Draft

Specific Conditions of the Application of the Principles and Guidelines of Good Manufacturing Practice for Certain Excipients

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1. Scope

The holder of a manufacturing authorization for a medicinal product shall at least be obliged to comply with the principles and guidelines of good manufacturing practice as referred to in Article 46 and 47 of Directive 2001/83/EC, as amended by Directive 2004/27/EC, while ensuring compliance with the information provided in the application for a marketing authorisation as accepted by the competent authorities. This also includes certain excipients. The list of excipients to which the principles described in this document shall apply is currently under discussion and needs to be elaborated. The following categories are currently under discussion:

(1) Excipients prepared from materials derived from a TSE-relevant animal species (excluding lactose) (Cf. Def. in Note for Guidance on minimizing risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products 2004/C 24/03)

(2) Excipients derived from human/ animal material with potential for viral contamination risk

(3) Excipients claimed to be sterile (sold as sterile) and used without further sterilisation

(4) Excipients, which, due to their nature, origin or manufacturing process are at significant risk of endotoxin/ pyrogen contamination and which are used in products which are required to be endotoxin/ pyrogen controlled, such as in parenteral products

(5) Propylene glycol

(6) Glycerol

The conditions for the application of the principles and guidelines of good manufacturing practice are laid down in No. 2.-14. A risk based approach shall be used in defining the point in the manufacturing process after which these GMP principles shall apply.

2. Definitions

The following definitions shall apply:

(1) Batch
A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous processing, a batch may correspond to a defined 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.

(2) Excipient
Substance which has been appropriately evaluated for safety and is intended to be used as starting material in the manufacture of medicinal products, but excluding active substances and packaging materials.

(3) Manufacture
Manufacture of excipients shall include both total and partial manufacture or import of an excipient and the various processes of receipt of materials, production, quality control, storage and release and includes the presentation prior to its incorporation into a medicinal product, such as dividing up, packaging, labelling, including repackaging or relabelling, such as carried out by a distributor.

(4) Material
A general term to denote raw materials (including reagents, solvents), process aids, intermediates, excipients, packaging and labelling materials.

(5) Production

All operations involved in the preparation of an excipient from receipt of materials through processing and packaging of the excipient.

(6) Quality Assurance
The sum total of the organised arrangements made with the objective to ensure that all excipients are of the quality required for their intended use and that quality systems are maintained.

(7) Quality Control
Activities, such as checking or testing that specifications are met.

(8) Records
Documents stating results achieved and/or providing evidence of activities performed.

(9) Retrieval
Process for the removal of an excipient from the distribution chain.

3. Quality management system

(1) An effective system for managing quality that involves the active participation of the management and appropriate manufacturing personnel shall be implemented and maintained by the manufacturer of the excipient.

(2) Written provisions for assignments of responsibilities, in particular for quality assurance, production, quality control and release of products shall be included. Responsibilities for quality assurance and quality control shall be separated from production.

(3) The system for managing quality shall encompass the organisational structure, procedures for all relevant operations, processes and resources, as well as activities necessary to ensure confidence that the excipient will meet its intended specifications for quality and purity. All quality related activities shall be defined and documented. A system of managing changes that could have an impact on excipient quality and compliance with agreed specifications shall be included.

(4) In order to verify compliance with the principles of the quality management system, regular internal audits shall be performed. Audit findings and corrective actions shall be documented and brought to the attention of responsible management of the company.

(5) Regular quality review of excipients shall be conducted with the objective of verifying the consistency of the process and conformance to regulatory requirements.

4. Personnel

(1) There shall be an adequate number of personnel qualified by appropriate education, training and/or experience to perform and supervise the manufacture of the excipient.

(2) The responsibilities of all personnel engaged in the manufacture of excipients shall be specified in writing.

(3) Training shall be regularly conducted by qualified individuals and shall cover at a minimum the particular operations that the employee performs and the quality system as it relates to the employee's functions.

(4) Personnel shall practice good sanitation and health habits.

5. Buildings, facilities, equipment

(1) Buildings, facilities and equipment used for the manufacture of excipients shall be appropriate for the type of excipient and the manufacturing operations to be performed.

(2) Buildings, facilities and equipment shall be located, designed and constructed in such a way as to to facilitate cleaning, maintenance and manufacturing operations, to prevent possible mix-ups and to minimise potential contamination.

(3) Buildings and facilities shall have adequate space for the orderly placement of equipment and materials.

(4) Critical equipment shall be qualified. The extent of qualification under the responsibility of the manufacturer should be appropriate to the manufacturing stage.

(5) It should be ensured that equipment is functioning within its qualified operating range.

(6) A preventive maintenance programme shall be in place.

6. Documentation and Records

(1) A documentation system covering the various operations performed shall be established and maintained.

(2) Specific records for the manufacture shall be kept to enable the history of the each batch to be traced. These shall be retained for a defined period consistent with the retest or expiry date of the excipient.

(3) All quality related activities shall be recorded at the time they are performed. Documents shall be clear, and kept up to date.

(4) When electronic, photographic or other data processing systems are used instead of written records, the manufacturer shall ensure the integrity of the data throughout the retention period. The stored data shall be protected against accidental modification, loss or damage of data, and audit trails shall be maintained.

7. Materials management

(1) There shall be written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing, and approval or rejection of materials.

(2) Materials used in the manufacture of an excipient shall be tested or verified and purchased against agreed specifications from a supplier evaluated by excipient manufacturer.

(3) Materials shall be handled and stored in a manner to prevent degradation, contamination, and cross-contamination.

8. Production and in-process controls

(1) The manufacturer of the excipient should demonstrate the consistent operation of each manufacturing process. A validation programme should be established to such an extent as deemed necessary through an assessment of risks based on acknowledged principles.

(2) The different production operations, including in-process controls and sampling shall be carried out in accordance with pre-established instructions and procedures.

(3) Appropriate technical or organisational measures shall be taken to avoid cross contamination and mix-ups.

(4) The manufacturing processes shall provide excipient of consistent quality as defined in the specifications. Changes which may have an impact on the quality of the excipient shall be appropriately documented and evaluated. Customers should be informed about such changes and holders of the manufacturing authorisation of a medicinal product should ensure they receive this information. Deviations from established procedures shall be documented and explained. Critical deviations shall be thoroughly investigated, and the investigations and their conclusions shall be documented

9. Packaging and identification labelling of excipients

(1) Excipients shall be packaged in such a way as to avoid deterioration, contamination or cross-contamination that may occur during transportation and recommended storage.

(2) Packaging and labelling operations shall be designed to prevent mix-ups.

(3) There shall be documented procedures designed to ensure that correct packaging materials and labels are used.

(4) Labelling operations shall enable identification of the excipient and ensure its traceability.

(5) These requirements shall accordingly apply to repackaging and relabelling.

10. Storage and distribution

(1) Facilities shall be available for the storage of all materials under appropriate conditions

(2) Excipients shall be transported in a manner that does not adversely affect their quality.

(3) A system shall be in place to allow complete traceability of each batch of the excipient throughout the distribution chain to permit its effective retrieval shall this be necessary.

(4) A system shall be in place by which the distribution of each batch of an excipient, including its intermediates, can be readily determined to permit its retrieval.

11. Quality control

(1) For each batch, appropriate checks and tests shall be conducted to determine conformance with specifications. Any out of specification result obtained shall be investigated and documented.

(2) The quality control system shall take into account, prior to the release of an excipient and in addition to analytical results, essential information such as the production conditions, the results of in-process controls, and the results of a review of the manufacturing documents.

(3) Upon request certificates of analysis shall be issued by the excipient manufacturer for each excipient batch. The certificate shall list each test performed in accordance with compendial or customer requirements, and include the specification, and the actual results obtained.

(4) Samples of each batch of excipient shall be retained as defined in guidelines of good manufacturing practices for medicinal products published in line with Article 47 of Directive 2001/83/EC.

12. Complaints and excipient retrieval

(1) The manufacturer shall implement a system for recording and reviewing quality related complaints, together with an effective system for promptly advising customers and retrieving excipients in the distribution network when the investigation determines this to be necessary. Returned and non-conforming excipient shall be handled according to documented procedures.

(2) In the event of a serious or potentially life-threatening adverse event occurring with a medicinal product, which can be attributed to the quality of the excipient, the competent authority shall be informed.

13. Contract manufacturers

(1) When the excipient manufacturer delegates any manufacturing operation to an external company (contract manufacturing), this delegation shall be accurately defined, agreed in writing in a contract and appropriately controlled to ensure the quality of the excipient is ensured. Special consideration shall be given to the prevention of cross-contamination, mix-ups and to maintaining traceability.

(2) The holder of the manufacturing or import authorisation shall make sure he is informed about any contract manufacturing concerning the excipient he purchases.

14. Obligations of the holder of the manufacturing/ import authorisation of the medicinal product

(1) Following Article 40 of Directive 2001/83/EC, the holder of the manufacturing or import authorisation for a medicinal product is obliged to ensure that excipients falling under the scope of the excipient Directive and which are used for the manufacture of the medicinal product have been manufactured in line with the above mentioned principles.

(2) The holder of the authorisation shall approve manufacturers or distributors of excipients on the basis of requirements defined in his own quality system in line with the excipient Directive and taking into account acknowledged principles of quality risk management. Specific consideration should be given to results of any audits performed and other means of assessment of compliance of the excipient manufacturer with the GMP requirements, such as an assessment of documents.

(3) Quality system requirements of the holder of the authorisation shall also include provisions for information exchange with the excipient manufacturer on aspects related to the manufacturing process, specifications and quality defects.

(4) Quality system requirements of the holder of the authorisation shall also include a review of the excipients received on an annual basis unless determined differently by applying a quality risk management process. This shall include a review of analytical testing results and any problems related to the quality of the excipients.