and approved by quality unit.

14.30. Batches that have been reworked should be subjected to appropriate quality control testing and stability testing, if required. A reworked batch should be released by the quality unit only once it has been evaluated and confirmed to meet the relevant specification.

14.31. Specific attention should be given to the review of the impurity profile of each reworked batch against batches manufactured by the established process. Appropriate analytical procedures should be used.

14.32. Records should be maintained.

Reprocessing

14.33. Reprocessing should only be undertaken if this activity has been evaluated and found to be acceptable.

14.34. Records should be maintained.

15. Qualification and validation

15.1. The scope and extent of qualification and validation should be determined based on risk management principles.

15.2. Manufacturers should be able to provide documented evidence to show that, for example, premises, equipment, utilities, procedures and processes are appropriate and are consistently rendering the specified outcome.

15.3. Authorized procedures, protocols and records should be maintained for qualification and validation executed.

15.4. The extent of qualification and validation may be further justified when considering

the data from development and scale up, process capability studies, and product quality reviews.

16. Quality control

16.1. The layout of the quality control section should be appropriate.

16.2. Personnel should be suitably qualified and trained.

16.3. Materials, including but not limited to raw materials, packaging materials and finished excipients for pharmaceutical use, should be tested for compliance with their specifications, by following authorized procedures.

16.4. Laboratory equipment and instruments should be appropriate for their intended use. These should be suitably designed, installed, labelled, used, maintained and calibrated (where so determined) according to written procedures. Records should be kept.

16.5. Laboratory equipment and instruments that are out of order, or out of calibration, should not be used.

16.6. Authorized procedures should be used for activities including sampling, operation of equipment and instruments, and analysis.

16.7. Risk assessments should be done to identify impurities and to determine controls and limits for impurities. Appropriate tests and test procedures should be developed, validated and used routinely to ensure that each batch meets the specification.

16.8. To facilitate traceability of each analysis, a record of analysis should be maintained. This includes a certificate of analysis.

16.9. Records of analysis should normally include at least the following:

a) name of the excipient for pharmaceutical use;

b) batch number;
c) test results and reference to any specifications (limits) and test procedures;
d) date(s) and reference number(s) of testing;
e) date and initials of the persons performed the testing and the person who verified the testing and the calculations, where appropriate; and
f) a clear statement of release or rejection (or other status decision) and the date and signature of the designated responsible person.

16.10. Test results should be incorporated into a certificate of analyst. Data should be reviewed and trended.

16.11. Out of specification results should be thoroughly investigated. Appropriate actions should be taken.

16.12. Reference and retention samples should be kept where identified.

16.13. Where stability testing is indicated, a procedure and programme should be followed. The procedure and program should include for example:
a) A written schedule that is reviewed at least annually;
b) Reference to the number of batches and frequency of a batch to be placed on stability;
c) Type of containers to be used;
d) Conditions of storage including stress conditions (e.g. elevated temperature, light, humidity or freezing) where appropriate;
e) Ensuring that stability-indicating test procedures are used;

16.14. The results from stability testing should be reviewed and trended. An expiry or re-test date should be allocated based on scientific data.

16.15. Storage conditions should be specified on the label if these are identified (e.g. protection from light, heat).

17. Life cycle and continuous improvement principles

17.1. Manufacturers of excipients for pharmaceutical use should implement the life cycle approach and continuous improvement philosophy. These principles should be applied in the relevant areas of the premises, equipment, instruments, utilities, products and processes.

17.2. Manufacturers should implement measures to continuously improve the quality management system, manufacturing and testing procedures and the quality of their products. These measures may include for example the review of root causes of non-conformances, quality complaint investigations and outcomes, results from self-inspections and audits and other trends.

18. Storage and distribution

Storage

18.1. Storage areas should be appropriately designed, constructed and maintained. They should be kept clean and dry. There should be sufficient space and suitable ventilation.

18.2. Storage areas should normally be under cover with sufficient space. Where excipients for pharmaceutical use are stored outside buildings, risk assessment should be done to determine the necessary controls to protect the products from contamination and deterioration.

18.3. Excipients for pharmaceutical use should be stored in suitable containers, under appropriate storage conditions. Where special storage conditions are required, these should be provided, controlled, monitored and recorded

18.4. There should be a written programme for pest control.

Distribution

18.5. Excipients for pharmaceutical use should be distributed through traceable routes. Product, batch and container identity should be maintained at all times. All labels should remain legible.

18.6. Excipients for pharmaceutical use should be transported in accordance with the conditions stated on the labels.

18.7. Distribution records should be sufficiently detailed to allow for traceability in case of a recall, when required.

Note: See WHO Good trade and distribution practices for pharmaceutical starting materials (2)

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