Annex 2

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, Annex 5, 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 excipient manufacturer 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.

Excipient manufacturers should be required to apply the appropriate principles of good manufacturing practices (GMPs) in producing pharmaceutical excipients. Reports of pharmaceutical products that contain contaminated excipients, or excipients with impurities leading to the death of patients, have further highlighted the importance of reviewing the original guideline. Furthermore, the concept of ongoing improvement, the 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 quality throughout the supply chain, as applicable.

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 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 GMP 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.

Contents

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, or safety aspects for the personnel engaged in the manufacture and control of excipients.

1.3 Excipients are often used in large quantities in industrial chemistry, as well as in 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 should be of appropriate quality, as they could affect the safety, quality and efficacy 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 the presence of higher risk due to potential formation of toxic impurities during manufacturing or contamination during storage and distribution.

1.8 Manufacturers of excipients for pharmaceutical use should have a specific analytical testing procedure to ensure suitability for its intended use. Pharmacopoeial and regulatory requirements should be considered by the manufacturers as a reference for these analytical tests. Information in the public domain should 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, including key steps in the process, critical parameters (such as time, temperature or pressure), the use of recovered solvent or mother liquor, environmental conditions, equipment used, protection from contamination and monitoring points.

2. Glossary

2.1 The definitions given below apply to the terms used in this document. They have been aligned to the extent possible with the terminology in related WHO guidelines and good practices included in the WHO Quality Assurance of Medicines Terminology Database – List of Terms and related guidelines,[5] but may have different meanings in other contexts.

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

adulterated. Pertaining to an intermediate or product (in part or in whole) that is contaminated, unsafe, not shown to be safe, filthy, or produced under unsanitary conditions, or found to have been produced, controlled, stored or distributed not in compliance with good manufacturing practices (such as described in this guideline); or contains any substance that may reduce its quality or purity or render it injurious to health.

auditing. An independent and objective activity designed to add value to and improve an organization's operations by helping it to accomplish its objectives, using a systematic, disciplined approach to evaluate and improve the effectiveness of risk management, control and governance processes.

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 defined

[5] https://www.who.int/publications/m/item/quality-assurance-of-medicines-terminology-database.

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 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.

change control. A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect a validated status. The intent is to determine the need for action that would ensure that the system is maintained in a validated state.

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 onto 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. Substance, other than the active ingredient, that has been appropriately evaluated for safety and is included in a drug delivery system to (a) aid in the processing of the drug delivery system during its manufacture; (b) protect, support or enhance stability, bioavailability or patient acceptability; (c) assist in product identification; and (d) 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 defined conditions and after which it should not be used.

finished pharmaceutical product. WHO: A product that has undergone all stages of production, including packaging in its final container and labelling. A finished pharmaceutical product may contain one or more active pharmaceutical ingredients.

impurity. An undesired component in an excipient.

impurity profile. A description of the impurities present in an excipient.

in-process control (or process control). Checks performed during production in order to monitor and, if appropriate, to adjust the process 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 an excipient and related controls.

material. A general term used to denote raw materials (starting materials, reagents, solvents), process aids, intermediates, active pharmaceutical ingredients, and packaging and labelling materials.

mother liquor. A concentrated solution from which the product is obtained by evaporation, freezing or crystallization. (Or: The residual liquid that remains after the crystallization or isolation processes. A mother liquor may contain unreacted materials, intermediates, levels of the excipient for pharmaceutical use, 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 (for example, filter aid or activated carbon).

production. All operations involved in the preparation of an 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. An organizational unit independent of production that fulfils both QA and 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 excipients 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 (for example, 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.

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 an intermediate or excipient of acceptable quality for pharmaceutical use (for example, recrystallizing with a different solvent).

shelf-life. The period of time during which an excipient, if stored correctly, is expected to comply with the specification, normally as determined by stability studies. The shelf-life is used to establish the retest or expiry date.

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.

verification. The application of methods, procedures, tests and other evaluations, in addition to monitoring, to determine compliance with established requirements and specifications.

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, 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:

- sufficient resources are available (for example, equipment, personnel, materials);
- excipients for pharmaceutical use are produced, 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;
- managerial roles, responsibilities and authorities are clearly specified in job descriptions;
- operations and other activities are clearly described in a written form, such as standard operating procedures and work instructions;
- appropriate arrangements are made for the manufacture, supply and use of the correct containers and labels;
- all necessary controls are in place;
- calibrations, verification or validations are carried out where necessary;
- the excipient for pharmaceutical use is correctly processed and checked according to the defined procedures and specifications;
- deviations, suspected product defects, out-of-specification test results and any other nonconformances or incidents are reported,

investigated and recorded. An appropriate level of root cause analysis is applied during such investigations and the most likely root causes are identified;

- proposed changes are evaluated and approved prior to implementation. After implementation of a change that could impact the quality or the product, an evaluation should be undertaken to confirm that the quality objectives were achieved and that there was no unintended adverse impact on product quality;
- appropriate corrective actions and preventive actions, as well as checks on the effectiveness of those actions (where appropriate), 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;
- a batch of an excipient for pharmaceutical use is not released and supplied before it has been released by the quality unit with the assurance that the batch has been produced and controlled in accordance with product specifications, and with the recommendations in this document and any other regulations relevant to the production, control and release of these products;
- there is a system for handling complaints, returns and recalls;
- there is a system for self-inspection;
- there is a system for product quality review.

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

3.10 The person or persons authorized to release excipients for pharmaceutical use should have appropriate qualifications, and be specified.

3.1 Quality risk management

3.11 There should be a system for managing risks (*1*). 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, packaging, 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 In order to perform an adequate excipient risk assessment, it would be useful to provide some high-level guidance using an appropriate risk profile or ranking using a question-based risk ranking and filtering system. For example:

- functionality of excipient in formulation
- route of administration
- potential for contamination
- excipient complexity
- prior knowledge or experience with excipient
- packaging size.

3.13 Similarly, a risk score should be calculated for the supply chain (for example, complexity of supply chain, prior knowledge of supply chain, excipient manufacturer performance history, packaging suitability, quality management system standard and certification)

3.14 Note: see *WHO guidelines on quality risk management* (*1*).

3.2 Management review

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

3.16 Management should ensure that the quality management system achieves its intended objectives and measures managing and performance in areas such as:

- self-inspections, inspections, quality audits and supplier's audits
- complaints, returns and recalls
- changes and deviations
- rejected batches
- quality control, out-of-specification results and out-of-trend results
- maintenance
- qualification and validation
- corrective and preventive actions
- risk management.

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

3.18 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:

- date of receiving the complaint;
- name, address and other relevant details of complainant;
- details of the complaint, including name of the excipient and batch number;
- details of the investigation and action taken;
- copy of the response provided;
- 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 prompt and effective recall of an excipient for pharmaceutical use. Where the recall is as a result of a contaminated or adulterated excipient, or any other reason where the excipient could cause harm to a patient, the manufacturer should report this to the relevant authority without delay.

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 procedure describing the handling of returned excipients for pharmaceutical use.

6.2 Returned investigational products should be clearly identified and stored in a dedicated area in a controlled manner.

6.3 Inventory records of returned products should be kept.

Destruction

6.4 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.

6.5 A certificate of destruction should be available containing the necessary detail to enable traceability of the product, batch and related information.

6.6 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 standard operating procedures and programmes for periodic self-inspections, quality audits and supplier audits.

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

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:

- premises
- personnel
- equipment
- maintenance and calibration
- storage conditions of materials and finished products

- production and in-process controls
- quality control
- documentation, data generation and data integrity
- change control and deviations management
- complaints and recalls
- qualification and validation
- 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 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. A 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, of manufacturing areas, equipment and utilities.

9.3 Personnel should practise good hygiene and health habits.

9.4 Personnel should wear clean clothing suitable for their activities. The wearing of appropriate protective clothing should apply to all persons entering production areas where products or materials are handled. 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 excipients for pharmaceutical use.

9.8 Jewellery and electronic devices such as mobile phones should only be used in authorized areas.

10. Documentation

10.1 Documents such as standard operating procedures, 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 in accordance with good documentation practices.

10.3 Documents should be retained for a defined period of time. The retention time of the documents should be justified to ensure availability of information in case of need. This time should be longer than the product retest or expiry date.

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 good practices for computerized systems.

10.1 Standard operating procedures and records

10.7 Standard operating procedures and associated records should be available for at least the following:

- equipment
- analytical apparatus and instruments
- out-of-specification results
- maintenance and calibration
- cleaning and sanitization
- personnel matters, such as training, clothing and hygiene
- qualification and validation
- self-inspection and audits
- complaints
- recalls
- returns.

10.8 The standard operating procedures for sampling should specify the person or section authorized to take samples and the sampling instructions.

10.9 The standard operating procedures 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.

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.

10.2 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 pharmacopoeial 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 ensure consistency in protecting the product during storage and transport, to maintain the stability of the product, and to protect against contamination and infestation.

10.3 Batch documentation

10.20 Procedures such as 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 the following:

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

10.22 A record should be available for the excipient for pharmaceutical use produced. It should contain detailed information relating to the production and control thereof.

10.23 The manufacturing record should provide traceable information, including the following:

- the batch number
- dates and, when appropriate, times
- identification number of equipment used
- actual results from testing
- information regarding any sampling performed
- signatures of operators and supervisors
- records of packaging, packaging materials and labels
- records of any deviations that occurred
- results of release testing.

10.24 The manufacturer should demonstrate that:

- the batch is homogeneous and compliant with its specification;
- a capable process is used to ensure batch-to-batch consistency;
- a batch has not been commingled with material from other batches for the purpose of either hiding or diluting an adulterated substance;
- samples have been taken, where required, in accordance with a sampling plan that ensures a representative sample was taken;
- the batch has been analysed using scientifically established tests and procedures;
- the shelf-life of the excipient for pharmaceutical use is supported by scientific justification, including data and literature citations, taking account of the stability of the excipient in its packaging.

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 computerized systems are in use, aspects such as access and privileges, data integrity, audit trail, and back-up systems should be considered during risk assessment, with appropriate controls identified and implemented.

10.4 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. Procedures for handling incorrect labelling

should be established, covering the investigation, evaluation and treatment of nonconforming products.

10.28 Information on labels should include as a minimum the following:

- the name of the excipient and grade;
- the batch number assigned by the manufacturer;
- the expiry or retest date, if applicable;
- any special storage conditions or handling precautions that may be necessary;
- warnings and any other appropriate precautions;
- the name and address of the manufacturer.

10.29 For further information, see WHO *Guideline on data integrity and WHO Good manufacturing practices: guidelines on validation. Appendix 5: Validation of computerized systems* (*2*, *3*).

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 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 The decision to use a separate or dedicated facility for the manufacturing of high-risk excipients used in pharmaceutical manufacturing should be based on the outcome of a holistic risk assessment performed by the excipient manufacturer. The risk assessment should take into account the requirement of health-based exposure limits, as described in the literature (*4*, *5*).

11.7 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. These include those used in production and quality control. The control programme should include standardization, verification, and calibration of reagents, instruments, apparatus, gauges, and recording devices at defined, suitable intervals. Written procedures should contain specific instructions, schedules, acceptance limits and handling of the excursions. 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 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 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, utilities and computer systems 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, should not have any negative impact on either operations or the quality of the excipient for pharmaceutical use, and should 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 and that specified environmental conditions, where required, are achieved and maintained, at the required 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 and tested, and should meet 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 requiring calibration 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 and supplier monitoring should be followed. Records should be maintained.

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

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 pharmacopoeial 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 should be approved by the quality unit and recorded.

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

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

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

13.11 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 The material to be used in production should be kept in suitable containers bearing labels with required details, such as the name of the material and a traceable control number.

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

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

14.8 Batches should be produced following written procedures or instructions.

14.9 The 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 includes requirements specified in the recognized pharmacopoeia, transmissible spongiform encephalopathy (TSE) or bovine spongiform encephalopathy (BSE), and impurities.

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

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

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

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

14.14 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.

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

14.16 Each batch of product to be mixed should be produced in accordance with the batch manufacturing document, be tested separately, and meet the corresponding specifications. The mixed batch should be tested and should be in compliance with its specification.

14.17 Blending or mixing of batches should be controlled and validated. Procedures and records should be maintained. Blending of batches to salvage out-of-specification batches or adulterated material is not an acceptable practice.

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

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

14.20 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, and should not be reactive, additive or absorptive.

14.21 Printed packaging materials such as labels should be in the prescribed format.

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

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

14.24 Batch coded labels not used for the specified batch, and obsolete and outdated labels, should be destroyed. Reconciliation should be done. Records should be maintained.

14.25 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.

14.1 Rework

14.26 Reworking should only be undertaken when the outcome of a risk assessment indicates that this is acceptable and approved by the quality unit.

14.27 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 when it has been determined, by applying the relevant analytical testing procedures, that the specification has been met.

14.28 Records should be maintained.

14.2 Reprocessing

14.29 Reprocessing should only be undertaken if this activity and process have been evaluated internally and found to be acceptable.

14.30 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 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 performed.

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 raw materials, packaging materials (as applicable) and excipients for pharmaceutical use, should be tested for compliance with their current specifications by following authorized procedures. as described in pharmacopoeias, if available, or by validated in-house procedures.

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

16.5 Equipment and instruments that are out of order or out of calibration should be clearly identified to indicate that they are not to be used.

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

16.7 Analytical test procedures should be developed and validated to control potential and actual impurities that have been identified following a risk assessment 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:

- name of the excipient for pharmaceutical use;
- batch number;
- test results and reference to any specifications (limits) and test procedures;

- date and reference number of testing;
- date and initials of the persons who performed the testing and the person who verified the testing and the calculations, where appropriate;
- 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 analysis.

16.11 Out-of-specification results should be thoroughly investigated and documented as per defined procedures. Appropriate actions should be taken.

16.12 Reference and retention samples should be kept in a secure, suitable location under appropriate conditions. An appropriate quantity should be kept to allow investigation and testing, when these are required.

16.13 Where stability testing is indicated, a procedure and programme should be followed. The procedure and programme should include:

- a written schedule that is reviewed at least annually;
- reference to the number of batches and frequency of a batch to be placed on stability;
- type of containers to be used;
- conditions of storage, including stress conditions (such as elevated temperature, light, humidity or freezing), where appropriate;
- use of stability-indicating test procedures, as applicable.

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

16.15 Storage conditions should be specified on the label if these are identified (for example, protection from light, temperature).

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, to 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 the review of root causes of nonconformances, quality complaint investigations and outcomes, and results from self-inspections, audits and other trends.

18. Storage and distribution

18.1 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 in storage and other relevant areas.

18.2 Distribution

18.5 Excipients for pharmaceutical use should be distributed through traceable routes. Product, batch, container identity and integrity 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 traceability in case of a recall.

18.8 Note: for further information, see WHO *Good trade and distribution practices for pharmaceutical starting materials* (6).

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Appendices

Note: The following appendices to the *WHO good manufacturing practices for excipients used in pharmaceutical products* will be developed and included:

Appendix 1. Points to consider document focusing on a risk management-based approach for excipients with possible impurities.

Appendix 2. List of high-risk excipients (for example, considering contamination with diethylene glycol, ethylene glycol, nitrosamines).