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Guidelines

of 19 March 2015

on principles of Good Distribution Practice of active substances for medicinal products for human use

(Text with EEA relevance)

(2015/C 95/01)

Introduction

These guidelines are based on the fourth paragraph of Article 47 of Directive 2001/83/EC ([1]).

They follow the same principles that underlie the guidelines of EudraLex Volume 4, Part II, Chapter 17, with regard to the distribution of active substances and the Guidelines of 5 November 2013 on Good Distribution Practice of medicinal products for human use ([2]).

These guidelines provide stand-alone guidance on Good Distribution Practice (GDP) for importers and distributors of active substances for medicinal products for human use. They complement the rules on distribution set out in the guidelines of EudraLex Volume 4, Part II, and apply also to distributors of active substances manufactured by themselves.

Any manufacturing activities in relation to active substances, including re-packaging, re-labelling or dividing up, are subject to Commission Delegated Regulation (EU) No 1252/2014 ([3]) and EudraLex Volume 4, Part II.

Additional requirements apply to the importation of active substances, as laid down in Article 46b of Directive 2001/83/EC.

Distributors of active substances for medicinal products for human use should follow these guidelines as of 21 September 2015.

CHAPTER 1 — SCOPE

1.1. These guidelines apply to distribution of active substances, as defined in Article 1(3a) of Directive 2001/83/EC, for medicinal products for human use. According to that provision, an active substance is any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a medical diagnosis.

([1]) Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67).
([2]) OJ C 343, 23.11.2013, p. 1.
([3]) Commission Delegated Regulation (EU) No 1252/2014 of 28 May 2014 supplementing Directive 2001/83/EC of the European Parliament and of the Council with regard to principles and guidelines of good manufacturing practice for active substances for medicinal products for human use (OJ L 337, 25.11.2014, p. 1).

1.2. For the purpose of these guidelines, distribution of active substances shall comprise all activities consisting of procuring, importing, holding, supplying or exporting active substances, apart from brokering.

1.3. These guidelines do not apply to intermediates of active substances.

CHAPTER 2 — QUALITY SYSTEM

2.1. Distributors of active substances should develop and maintain a quality system setting out responsibilities, processes and risk management principles. Examples of the processes and applications of quality risk management can be found in EudraLex Volume 4, Part III: GMP related documents, ICH guideline Q9 on Quality Risk Management (ICH Q9).

2.2. The quality system should be adequately resourced with competent personnel, and suitable and sufficient premises, equipment and facilities. It should ensure that:

(i) active substances are procured, imported, held, supplied or exported in a way that is compliant with the requirements of GDP for active substances;

(ii) management responsibilities are clearly specified;

(iii) active substances are delivered to the right recipients within a satisfactory time period;

(iv) records are made contemporaneously;

(v) deviations from established procedures are documented and investigated;

(vi) appropriate corrective and preventive actions, commonly known as 'CAPA', are taken to correct deviations and prevent them in line with the principles of quality risk management;

(vii) changes that may affect the storage and distribution of active substances are evaluated.

2.3. The size, structure and complexity of the distributor's activities should be taken into consideration when developing or modifying the quality system.

CHAPTER 3 — PERSONNEL

3.1. The distributor should designate a person at each location where distribution activities are performed who should have defined authority and responsibility for ensuring that a quality system is implemented and maintained. The designated person should fulfil his responsibilities personally. The designated person can delegate duties but not responsibilities.

3.2. The responsibilities of all personnel involved in the distribution of active substances should be specified in writing. The personnel should be trained on the requirements of GDP for active substances. They should have the appropriate competence and experience to ensure that active substances are properly handled, stored and distributed.

3.3. Personnel should receive initial and continuing training relevant to their role, based on written procedures and in accordance with a written training programme.

3.4. A record of all training should be kept, and the effectiveness of training should be periodically assessed and documented.

CHAPTER 4 — DOCUMENTATION

4.1. Documentation comprises all written procedures, instructions, contracts, records and data, in paper or in electronic form. Documentation should be readily available or retrievable. All documentation related to compliance of the distributor with these guidelines should be made available on request of competent authorities.

4.2. Documentation should be sufficiently comprehensive with respect to the scope of the distributor's activities and in a language understood by personnel. It should be written in clear, unambiguous language and be free from errors.

4.3. Any alteration made in the documentation should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.

4.4. Each employee should have ready access to all necessary documentation for the tasks executed.

Procedures

4.5. Written procedures should describe the distribution activities which affect the quality of the active substances. This could include receipt and checking of deliveries, storage, cleaning and maintenance of the premises (including pest control), recording of the storage conditions, security of stocks on site and of consignments in transit, withdrawal from saleable stock, handling of returned products, recall plans, etc.

4.6. Procedures should be approved, signed and dated by the person responsible for the quality system.

4.7. Attention should be paid to the use of valid and approved procedures. Documents should be reviewed regularly and kept up to date. Version control should be applied to procedures. After revision of a document a system should exist to prevent inadvertent use of the superseded version. Superseded or obsolete procedures should be removed from workstations and archived.

Records

4.8. Records should be clear, be made at the time each operation is performed and in such a way that all significant activities or events are traceable. Records should be retained for at least 1 year after the expiry date of the active substance batch to which they relate. For active substances with retest dates, records should be retained for at least 3 years after the batch is completely distributed.

4.9. Records should be kept of each purchase and sale, showing the date of purchase or supply, name of the active substance, batch number and quantity received or supplied, and name and address of the supplier and of the original manufacturer, if not the same, or of the shipping agent and/or the consignee. Records should ensure the traceability of the origin and destination of products, so that all the suppliers of, or those supplied with, an active substance can be identified. Records that should be retained and be available include:

(i) identity of supplier, original manufacturer, shipping agent and/or consignee;

(ii) address of supplier, original manufacturer, shipping agent and/or consignee;

(iii) purchase orders;

(iv) bills of lading, transportation and distribution records;

(v) receipt documents;

(vi) name or designation of active substance;

(vii) manufacturer's batch number;

(viii) certificates of analysis, including those of the original manufacturer;

(ix) retest or expiry date.

CHAPTER 5 — PREMISES AND EQUIPMENT

5.1. Premises and equipment should be suitable and adequate to ensure proper storage, protection from contamination, e.g. narcotics, highly sensitising materials, materials of high pharmacological activity or toxicity, and distribution of active substances. They should be suitably secure to prevent unauthorised access. Monitoring devices that are necessary to guarantee the quality attributes of the active substance should be calibrated according to an approved schedule against certified traceable standards.

CHAPTER 6 — OPERATIONS

Orders

6.1. Where active substances are procured from a manufacturer, importer or distributor established in the EU, that manufacturer, importer or distributor should be registered according to Article 52a of Directive 2001/83/EC.

Receipt

6.2. Areas for receiving active substances should protect deliveries from prevailing weather conditions during unloading. The reception area should be separate from the storage area. Deliveries should be examined at receipt in order to check that:

(i) containers are not damaged;

(ii) all security seals are present with no sign of tampering;

(iii) correct labelling, including correlation between the name used by the supplier and the in-house name, if these are different;

(iv) necessary information, such as a certificate of analysis, is available; and

(v) the active substance and the consignment correspond to the order.

6.3. Active substances with broken seals, damaged packaging, or suspected of possible contamination should be quarantined either physically or using an equivalent electronic system and the cause of the issue investigated.

6.4. Active substances subject to specific storage measures, e.g. narcotics and products requiring a specific storage temperature or humidity, should be immediately identified and stored in accordance with written instructions and with relevant legislative provisions.

6.5. Where the distributor suspects that an active substance procured or imported by him is falsified, he should segregate it either physically or using an equivalent electronic system and inform the national competent authority of the country in which he is registered.

6.6. Rejected materials should be identified and controlled and quarantined to prevent their unauthorised use in manufacturing and their further distribution. Records of destruction activities should be readily available.

Storage

6.7. Active substances should be stored under the conditions specified by the manufacturer, e.g. controlled temperature and humidity when necessary, and in such a manner to prevent contamination and/or mix up. The storage conditions should be monitored and records maintained. The records should be reviewed regularly by the person responsible for the quality system.

6.8. When specific storage conditions are required, the storage area should be qualified and operated within the specified limits.

6.9. The storage facilities should be clean and free from litter, dust and pests. Adequate precautions should be taken against spillage or breakage, attack by micro-organisms and cross-contamination.

6.10. There should be a system to ensure stock rotation, e.g. 'first expiry (retest date), first out', with regular and frequent checks that the system is operating correctly. Electronic warehouse management systems should be validated.

6.11. Active substances beyond their expiry date should be separated, either physically or using an equivalent electronic system, from approved stock and not be supplied.

6.12. Where storage or transportation of active substances is contracted out, the distributor should ensure that the contract acceptor knows and follows the appropriate storage and transport conditions. There must be a written contract between the contract giver and contract acceptor, which clearly establishes the duties of each party. The contract acceptor should not subcontract any of the work entrusted to him under the contract without the contract giver's written authorisation.

Deliveries to customers

6.13. Supplies within the EU should be made only by distributors of active substances registered according to Article 52a of Directive 2001/83/EC to other distributors, manufacturers or to dispensing pharmacies.

6.14. Active substances should be transported in accordance with the conditions specified by the manufacturer and in a manner that does not adversely affect their quality. Product, batch and container identity should be maintained at all times. All original container labels should remain readable.

6.15. A system should be in place by which the distribution of each batch of active substance can be readily identified to permit its recall.

Transfer of information

6.16. Any information or event that the distributor becomes aware of, which have the potential to cause an interruption to supply, should be notified to relevant customers.

6.17. Distributors should transfer all product quality or regulatory information received from an active substance manufacturer to the customer and from the customer to the active substance manufacturer.

6.18. The distributor who supplies the active substance to the customer should provide the name and address of the original active substance manufacturer and the batch number(s) supplied. A copy of the original certificate of analysis from the manufacturer should be provided to the customer.

6.19. The distributor should also provide the identity of the original active substance manufacturer to competent authorities upon request. The original manufacturer can respond to the competent authority directly or through its authorised agents. (In this context 'authorised' refers to authorised by the manufacturer.)

6.20. The specific guidance for certificates of analysis is detailed in Section 11.4 of Part II of Eudralex Volume 4.

CHAPTER 7 — RETURNS, COMPLAINTS AND RECALLS

Returns

7.1. Returned active substances should be identified as such and quarantined pending investigation.

7.2. Active substances which have left the care of the distributor, should only be returned to approved stock if all of the following conditions are met:

(i) the active substance is in the original unopened container(s) with all original security seals present and is in good condition;

(ii) it is demonstrated that the active substance has been stored and handled under proper conditions. Written information provided by the customer should be available for this purpose;

(iii) the remaining shelf life period is acceptable;

(iv) the active substance has been examined and assessed by a person trained and authorised to do so;

(v) no loss of information/traceability has occurred.

This assessment should take into account the nature of the active substance, any special storage conditions it requires, and the time elapsed since it was supplied. As necessary and if there is any doubt about the quality of the returned active substance, advice should be sought from the manufacturer.

7.3. Records of returned active substances should be maintained. For each return, documentation should include:

(i) name and address of the consignee returning the active substances;

(ii) name or designation of active substance, active substance batch number and quantity returned;

(iii) reason for return;

(iv) use or disposal of the returned active substance and records of the assessment performed.

7.4. Only appropriately trained and authorised personnel should release active substances for return to stock. Active substances returned to saleable stock should be placed such that the stock rotation system operates effectively.

Complaints and recalls

7.5. All complaints, whether received orally or in writing, should be recorded and investigated according to a written procedure. In the event of a complaint about the quality of an active substance the distributor should review the complaint with the original active substance manufacturer in order to determine whether any further action, either with other customers who may have received this active substance or with the competent authority, or both, should be initiated. The investigation into the cause for the complaint should be conducted and documented by the appropriate party.

7.6. Complaint records should include:

(i) name and address of complainant;

(ii) name, title, where appropriate, and phone number of person submitting the complaint;

(iii) complaint nature, including name and batch number of the active substance;

(iv) date the complaint is received;

(v) action initially taken, including dates and identity of person taking the action;

(vi) any follow-up action taken;

(vii) response provided to the originator of complaint, including date response sent;

(viii) final decision on active substance batch.

7.7. Records of complaints should be retained in order to evaluate trends, product related frequencies, and severity with a view to taking additional, and if appropriate, immediate corrective action. These should be made available during inspections by competent authorities.

7.8. Where a complaint is referred to the original active substance manufacturer, the record maintained by the distributor should include any response received from the original active substance manufacturer, including date and information provided.

7.9. In the event of a serious or potentially life-threatening situation, local, national, and/or international authorities should be informed and their advice sought.

7.10. There should be a written procedure that defines the circumstances under which a recall of an active substance should be considered.

7.11. The recall procedure should designate who should be involved in evaluating the information, how a recall should be initiated, who should be informed about the recall, and how the recalled material should be treated. The designated person (cf. Section 3.1) should be involved in recalls.

CHAPTER 8 — SELF-INSPECTIONS

8.1. The distributor should conduct and record self-inspections in order to monitor the implementation of and compliance with these guidelines. Regular self-inspections should be performed in accordance with an approved schedule.

ANNEX

Glossary of terms applicable to these guidelines

Terms	Definition
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 production, 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.
Batch 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.
Brokering of active substances	All activities in relation to the sale or purchase of active substances that do not include physical handling and that consist of negotiating independently and on behalf of another legal or natural person.
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.
Consignee	The person to whom the shipment is to be delivered whether by land, sea or air.
Contamination	The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or active substance during production, sampling, packaging or repackaging, storage or transport.
Distribution of active substances	All activities consisting of procuring, importing, holding, supplying or exporting of active substances, apart from brokering.
Deviation	Departure from an approved instruction or established standard.
Expiry date	The date placed on the container/labels of an active substance designating the time during which the active substance is expected to remain within established shelf life specifications if stored under defined conditions, and after which it should not be used.
Falsified active substance	Any active substance with a false representation of: a) its identity, including its packaging and labelling, its name or its components as regards any of the ingredients and the strength of those ingredients; b) its source, including its manufacturer, its country of manufacture, its country of origin; or c) its history, including the records and documents relating to the distribution channels used.
Holding	Storing active substances.
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 distribution of an active substance.

Terms	Definition
Procuring	Obtaining, acquiring, purchasing or buying active substances from manufacturers, importers or other distributors.
Quality risk management	A systematic process for the assessment, control, communication and review of risks to the quality of an active substance across the product lifecycle.
Quality system	The sum of all aspects of a system that implements quality policy and ensures that quality objectives are met (ICH Q9).
Quarantine	The status of materials isolated physically or by other effective means pending a decision on the subsequent approval or rejection.
Retest date	The date when a material should be re-examined to ensure that it is still suitable for use.
Supplying	All activities of providing, selling, donating active substances to distributors, pharmacists, or manufacturers of medicinal products.
Signed (signature)	The record of the individual who performed a particular action or review. This record can be initials, full handwritten signature, personal seal, or authenticated and secure electronic signature.
Transport (transportation)	Moving active substances between two locations without storing them for unjustified periods of time.
Validation	A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting pre-determined acceptance criteria.

Guidelines

of 19 March 2015

on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use

(Text with EEA relevance)

(2015/C 95/02)

Introduction

These guidelines are based on the fifth paragraph of Article 47 of Directive 2001/83/EC [1].

According to the second paragraph of Article 46(f) of Directive 2001/83/EC, the manufacturing authorisation holder is required to ensure that the excipients are suitable for use in medicinal products by ascertaining what the appropriate good manufacturing practice (GMP) is. The appropriate GMP for excipients of medicinal products for human use shall be ascertained on the basis of a formalised risk assessment in accordance with these guidelines. The risk assessment shall take into account requirements under other appropriate quality systems as well as the source and intended use of the excipients and previous instances of quality defects. The manufacturing authorisation holder shall ensure that the appropriate GMP ascertained is applied. The manufacturing authorisation holder shall document the measures taken.

The excipient risk assessment/risk management procedure should be incorporated in the pharmaceutical quality system of the manufacturing authorisation holder.

Manufacturing authorisation holders should have the risk assessment/management documentation for appropriate GMP for excipients available on site for review by GMP inspectors. Consideration should be given to sharing relevant information from the risk assessment with the excipient manufacturer to facilitate continuous improvement.

A risk assessment as set out in these guidelines should be carried out for excipients for authorised medicinal products for human use by 21 March 2016.

CHAPTER 1 — SCOPE

1.1. These guidelines apply to the risk assessment for ascertaining the appropriate GMP for excipients for medicinal products for human use. According to Article 1(3b) of Directive 2001/83/EC, an excipient is any constituent of a medicinal product other than the active substance and the packaging material.

1.2. These guidelines do not cover substances added to stabilise active substances that cannot exist on their own.

CHAPTER 2 — DETERMINATION OF APPROPRIATE GMP BASED ON TYPE AND USE OF EXCIPIENT

2.1. In EudraLex Volume 4, Guidelines for Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Part III: GMP related documents, ICH guideline Q9 on Quality Risk Management (ICH Q9), principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality, including excipients, can be found.

2.2. These quality risk management principles should be used to assess the risks presented to the quality, safety and function of each excipient and to classify the excipient in question, e.g. as low risk, medium risk or high risk. Quality risk management tools such as those listed in EudraLex Volume 4, Part III, ICH Q9 (e.g. hazard analysis and critical control points — HACCP) should be used for this purpose.

2.3. For each excipient from each manufacturer used, the manufacturing authorisation holder should identify the risks presented to the quality, safety and function of each excipient from its source — be that animal, mineral, vegetable, synthetic, etc. — through to its incorporation in the finished pharmaceutical dose form. Areas for consideration should include, but are not limited to:

(i) transmissible spongiform encephalopathy;

(ii) potential for viral contamination;

[1] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67).

(iii) potential for microbiological or endotoxin/pyrogen contamination;

(iv) potential, in general, for any impurity originating from the raw materials, e.g. aflatoxins or pesticides, or generated as part of the process and carried over, e.g. residual solvents and catalysts;

(v) sterility assurance for excipients claimed to be sterile;

(vi) potential for any impurities carried over from other processes, in absence of dedicated equipment and/or facilities;

(vii) environmental control and storage/transportation conditions including cold chain management, if appropriate;

(viii) supply chain complexity;

(ix) stability of excipient;

(x) packaging integrity evidence.

2.4. Additionally, with respect to the use and function of each excipient, the manufacturing authorisation holder should consider:

(i) the pharmaceutical form and use of the medicinal product containing the excipient;

(ii) the function of the excipient in the formulation, e.g. lubricant in a tablet product or preservative material in a liquid formulation, etc.;

(iii) the proportion of the excipient in the medicinal product composition;

(iv) daily patient intake of the excipient;

(v) any known quality defects/fraudulent adulterations, both globally and at a local company level related to the excipient;

(vi) whether the excipient is a composite;

(vii) known or potential impact on the critical quality attributes of the medicinal product;

(viii) other factors as identified or known to be relevant to assuring patient safety.

2.5. Having established and documented the risk profile of the excipient, the manufacturing authorisation holder should establish and document the elements of EudraLex Volume 4 that he believes are needed to be in place in order to control and maintain the quality of the excipient, e.g. Annex 1 or/and Annex 2; Part II: Basic Requirements for Active Substances used as Starting Materials.

2.6. These elements will vary depending on the source, the supply chain and the subsequent use of the excipient, but as a minimum the following high level GMP elements should be considered by the manufacturing authorisation holder:

(i) establishment and implementation of an effective pharmaceutical quality system;

(ii) sufficient competent and appropriately qualified personnel;

(iii) defined job descriptions for managerial and supervisory staff responsible for manufacturing and quality activities;

(iv) training programmes for all staff involved in manufacturing and quality activities;

(v) training programmes related to health, hygiene and clothing as identified as necessary to the intended operations;

(vi) provision and maintenance of premises and equipment appropriate to the intended operations;

(vii) documentation system(s) covering all processes and specifications for the various manufacturing and quality operations;

(viii) systems for coding and identifying starting materials, intermediates and excipients to allow full traceability;

(ix) qualification program of suppliers;

(x) system for quality control of the excipient and a responsible person independent from production to release the batches;

(xi) retention of records for incoming materials and excipients and retention of samples of excipients for the periods required by EudraLex Volume 4, Part II;

(xii) systems to ensure that any activity contracted out is subject to a written contract;

(xiii) maintenance of an effective system whereby complaints are reviewed and excipients may be recalled;

(xiv) change management and deviation management system;

(xv) self-inspection program;

(xvi) environmental control and storage conditions.

CHAPTER 3 — DETERMINATION OF EXCIPIENT MANUFACTURER'S RISK PROFILE

3.1. After determination of the appropriate GMP, a gap analysis of the required GMP against the activities and capabilities of the excipient manufacturer should be performed.

3.2. Data/evidence to support the gap analysis should be obtained through audit or from information received from the excipient manufacturer.

3.3. Certification of quality systems and/or GMP held by the excipient manufacturer and the standards against which these have been granted should be considered as such certification may fulfil the requirements.

3.4. Any gaps identified between the required GMP and the activities and capabilities of the excipient manufacturer should be documented. Furthermore, the manufacturing authorisation holder should perform a further risk assessment to determine the risk profile, e.g. low risk, medium risk or high risk, for that excipient manufacturer. EudraLex Volume 4, Part III, ICH Q9 should be used for that purpose. Quality risk management tools such as those listed there — HACCP etc. — should be used for this.

3.5. The manufacturing authorisation holder should have a series of strategies ranging from acceptance through control to unacceptable for the different risk profiles and based on these a control strategy, e.g. audit, document retrieval and testing, should be established.

CHAPTER 4 — CONFIRMATION OF APPLICATION OF APPROPRIATE GMP

4.1. Once the appropriate GMP for the excipient and the risk profile of the excipient manufacturer have been defined, ongoing risk review should be performed through mechanisms such as:

(i) number of defects connected to batches of excipient received;

(ii) type/severity of such defects;

(iii) monitoring and trend analysis of excipient quality;

(iv) loss of relevant quality system and/or GMP certification by excipient manufacturer;

(v) observation of trends in drug product quality attributes; this will depend on the nature and role of excipient;

(vi) observed organisational, procedural or technical/process changes at the excipient manufacturer;

(vii) audit/re-audit of excipient manufacturer;

(viii) questionnaires.

Based on the outcome of the risk review, the established control strategy should be reviewed and revised if needed.