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Advice on implementing measures under Article 95(8) of Regulation (EU) 2019/6 on veterinary medicinal products - Good distribution practices (GDP) for active substances used as starting materials in veterinary medicinal products

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Background

In July 2019, the European Commission sent a request to the European Medicines Agency (EMA) for scientific recommendations on good distribution practice for active substances used as starting materials in veterinary medicinal products.

The Agency was requested to provide the scientific recommendations by 30 June 2020 to inform the adoption of measures on GDP for active substances used as starting materials in veterinary medicinal products.

The GMP/GDP Inspectors Working Group formed one expert group to prepare the recommendations in relation to Good Distribution Practices for actives substances used as starting materials in veterinary medicinal products. The group was composed of 14 experts selected from the European network of experts, on the basis of recommendations by their respective national competent authorities, and one Agency staff member.

When addressing this request, the European Commission asked the Agency to consider:

- the view of the policy reasoning and purpose of GDP to ensure a quality warranty system on the movement of active substances used as starting materials from the premises where they have been manufactured to the manufacturer of veterinary medicinal products by means of various transport or storage methods;
- the experience gained with the application of the current EU system on the human medicines side as established in the *Guidelines of 19 March 2015 on principles of Good Distribution Practice of active substances for medicinal products for human use*;
- existing international standards and guidelines on GDP of active substances for medicinal products, e.g. WHO *Good trade and distribution practices for pharmaceutical starting materials*, the 2018 PIC/S *Guidelines on the principles of Good Distribution Practice of active substances for medicinal products for human use*;
- the similarities and potential differences between the requirements towards GDP for active substances used as starting materials in human and in veterinary medicinal products;
- the fact that more often than not GDP inspections are to be performed by the same experts for both types of medicines or that the same wholesaler distributes active substances used for both veterinary and human medicinal products and therefore, in order to avoid unnecessary administrative burden, it is not practicable to deviate significantly from the human side, unless practical needs dictate otherwise.

The expert group submitted their draft recommendations to the GMP/GDP Inspectors Working Group for comments on 4 March 2020.

The GMP/GDP Inspectors Working Group adopted the scientific advice on 2 June 2020.

Considerations and rationale for the recommendations

Article 95(8) of Regulation 2019/6 introduces provisions for measures on good distribution practice for active substances used as starting materials in veterinary medicinal products indicating that the European Commission shall by means of implementing acts adopt such measures.

Although no good distribution practice measures have been adopted up to now at EU level for active substances used in veterinary medicines, such measures have been established in the EU in relation to active substances for medicinal products for human use[1].

The experience gained with the application of the current EU system on the human medicines side was therefore taken into account and constitutes the basis for the recommendations made in relation to veterinary medicines.

For the preparation of the advice international standards and guidelines on good distribution practice of active substances for medicinal products such as the *WHO Good trade and distribution practices for pharmaceutical starting materials*, and the *2018 PIC/S Guidelines on the principles of Good Distribution Practice of active substances for medicinal products for human* use were also taken into account.

Regulation (EU) 2019/6 aims to reduce the administrative burden, enhance the internal market and increase the availability of veterinary medicinal products, while guaranteeing the highest level of public and animal health and environmental protection. Consideration was therefore given to all these aspects in the drafting of the recommendations.

Recommendations

The recommendations provided in this advice follow the principles of Good Distribution Practice of active substances for medicinal products for human use taking into account the specificities of the veterinary field but also the fact that a significant number of active substances are used as starting materials both in medicinal products for human and for veterinary use.

The alignment of the recommendations with the corresponding measures established for the good distribution practice of active substances for use in human medicinal products is also supported by the fact that Good Distribution Practice inspections for both types of medicine will often be carried out by the same inspectors and that the same wholesaler may distribute active substances for both veterinary and human medicinal products. Therefore, it is essential that the future Implementing Act does not introduce any requirements more stringent than the corresponding GDP guidance for the human sector.

Additional considerations and points to note

In addition to the recommendations made the below matters were addressed and are brought to the Commission's attention for consideration in the development of the Union's legal framework.

Any manufacturing activities in relation to active substances used as starting materials in veterinary medicinal products, including re-packaging, re-labelling or dividing up, are currently subject to Eudralex Volume 4, Part II. It should be considered that the regulatory interface between GMP and GDP is also maintained in future legislative developments.

In the preparation of the advice it was noted that there is no provision in Regulation (EU) 2019/6 equivalent to Article 46b of Directive 2001/83/EC, requiring that active substances used in medicinal products for human use are accompanied by a "written confirmation" issued by the competent authority of the exporting third country. In spite of this and also acknowledging that the quality requirements for active substances for use in veterinary medicines are similar to those for human

[1] Guidelines of 19 March 2015 on principles of Good Distribution Practice of active substances for medicinal products for human use

medicines it was considered that the potential risk of imported active substances for use as starting materials in veterinary medicinal products being diverted for use in human medicinal products and the likelihood of falsification of veterinary medicines are similar to that of human medicines. In addition, the national good manufacturing practice regulatory frameworks, control and enforcement activities applied to veterinary active substances in the countries of origin contribute to the quality, efficacy and safety of products imported into the Union. These facts would support the introduction of similar safeguards and requirements for the veterinary sector.

Advice on implementing measures for Good Distribution Practice (**GDP) for active substances** used as starting materials in veterinary medicinal products

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Introduction

This advice provides stand-alone measures on Good Distribution Practice (GDP) for manufacturers, importers and distributors of active substances used as starting materials in veterinary medicinal products. It should also complement the rules on distribution set out in the guidelines of EudraLex Volume 4, Part II or any subsequent revision thereof as a consequence of the implementation of Article 93(2) of Regulation (EU) 2019/6, and apply to distributors of active substances used as starting materials in veterinary medicinal products manufactured by themselves.

1. Scope and definitions

1.1. Scope

The measures proposed in this advice for good distribution practice apply to import and distribution of active substances used as starting materials in veterinary medicinal products, as defined in Article 95 (1) of Regulation (EU) 2019/6 on veterinary medicinal products.

For the purpose of this advice, the distribution of active substances comprises all activities consisting of procuring, importing, holding, supplying or exporting active substances, apart from brokering[2].

In analogy to the human medicines sector, intermediates of active substances used in veterinary medicines are outside the scope of the measures for good distribution practice proposed in this advice.

1.2. Definitions

In alignment with the human medicines sector and in order to complement the definitions included in Regulation 2019/6, the following definitions required for a good understanding of the terminology used in this advice, are proposed:

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

'Calibration' means 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' means the person to whom the shipment is to be delivered whether by land, sea or air;

'Contamination' means 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;

[2] In the context of distribution of medicinal products for human use brokering of active substances is defined as 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.

'Distribution of active substances used as starting material in veterinary medicinal products' means all activities consisting of procuring, importing, holding, supplying or exporting of active substances used as starting materials in veterinary medicinal products, apart from brokering[2];

'Deviation' means departure from an approved instruction or established standard;

'Expiry date' means the date placed on the container/labels of an active substance designating the time during which the active substance used as starting materials in veterinary medicinal products 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 used as starting material in veterinary medicinal products' means any active substance used as starting materials in veterinary medicinal products with a false representation of:

- its identity, including its packaging and labelling, its name or its components as regards any of the ingredients and the strength of those ingredients,
- its source, including its manufacturer, its country of manufacture, its country of origin, or
- its history, including the records and documents relating to the distribution channels used;

'Holding' means storing active substances used as starting materials in veterinary medicinal products;

'Procedure' means 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 used as starting materials in veterinary medicinal products;

'Procuring' means obtaining, acquiring, purchasing or buying active substances used as starting materials in veterinary medicinal products from manufacturers, importers or other distributors;

'Quality risk management' means a systematic process for the assessment, control, communication and review of risks to the quality of an active substance used as starting materials in veterinary medicinal products across the product lifecycle;

'Quality system' means the sum of all aspects of a system that implements quality policy and ensures that quality objectives are met;

'Quarantine' means the status of materials isolated physically or by other effective means pending a decision on the subsequent approval or rejection;

'Retest date' means the date when a material should be re-examined to ensure that it is still suitable for use;

'Supplying' means all activities of providing, selling, donating active substances used as starting materials in veterinary medicinal products to distributors, pharmacists, manufacturers of medicinal products or to entities/persons permitted by national legislation;

'Signed (signature)' means 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)' means moving active substances used as starting materials in veterinary medicinal products between two locations without storing them for unjustified periods of time;

'Validation' means 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.

2. Quality system

Distributors of active substances used as starting materials in veterinary medicinal products 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).

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

- active substances used as starting materials in veterinary medicinal products are procured, imported, held, supplied or exported in a way that is compliant with the requirements of good distribution practice for active substances used as starting materials in veterinary medicinal products;
- management responsibilities are clearly specified;
- active substances used as starting materials in veterinary medicinal products are delivered to the right recipients within a satisfactory time period;
- records are made contemporaneously;
- deviations from established procedures are documented and investigated;
- 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;
- changes that may affect the storage and distribution of active substances used as starting materials in veterinary medicinal products are evaluated.

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

3. Personnel

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.

The responsibilities of all personnel involved in the distribution of active substances used as starting materials in veterinary medicinal products should be specified in writing. The personnel should be trained on the requirements of good distribution practice for active substances. They should have the appropriate competence and experience to ensure that active substances used as starting materials in veterinary medicinal products are properly handled, stored and distributed.

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

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

4. Documentation

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 this good distribution practice for active substances used as starting materials in veterinary medicinal products should be made available on request of competent authorities.

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. All types of documents should be defined and adhered to.

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.

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

4.1. Procedures

Written procedures should describe all distribution activities which affect the quality of the active substances used as starting materials in veterinary medicinal products. This includes but is not limited to: 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.

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

Valid and approved procedures should be used. 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.

Relationships and control measures between original documents and official copies, data handling and records need to be stated for all paper based, electronic and hybrid systems.

4.2. Records

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.

Records should be kept of each purchase and sale, showing the date of purchase or supply, name of the active substances used as starting materials in veterinary medicinal products, 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 and take into account additional requirements specified by national legislation. 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 used as

starting materials in veterinary medicinal products can be identified. Records that should be retained and be available include:

- identity of supplier, original manufacturer, shipping agent and/or consignee;
- address of supplier, original manufacturer, shipping agent and/or consignee;
- purchase orders;
- bills of lading, transportation and distribution records;
- receipt documents;
- name or designation of active substance used as starting materials in veterinary medicinal products;
- manufacturer's batch number;
- certificates of analysis, including those of the original manufacturer;
- retest or expiry date.

5. Premises and equipment

Premises and equipment should be suitably located, designed, constructed and maintained to ensure appropriate operations such as receiving, proper storage, picking, packing and dispatch and to ensure protection from contamination, amongst other through narcotics, highly sensitising materials, materials of high pharmacological activity or toxicity, and distribution of active substances used as starting materials in veterinary medicinal products. There should be sufficient space, lighting and ventilation to ensure required segregation, appropriate storage conditions and cleanliness.

Access should be controlled and premises should be suitably secure to prevent unauthorised access. Monitoring devices that are necessary to guarantee the quality attributes of the active substance used as starting materials in veterinary medicinal products should be calibrated according to an approved schedule against certified traceable standards.

Receiving and dispatch activities should be separated in space or at least in time.

Cleaning equipment and cleaning agents should not become possible sources of contamination.

Premises should be protected from the entry of birds, rodents, insects and other animals. A rodent and a pest control programme should be implemented and maintained. Its effectiveness should be monitored.

Defective equipment should not be used and should either be removed or labelled as defective. Equipment should be disposed of in such a way as to prevent any misuse.

Segregated areas should be provided for the storage of received, quarantined, rejected, recalled and returned product, including products with damaged packaging. Any system replacing physical segregation, such as electronic segregation based on a computerized system, should provide equivalent security and should be appropriately qualified and validated.

Segregated areas and products should be appropriately identified.

6. Operations

6.1. Orders

Where active substances used as starting materials in veterinary medicinal products are procured from a manufacturer, importer or distributor established in the EU, that manufacturer, importer or distributor should be registered according to Article 95(1) of Regulation (EU) 2019/6.

6.2. Receipt

Areas for receiving active substances used as starting materials in veterinary medicinal products 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:

- containers are not damaged;
- all security seals are present with no sign of tampering;
- correct labelling, including correlation between the name used by the supplier and the in-house name, if these are different;
- necessary information, such as a certificate of analysis, is available; and
- the active substance used as starting materials in veterinary medicinal products and the consignment correspond to the order.

Active substances used as starting materials in veterinary medicinal products with broken seals, damaged packaging, or suspected of possible contamination should be separated physically and electronically, if an electronic system is available and the cause of the issue investigated.

Active substances used as starting materials in veterinary medicinal products subject to specific storage measures, such as 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.

Where the distributor suspects that an active substance used as starting materials in veterinary medicinal products procured or imported by him is falsified, he should segregate it physically and electronically, if an electronic system is available and inform the national competent authority of the country in which he is registered.

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.

6.3. Storage

Active substances used as starting materials in veterinary medicinal products should be stored under the conditions specified by the manufacturer, such as 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.

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

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

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

Active substances used as starting materials in veterinary medicinal products beyond their expiry date should be separated physically and electronically, if an electronic system is available, from approved stock and not be supplied.

Where storage or transportation of active substances used as starting materials in veterinary medicinal products is contracted out, the distributor should ensure, amongst other through audits, 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.

6.4. Deliveries to customers

Supplies within the EU should be made only by distributors of active substances used as starting materials in veterinary medicinal products registered according to Article 95(1) of Regulation (EU) 2019/6 to other distributors, manufacturers, dispensing pharmacies or to entities/persons permitted by national legislation.

Active substances used as starting materials in veterinary medicinal products 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. Actions should be taken to prevent unauthorised access to the products being transported.

A system should be in place by which the distribution of each batch of active substance used as starting materials in veterinary medicinal products can be readily identified to permit its recall.

6.5. Transfer of information

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.

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.

The distributor who supplies the active substance used as starting materials in veterinary medicinal products 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.

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.)

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

7. Returns, complaints and recalls

7.1. Returns

Returned active substances used as starting materials in veterinary medicinal products should be identified as such and quarantined pending investigation.

Active substances used as starting materials in veterinary medicinal products which have left the care of the distributor, should only be returned to approved stock if all of the following conditions are met:

- the active substance used as starting material in veterinary medicinal products is in the original unopened container(s) with all original security seals present and is in good condition;
- it is demonstrated that the active substance used as starting material in veterinary medicinal products has been stored and handled under proper conditions. Written information provided by the customer should be available for this purpose;
- the remaining shelf life period is acceptable;
- the active substance used as starting material in veterinary medicinal products has been examined and assessed by a person trained and authorised to do so;
- no loss of information/traceability has occurred.

This assessment should take into account the nature of the active substance used as starting materials in veterinary medicinal products, 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.

Records of returned active substances used as starting materials in veterinary medicinal products should be maintained. For each return, documentation should include:

- name and address of the consignee returning the active substances used as starting materials in veterinary medicinal products;
- name or designation of active substance used as starting materials in veterinary medicinal products, active substance used as starting materials in veterinary medicinal products batch number and quantity returned;
- reason for return;
- use or disposal of the returned active substances used as starting materials in veterinary medicinal products and records of the assessment performed.

Only appropriately trained and authorised personnel should release active substances used as starting materials in veterinary medicinal products for return to stock. Active substances used as starting materials in veterinary medicinal products returned to saleable stock should be placed such that the stock rotation system operates effectively.

7.2. Complaints and recalls

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 used as starting materials in veterinary medicinal products 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 used as starting materials in veterinary medicinal products 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.

Complaint records should include:

- name and address of complainant;
- name, title, where appropriate, and phone number of person submitting the complaint;
- complaint nature, including name and batch number of the active substance used as starting materials in veterinary medicinal products;
- date the complaint is received;
- action initially taken, including dates and identity of person taking the action;
- any follow-up action taken;
- response provided to the originator of complaint, including date response sent;
- final decision on active substance batch.

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.

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.

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

There should be a written procedure that defines the circumstances under which a recall of an active substance used as starting materials in veterinary medicinal products should be considered.

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.

8. Self-Inspections

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. The team conducting the inspection should be free from bias and individual members should have appropriate knowledge and experience. The results of all self-inspections should be recorded. Reports should contain all observations made during the inspection and presented to the

relevant personnel as well as management. Necessary CAPAs should be taken and the effectiveness of the CAPAs should be reviewed.