Official Journal
of the European Union

EN
L series

2025/2154

27.10.2025

COMMISSION IMPLEMENTING REGULATION (EU) 2025/2154

of 17 October 2025

laying down good manufacturing practice for active substances used as starting materials in veterinary medicinal products in accordance with Regulation (EU) 2019/6 of the European Parliament and of the Council

(Text with EEA relevance)

THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC ([1]), and in particular Article 93(2) thereof,

Whereas:

(1) In accordance with Regulation (EU) 2019/6, veterinary medicinal products manufactured in the Union, including veterinary medicinal products intended for export as well as veterinary medicinal products imported into the Union, are to be manufactured in accordance with good manufacturing practice and contain as starting materials only active substances which have been manufactured in accordance with good manufacturing practice for active substances.

(2) The Commission is to adopt good manufacturing practice for active substances used as starting materials in veterinary medicinal products (the 'active substances') applicable in the Union. The good manufacturing practices applicable in the Union should continue to be aligned with relevant international standards.

(3) Compliance with the requirements for good manufacturing practice for active substances applicable in the Union should be ensured by manufacturers of active substances ('manufacturers'). To avoid placing any restraint upon the development of any new concepts or new technologies, manufacturers of active substances should be allowed to implement alternative approaches to those set out in this Regulation only if they are able to demonstrate that the alternative approach is capable of meeting the same objectives and that the quality and purity of the active substances is ensured.

(4) The manufacture of sterile active substances presents specific risks that should be addressed with a view to ensure the quality of such active substances. To this end, the sterilisation and aseptic processing of sterile active substances should be performed in accordance with the requirements set out in Annex I to Commission Implementing Regulation (EU) 2025/2091 ([2]) on good manufacturing practice for veterinary medicinal products.

(5) The manufacture of active substances from biological origin present specific characteristics that should be addressed with a view to ensure the quality of such active substances. To this end, requirements set out in Annex II to Implementing Regulation (EU) 2025/2091 on good manufacturing practice for veterinary medicinal products should be applied as relevant.

(6) The manufacture of active substances from herbal origin present specific characteristics that should be addressed with a view to ensure the quality of such active substances. To this end, requirements set out in Annex III to Implementing Regulation (EU) 2025/2091 on good manufacturing practice for veterinary medicinal products should be applied as relevant.

([1]) OJ L 4, 7.1.2019, p. 43, ELI: http://data.europa.eu/eli/reg/2019/6/oj.

([2]) Commission Implementing Regulation (EU) 2025/2091 of 17 October 2025 laying down good manufacturing practice for veterinary medicinal products in accordance with Regulation (EU) 2019/6 of the European Parliament and of the Council (OJ L, 2025/2091, 27.10.2025, ELI: http://data.europa.eu/eli/reg_impl/2025/2091/oj).

(7) Active substances used in parasiticidal veterinary medicinal products for the target species bees and active substances used in ectoparasiticidal veterinary medicinal products for external application are often produced for use in other types of products and the quantity needed for the production of veterinary medicinal products is too small to be economically viable. In order to ensure availability of parasiticidal veterinary medicinal products for bees and ectoparasiticidal veterinary medicinal products, this Regulation should not apply to the production of those active substances. However, the manufacturing process thereof should be adequate to ensure the quality and purity of the active substances. Additionally, the specifications provided for by the manufacturer of the veterinary medicinal product should be complied with.

(8) Where there is a continuous process from the sourcing or isolation of an active substance from a biological source to the manufacturing of the finished product, such as in the case of veterinary medicinal products that consist of cells, viral-based vaccines or phages, the entire manufacturing process is subject to Implementing Regulation (EU) 2025/2091 on good manufacturing practice for veterinary medicinal products and this Regulation should therefore not apply to them.

(9) Where there is a continuous process from the manufacture of the active substance gas to the manufacturing of the finished product, the entire manufacturing process is subject to Implementing Regulation (EU) 2025/2091 on good manufacturing practice for veterinary medicinal products and this Regulation should therefore not apply to them.

(10) Manufacturers should ensure the identity, integrity, traceability and consistent quality of the active substances during their production. To achieve this objective, manufacturers should implement a comprehensive quality management system.

(11) Through product quality reviews, manufacturers should verify the consistency of the existing processes, the appropriateness of current specifications, detect trends, and identify product and process improvements. Where appropriate, the outcome of such reviews should lead to the implementation of corrective or preventive measures.

(12) In order to ensure that the active substances meet the required quality standards and comply with the terms of the marketing authorisation and with good manufacturing practice, manufacturers should perform regular self-inspections.

(13) In order to ensure the quality of the active substances, manufacturers should have an adequate number of competent personnel with clear responsibilities. Initial and on-going training relevant to the assigned tasks should be provided to the personnel.

(14) Appropriate hygiene standards should be maintained at all times during the manufacturing process.

(15) In order to ensure the quality of the active substances, manufacturers should have suitable premises and equipment for the manufacture and control of the active substances as well as suitable premises for the storage of materials and products. Such premises and equipment should be adequately maintained. Qualification and validation of the premises and equipment, including utilities and systems used during manufacture of active substances, should be set out as a basic requirement of good manufacturing practice.

(16) In order to ensure that the use of computerised systems does not increase the risks to the quality of the active substances, certain requirements for the use of such systems should be laid down.

(17) A comprehensive documentation system should be set out as a key component of the quality management system. The documentation system should ensure that appropriate instructions and specifications are laid down, including relevant controls and monitoring procedures, with a view to ensuring the quality of the active substances. Additionally, the documentation system should ensure that all the activities that, directly or indirectly, may affect the quality of the active substances are duly recorded and that the integrity of the data is maintained throughout the relevant retention period.

(18) Requirements concerning the handling of materials and products, the qualification of suppliers, the prevention of cross-contamination and packaging operations should be set out.

(19) Production and in-process controls should be performed in order to assure the quality of the active substance and intermediates thereof.

(20) Laboratory control procedures should be implemented to ensure that materials are not released for use and products are not released for supply until their quality has been verified. As such, laboratory control should encompass sampling, specifications and testing, as well as organisational measures, documentation and release procedures.

(21) Correct sampling is essential to ensure the quality of the manufactured products. Reference samples should be kept as a record of the batch of active substance and for assessment in the case of quality investigations.

(22) In order to ensure that quality problems are swiftly identified and addressed, a system to record and investigate suspected quality defects and quality-related complaints should be put in place by manufacturers. In addition, procedures should be established to deal with recalls.

(23) In order to ensure that the outsourcing of activities related to the manufacture and control of active substances does not increase the risks to the quality of the active substances, certain requirements should be laid down. In particular, the outsourcing should be done in writing and there should be a clear delineation of the responsibilities of each party.

(24) The manufacture of certain types of active substances warrants specific consideration. Additional requirements should be implemented in the manufacture of active substances or intermediates thereof manufactured by cell culture or fermentation and in the manufacture of active substances gases. It is therefore necessary to set out certain adjustments to the good manufacturing practice requirements or, where appropriate, additional requirements for those products.

(25) While the good manufacturing practice requirements set out in this Regulation remain aligned with applicable requirements under Directive 2001/82/EC of the European Parliament and of the Council ([3]), time should be given to competent authorities and concerned stakeholders to become acquainted with the provisions of this Regulation. Accordingly, the application thereof should be deferred.

(26) The measures provided for in this Regulation are in accordance with the opinion of the Standing Committee on Veterinary Medicinal Products,

HAS ADOPTED THIS REGULATION:

CHAPTER I

GENERAL PROVISIONS

Article 1

Subject matter and scope

1. This Regulation lays down the requirements for good manufacturing practice for active substances used as starting materials in veterinary medicinal products ('active substances').

2. This Regulation applies to the manufacture of sterile active substances only up to the point immediately prior to the active substance being rendered sterile. The sterilisation and aseptic processing shall be performed in accordance with the requirements set out in Annex I to Implementing Regulation (EU) 2025/2091 on good manufacturing practice for veterinary medicinal products.

([3]) Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products (OJ L 311, 28.11.2001, p. 1, ELI: http://data.europa.eu/eli/dir/2001/82/oj).

3. The manufacture of biological active substances shall comply with the additional requirements set out in Annex II to Implementing Regulation (EU) 2025/2091 on good manufacturing practice for veterinary medicinal products, with the exception of active substances referred to in paragraph 7.

4. The manufacture of herbal active substances shall be subject to the additional requirements set out in Annex III to Implementing Regulation (EU) 2025/2091 on good manufacturing practice for veterinary medicinal products.

5. This Regulation, except its Chapter XVII, applies to manufacturers of active substances other than the substances referred to in paragraph 7 of this Article.

6. Chapter XVII applies to entities involved in the repackaging or relabelling of active substances other than the substances referred to in paragraph 7 of this Article.

7. This Regulation does not apply to the following active substances:

(a) active substances to be used in parasiticidal veterinary medicinal products for the target species bees;

(b) active substances to be used in ectoparasiticidal veterinary medicinal products for external application to animals;

(c) biological active substances where there is a continuous process from the sourcing or isolation of the active substance from a biological source to the manufacture of the finished product;

(d) gases where there is a continuous manufacturing and no intermediate storage of gas between the manufacture of the active substance and the manufacture of the veterinary medicinal product is possible.

8. Chapter VII does not apply to the production of active substance gases performed by air separation.

9. Articles 48 and 49 do not apply to the production of active substance gases for which the initial stability studies have been replaced by bibliographic data.

10. Article 50 does not apply to the production of active substance gases, unless otherwise specified.

11. Whilst meeting the requirements laid down in this Regulation demonstrates compliance with good manufacturing practice, the manufacturer of active substances (the 'manufacturer') may implement alternative approaches to the requirements provided for in this Regulation where it is duly justified that the alternative approach is capable of meeting the same objectives and that the quality and purity of the active substance is ensured.

Article 2

Definitions

For the purposes of this Regulation, the following definitions shall apply:

(1) 'signed' means the record of the individual who performed a particular action or review. This record can be initials, a full handwritten signature, a personal seal, or an advanced electronic signature as defined in Article 3(11) of Regulation (EU) No 910/2014 of the European Parliament and of the Council ([4]);

(2) 'quality risk management' means a systematic process, applied both proactively and retrospectively, for the assessment, control, communication and review of risks to the quality of the active substance;

(3) 'intermediate' means a material produced during steps of the processing of an active substance that undergoes further molecular change or purification before it becomes an active substance;

([4]) Regulation (EU) No 910/2014 of the European Parliament and of the Council of 23 July 2014 on electronic identification and trust services for electronic transactions in the internal market and repealing Directive 1999/93/EC (OJ L 257, 28.8.2014, p. 73, ELI: http://data.europa.eu/eli/reg/2014/910/oj).

(4) ‘qualification’ means the process of demonstrating that entities, premises, equipment, utilities, systems or materials are suitable for the intended task and can deliver the expected outcomes;

(5) ‘in-process controls’ means the checks performed during production in order to monitor and, if necessary, adjust the process to ensure that the intermediate or active substance conforms to the required specifications;

(6) ‘validation’ means the process of demonstrating that a method or process is suitable for its intended use;

(7) ‘batch’ means a defined quantity of materials or product that undergo the same process(es) so that it can be expected to be homogeneous. In the case of continuous manufacturing, a batch corresponds to a defined fraction of the production, characterised by its intended homogeneity;

(8) ‘raw material’ means starting materials, reagents, and solvents intended for use in the production of intermediates or active substances;

(9) ‘area’ means a space. A specific set of rooms within a building associated with the manufacture of one or more products that has a common air handling unit is considered as a single area;

(10) ‘cross-contamination’ means the contamination of a material or product with another material or product;

(11) ‘quarantine’ means the isolation -physically or by other effective means- of materials, intermediate or active substances whilst awaiting a decision on their release or refusal;

(12) ‘reprocessing’ means introducing an intermediate or active substance, including one that does not conform to standards or specifications, back into the manufacturing process and repeating a crystallisation step or other appropriate chemical or physical manipulation steps that are part of the established manufacturing process; excluding continuation of a process step after an in-process control test has shown that the step is incomplete;

(13) ‘campaign manufacture’ means the manufacture of a series of batches of the same product in sequence in a given period of time followed by strict adherence to preestablished control measures before transfer to another product. Use of the same equipment for distinct products is possible in campaign manufacture provided that appropriate control measures are applied;

(14) ‘bulk’ means any product which has completed all processing stages up to, but not including, final packaging;

(15) ‘blending’ means the process of combining materials complying with the same specification to produce a homogeneous intermediate or active substance;

(16) ‘primary reference standard’ means a substance that has been shown by an extensive set of analytical tests to be authentic material of high purity and that is obtained from an officially recognised source, or prepared by independent synthesis, or obtained from existing production material of high purity, or prepared by further purification of existing production material;

(17) ‘secondary reference standard’ means a substance of established quality and purity, as shown by comparison to a primary reference standard, used as a reference standard for routine laboratory analysis;

(18) ‘reference sample’ means a sample of a batch of materials used in the manufacture of the active substances used as starting materials in veterinary medicinal products which is stored for the purpose of being analysed should the need arise during the shelf life of the batch concerned;

(19) ‘reworking’ means subjecting an intermediate or active substance that does not conform to standards or specifications to one or more processing steps that are different from the established manufacturing process to obtain acceptable quality intermediate or active substance;

(20) ‘mother liquor’ means the residual liquid which remains after the crystallisation or isolation processes;

(21) ‘classical fermentation’ refers to processes that use microorganisms existing in nature or modified by conventional methods such as irradiation or chemical mutagenesis, to produce active substances used as starting materials.

Article 3

Starting point for the manufacture of active substances

1. The starting point at which the manufacture of an active substance starts shall be determined in accordance with the Annex to this Regulation. The reasons for the implemented approach shall be documented.

2. From the point determined in accordance with paragraph 1, the requirements set out in this Regulation shall apply.

CHAPTER II

QUALITY MANAGEMENT SYSTEM

Article 4

Implementation of a quality management system

1. Manufacturers shall have in place a comprehensive quality management system designed to ensure the quality of active substances.

2. Compliance with good manufacturing practice and the terms of the marketing authorisation, when applicable, shall be an essential part of the quality management system.

Article 5

Requirements of the quality management system

1. The design of the quality management system shall be based on the following risk management principles:

(a) the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the user and the safety of the animals treated;

(b) the level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.

2. The manufacturer shall document the quality management system and shall monitor its effectiveness.

3. The quality management system shall specify:

(a) the organisational structure of the manufacturer;

(b) procedures, processes and resources and activities necessary to ensure the quality and purity of the active substance;

(c) the persons authorised to release active substances and intermediates thereof.

4. The quality management system shall ensure that:

(a) there is an adequate number of personnel with the necessary qualifications and adequate training and there is clear allocation of responsibilities, including managerial responsibilities;

(b) there is a quality unit in place, which is independent from production, and that fulfils both quality assurance and quality control responsibilities;

(c) the premises and equipment are suitable for the intended use and they are appropriately maintained;

(d) all quality-related activities are recorded at the time they are performed and that the records identify the person making the entry;

(e) there is an adequate documentation system that ensures that appropriate specifications are laid down for materials used in the manufacture of the active substance and intermediates thereof, that the production and quality control procedures are clearly defined, and that appropriate records are kept;

(f) the manufacturing process is systematically reviewed to ensure that it is capable of consistently delivering a product of the required quality in compliance with the relevant specifications;

(g) appropriate controls, including in-process controls and validations are carried out;

(h) the results of product and process monitoring are taken into account in the context of batch release and in the investigation of deviations;

(i) quality defects, deviations and other problems or unusual events that may have an impact on the quality of the active substance are identified, the causes investigated, and appropriate corrective and/or preventive measures are taken;

(j) arrangements are put in place for the prospective evaluation of planned changes and their approval prior to the implementation thereof taking into account applicable regulatory requirements, as well as for the evaluation of changes implemented (change control);

(k) no materials are released or used before the satisfactory completion of evaluation by the quality unit unless there are appropriate systems in place to allow for such use;

(l) procedures are in place for notifying the management in a timely manner of regulatory inspections, serious GMP deficiencies, product defects and related actions;

(m) there is a process of self-inspection and/or quality audit which regularly appraises the effectiveness of the management quality system.

Article 6

Responsibilities of the quality unit

1. The quality unit shall be responsible for both quality assurance and quality control.

2. The responsibilities of the quality unit shall include, among others, the following elements:

(a) release or rejection of active substances and intermediates thereof;

(b) establishment of a system to release or reject raw materials, intermediates, packaging and labelling materials;

(c) review of production batch and laboratory control records for critical process parameters before release of the active substance;

(d) approval of:

  (i) specifications and master production instructions;

  (ii) procedures impacting the quality of active substances or intermediates thereof;

  (iii) intermediate and active substance contract manufacturers;

  (iv) changes potentially impacting the quality of the active substance or intermediates thereof;

(e) review and approval of all appropriate quality-related documents;

(f) ensuring that:

  (i) critical deviations are investigated and resolved;

  (ii) self-inspections and/or internal audits are performed;

  (iii) quality-related complaints are investigated and resolved;

  (iv) effective systems are used for maintaining and calibrating critical equipment;

(v) materials are appropriately tested and the results are reported;

(vi) stability data to support retest of active substances or intermediates is available, where appropriate;

(g) performance of product quality reviews referred to in Article 8.

3. The responsibilities of the quality unit shall be documented in writing and shall not be delegated.

Article 7

Responsibilities of the production unit

The responsibilities for production activities shall be documented in writing, and shall include at least the following elements:

— preparation, review, approval and distribution of the instructions for the production of active substances or intermediates thereof in accordance with written procedures;

— production of active substances and, when appropriate, intermediates in accordance with pre-approved instructions;

— review of all production batch records and ensuring that they are completed and signed;

— reporting and evaluation of all production deviations, investigation of critical deviations and recording of the conclusions;

— cleaning and when appropriate disinfection of production premises;

— performing of the calibrations and keeping the records of those calibrations;

— maintenance of the premises and equipment and keeping the records of the maintenance activities;

— review and approval of the validation protocols and reports;

— evaluation of proposed changes in product, process or equipment;

— ensuring the qualification of new and modified facilities and equipment.

Article 8

Product quality reviews

1. Product quality reviews shall be conducted and documented annually for each active substance, taking into account previous reviews and shall include at least a review of the following elements:

(a) critical in-process controls and critical active substance test results;

(b) all batches that failed to meet established specifications;

(c) all critical deviations or non-conformities and the investigation thereof;

(d) all changes carried out to the manufacturing process or analytical methods;

(e) the results of the stability monitoring programme;

(f) all quality-related returns, complaints and recalls;

(g) adequacy of corrective actions.

2. The results of the product quality review shall be evaluated and it shall be assessed whether corrective and/or preventive actions are required. Reasons for corrective actions shall be documented and agreed corrective actions shall be completed in a timely and effective manner.

Article 9

Self-inspection

1. Regular self-inspections shall be conducted to monitor the implementation of the arrangements regarding personnel, premises, equipment, documentation, production, quality control, quality management system, batch release and arrangements to deal with quality-related complaints and recalls.

2. The self-inspections shall verify the suitability of arrangements referred to in paragraph 1, ensuring that the active substances meet the required quality standards and comply with good manufacturing practice.

3. Self-inspections shall be recorded. Reports shall include the observations made and, where applicable, proposals for corrective measures. The actions subsequently taken shall also be recorded.

CHAPTER III

PERSONNEL

Article 10

General requirements for personnel

1. At each manufacturing site there shall be sufficient number of personnel with the necessary qualifications and practical experience having regard to the intended operations. The individual responsibilities of personnel shall be clearly laid out.

2. Consultants shall have adequate education, training, and experience to advise on the subject for which they are retained. Records of the qualifications and type of service provided by the consultants shall be kept.

Article 11

Training

1. All personnel shall receive initial and continuous training relevant to the tasks assigned. Training on the quality management system and good manufacturing practice shall be provided for personnel whose duties take them into production and storage areas or into control laboratories. Personnel working in areas where contamination is a hazard, such as clean areas or areas where highly active, toxic, infectious or sensitising materials are handled, shall be given specific training. Training shall also include the hygiene programmes referred to in Article 12.

2. The practical effectiveness of training shall be periodically assessed. Records of the trainings shall be kept.

Article 12

Hygiene

1. Detailed hygiene programmes adapted to the different needs within the manufacturing site shall be established. Such programmes shall include procedures relating to the health, hygiene practices and clothing of personnel. Particular attention shall be paid to hygiene measures necessary for the manufacture of sterile and biological preparations. Hygiene procedures shall be strictly followed by every person entering the production and control areas.

2. Persons affected by an infectious disease or having open lesions on the exposed surface of the body shall not be involved in activities that could result in compromising the safety or quality of the active substances.

3. Every person entering the manufacturing areas shall wear protective clothing appropriate to the operations to be carried out, which shall be changed when appropriate. The clothing and its quality shall be appropriate for the process and the grade of the working area. It shall be worn in such a way as to protect the product from the risk of contamination.

4. Direct contact between the operator and the exposed product as well as with any part of the equipment that comes into contact with the products shall be avoided.

5. Eating, drinking, chewing or smoking, or the storage of food, drinks, smoking materials in the production and storage areas shall be prohibited.

CHAPTER IV

PREMISES

Article 13

General requirements for premises

1. Premises used for manufacture of active substances shall be suitable for the intended operations. In particular, the premises shall be designed or adapted, equipped, operated, cleaned and maintained to minimise the opportunity for extraneous contamination, cross-contamination, the risk of errors and any adverse effect on the quality of the active substances.

2. The flow of materials and personnel throughout the premises shall be designed to avoid mix-ups or contamination.

3. Defined areas or control systems shall be in place for the following actions:

(a) receipt, identification, sampling, and quarantine of incoming materials, pending their release or rejection;

(b) production operations;

(c) laboratory operations;

(d) packaging and labelling operations;

(e) quarantine before release or rejection of active substances and intermediates thereof;

(f) sampling of active substances and intermediates thereof;

(g) storage of released materials;

(h) holding rejected materials before further disposition (e.g. return, reprocessing or destruction).

4. Adequate washing and toilet facilities for personnel shall be provided. Washing facilities shall be maintained in clean state and equipped with hot and cold water as appropriate, soap or detergent, and air dryers or single service towels. The washing and toilet facilities shall be separate from manufacturing areas.

5. Adequate facilities for showering or changing clothes shall be provided, where appropriate.

6. Laboratory areas and operations shall generally be separated from production areas.

7. By way of derogation from paragraph 6, laboratory areas, may be located in production areas, provided the following conditions are met:

(a) operations of the production process do not adversely affect the accuracy of the laboratory measurements;

(b) the laboratory and its operations do not adversely affect the production process, or the active substances or intermediates thereof.

8. All utilities affecting product quality shall be qualified and monitored (e.g. steam, gases, compressed air, heating, ventilation and air conditioning). Action shall be taken when limits for those utilities are exceeded. Drawings for those utility systems shall be available.

9. Adequate ventilation, air filtration and exhaust systems shall be provided, where appropriate. Those systems shall be designed and constructed to minimise risks of contamination and cross-contamination and shall include equipment for control of air pressure, microorganisms, if appropriate, dust, humidity, and temperature, as appropriate to the stage of manufacture. Particular attention to minimise the risks of contamination and cross-contamination shall be given to areas where active substances are exposed to the environment.

10. If air is recirculated to production areas, appropriate measures shall be taken to control risks of contamination and cross-contamination.

11. Fixed pipework shall be appropriately identified by identifying individual lines, documentation, computer control systems, or by alternative means.

12. Drains shall be of adequate size and shall be provided with an air break or a suitable device to prevent back-flow, where appropriate.

13. Adequate lighting shall be provided in all areas to facilitate cleaning, maintenance, and proper operations.

14. Sewage, refuse, and other waste in and from buildings and the immediate surrounding area shall be disposed of in a safe, timely, and sanitary manner. Containers and pipes for waste material shall be clearly labelled.

15. A site master file shall be prepared for every manufacturing site, which shall provide a high-level description of the premises, of the activities conducted at the manufacturing site and the quality system implemented. The site master file shall follow the template provided for in Annex VI to Implementing Regulation (EU) 2025/2091 on good manufacturing practice for veterinary medicinal products.

Article 14

Water

1. Water used in the manufacturing process of active substances shall be suitable for its intended use.

2. Water used in the manufacturing of active substances shall be at least of drinking water quality, unless otherwise justified.

3. When drinking water quality is insufficient to ensure active substance quality and more stringent water quality specifications are needed, appropriate specifications for physical, chemical, microbiological attributes, objectionable organisms, and endotoxins shall be established.

4. Where water used in the manufacture of active substances is processed by the manufacturer to achieve a defined quality, the process applied to the water shall be validated and monitored and action limits shall be set to ensure the quality of the water.

5. Water used in the final isolation and purification steps in the production of a non-sterile active substance intended for the production of a sterile veterinary medicinal product, shall be monitored and controlled for total microbial counts, objectionable organisms, and endotoxins.

Article 15

Containment

1. Unless validated inactivation and cleaning procedures are established and maintained, dedicated production areas shall be used when materials of infectious nature or high pharmacological activity or toxicity are involved.

2. Appropriate measures shall be established and implemented to prevent cross- contamination from among others, personnel or materials moving from one area to another.

3. Production activities (including weighing, milling, or packaging) of highly toxic nonpharmaceutical materials such as biocides and plant protection products shall not take place in premises being used for the production of active substances.

4. Handling and storage of highly toxic nonpharmaceutical materials shall be separated from active substances.

5. A comprehensive and effective quality system incorporating adequate quality controls and quality risk management shall be used for determining the necessity for and the extent to which production areas may be used for the production of multiple active substances and to mitigate the risk of contamination.

Article 16

Sanitation and maintenance

1. Written procedures shall be established assigning responsibility for sanitation and describing the cleaning schedules, methods, equipment, and materials to be used in cleaning buildings and premises.

2. Written procedures shall be established for the use of suitable rodenticides, insecticides, fungicides, fumigating agents, cleaning and sanitising agents to prevent the contamination of equipment, raw materials, packaging or labelling materials, active substances or intermediates thereof.

CHAPTER V

EQUIPMENT

Article 17

Design and construction

1. Equipment for manufacturing operations of active substances or intermediates thereof shall meet the following conditions:

(a) be of appropriate design and adequate size, and suitably located and qualified for its intended use;

(b) be cleaned, sanitised, where appropriate and maintained;

(c) be constructed so that contact surfaces do not alter the quality of the products beyond the established specifications for the active substance;

(d) be used within its qualified operating range.

2. Major equipment and permanently installed processing lines used during the production of active substances or intermediates thereof shall be appropriately identified.

3. Substances required for the operation of equipment used in manufacturing operations, such as lubricants, heating fluids or coolants, shall not come into contact with the active substances or intermediates thereof. Deviations from this requirement shall be evaluated to check whether there are no detrimental effects to the fitness for purpose of the active substances or intermediates thereof. Wherever possible, food grade lubricants and oils shall be used during the operation of equipment used in manufacturing operations.

4. Closed or contained equipment shall be used when appropriate. Where open equipment is used, or equipment is opened, appropriate precautions shall be taken to minimise the risk of contamination.

5. The manufacturer shall ensure that up-to-date drawings are kept for equipment used in manufacturing operations and critical installations such as instrumentation and utility systems.

Article 18

Maintenance and cleaning

1. Manufacturers shall establish:

(a) schedules and procedures, including assignment of responsibilities, for the maintenance of equipment used in manufacturing operations;

(b) written procedures for cleaning of equipment and its subsequent release for use in the manufacture of active substances and intermediates thereof.

2. The cleaning procedures shall be sufficiently detailed to allow cleaning of each type of equipment in a reproducible and effective manner, and shall include the description of the following:

(a) assignment of responsibilities for cleaning of equipment;

(b) cleaning schedules, including, where appropriate, sanitising schedules;

(c) the methods and materials, including dilution of cleaning agents used to clean equipment;

(d) instructions for disassembling and reassembling each article of equipment to ensure proper cleaning, where appropriate;

(e) instructions for the removal or obliteration of previous batch identification;

(f) instructions for the protection of clean equipment from contamination prior to use;

(g) inspection of equipment for cleanliness immediately before use, if practical;

(h) the maximum time that may elapse between the completion of processing and equipment cleaning, where appropriate.

3. Equipment and utensils shall be cleaned, stored, and, where appropriate, sanitised or sterilised to prevent contamination or carry-over of a material that would alter the quality of the active substances or intermediates thereof beyond the established specifications of the active substances or intermediates thereof.

4. Where equipment is assigned to continuous production or campaign manufacture of successive batches of the same active substance or intermediate thereof, equipment shall be cleaned at appropriate intervals to prevent build-up and carry-over of contaminants.

5. Equipment which is not assigned to continuous production or campaign manufacture of successive batches of the same active substance or intermediate thereof shall be cleaned between production of different materials to prevent cross-contamination.

6. Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents shall be defined and the reasons for choosing them shall be documented.

7. Equipment shall be identified as to its contents and its cleanliness status.

Article 19

Calibration

1. Manufacturers shall ensure that the following requirements are met:

(a) control, weighing, measuring, monitoring and test equipment that is critical for ensuring the quality of the active substances or intermediates thereof is calibrated in accordance with written procedures and an established schedule;

(b) equipment calibrations are performed using standards which ensure traceability to certified standards, where available;

(c) records of the calibrations referred to in point (b) are kept;

(d) the calibration status of equipment that is critical to the quality of the active substances or intermediates thereof is known and verifiable;

(e) instruments that do not meet calibration criteria are not used.

2. Deviations from certified standards of calibration on critical equipment shall be investigated to determine the potential impact on the quality of the active substances or intermediates thereof manufactured using the concerned equipment since the last successful calibration.

Article 20

Computerised systems

1. Computerised systems related to the good manufacturing practices for active substances shall be validated, taking into account the diversity, complexity and criticality of the computerised system.

2. Appropriate installation qualification and operational qualification shall demonstrate the suitability of computer hardware and software to perform assigned tasks.

3. Commercially available software that has been qualified shall not require the same level of testing as non-commercially available software. Where an existing computerised system is not validated at the time of installation, a retrospective validation shall be conducted if appropriate documentation is available.

4. Computerised systems shall have controls preventing unauthorised access, changes to data and omissions in data. All changes in data shall be recorded and reviewed in the audit trail.

5. Written procedures shall be available for the operation and maintenance of computerised systems.

6. Where critical data are entered manually, an additional check on the accuracy of the entry shall be performed by a second operator or by the system itself.

7. Incidents related to computerised systems potentially affecting the quality of the active substances or intermediates thereof, or the reliability of records or test results, shall be recorded and investigated.

8. Changes to the computerised system shall be made in accordance with a change control procedure and shall be formally approved, documented and tested, where appropriate. Records shall be kept of all changes to the computerised system., including modifications and enhancements made to the hardware, software and any other critical component of the system. Those records shall demonstrate that the computerised system is maintained in a validated state.

9. A back-up system shall be in place to prevent computerised system breakdowns or failures resulting in the permanent loss of records.

10. Data protection shall be ensured for all computerised systems.

11. In addition to the computerised system, data may be recorded by a different means.

CHAPTER VI

DOCUMENTATION

Article 21

Documentation system

1. A documentation system that is adequate to achieve the objectives of the quality management system shall be established and maintained.

2. The documentation system shall cover in a comprehensive manner the instructions and specifications related to the manufacture of active substances and intermediates thereof, as well as other documentation relevant to the quality management system and shall ensure that records are made of the activities which may directly or indirectly affect the quality of the active substances or intermediates thereof. The documentation system shall specify the retention period for each of the documents or records.

3. All production, control, and distribution records of a batch shall be retained for at least 1 year after the expiry date of the batch.

4. By derogation from paragraph 3, records for active substances with retest dates shall be retained for at least 3 years after the batch is completely distributed.

5. The content of documents shall be unambiguous and be kept up to date.

6. Documentation may be kept in a variety of forms and the requirements set out in this Chapter are applicable irrespective of form. Where electronic, photographic media, video recording or other data processing systems are used, the relevant systems shall be validated first to ensure that such systems are adequate to appropriately store the data during the required period of storage.

7. Suitable retrieval equipment and a means to produce hard copies shall be readily available in case reduction techniques such as microfilming or electronic records are used to retain specifications, instructions, procedures or records.

8. During the retention period, the documents and records shall be readily available at the establishment where the activities described in those documents and records occurred.

9. Electronic signatures on the documents and records shall be authenticated and secure.

Article 22

Specifications

1. Specifications shall be established and laid down for:

(a) raw materials;

(b) intermediates;

(c) active substances;

(d) labelling and packaging materials.

2. Specifications shall be established for any other materials used during the production of active substances and intermediates thereof that could critically impact the quality of active substances and intermediates thereof.

3. Acceptance criteria shall be established and documented for in-process controls.

Article 23

Equipment cleaning, maintenance and use records

1. Records of major equipment use, cleaning, sanitisation and sterilisation and maintenance shall be kept. Those records shall include:

(a) the date and, if appropriate, the time;

(b) product, and batch number of each batch processed in the equipment;

(c) the person who performed the cleaning and maintenance.

2. Individual equipment records are not required for equipment dedicated to manufacture of only one active substance or intermediate thereof, provided that batches follow in traceable sequence.

3. Records of major equipment use, cleaning, sanitisation or sterilisation, and maintenance may either be part of the batch record or kept separately.

Article 24

Records for raw materials, intermediates, active substance labelling and packaging materials

1. Adequate records shall be kept to enable the entire history of a batch to be traced.

2. Receipt and batch processing records shall be kept for each delivery of materials used in the manufacturing, including raw materials, intermediate as well as labelling and packaging materials. Those records shall include:

(a) the name of the manufacturer of the delivered material;

(b) identity and quantity of each delivery of each batch of raw materials, intermediates or labelling and packaging materials for active substances;

(c) the name of the supplier;

(d) the supplier's identification number;

(e) the identification number allocated upon receipt and the date of receipt;

(f) the results of any test or examination performed and the conclusions thereon;

(g) records tracing the use of materials;

(h) documentation of the examination and review of active substance labelling and packaging materials for conformity with established specifications;

(i) the final decision regarding rejected raw materials, intermediates or active substance labelling and packaging materials.

3. Master labels shall be maintained for comparison to issued labels.

Article 25

Master production instructions

1. Master production instructions for each active substance and intermediate thereof shall be prepared, dated, and signed by one person and independently checked, dated, and signed by a person in the quality unit.

2. The master production instructions referred to in paragraph (1) shall include:

(a) the name of the active substance or intermediate thereof being manufactured and an identifying document reference code, if applicable;

(b) a complete list of raw materials and intermediates designated by names or codes sufficiently specific to identify any special quality characteristics;

(c) an accurate statement of the quantity or ratio of each raw material or intermediate to be used, including the unit of measure. Where the quantity is not fixed, the calculation for each batch size or rate of production shall be included. Variations to the quantities of raw materials or intermediates used shall be included where they are justified;

(d) the production location and major production equipment to be used;

(e) detailed production instructions, including:

— sequences to be followed,

— ranges of process parameters to be used,

— sampling instructions and in-process controls with their acceptance criteria, where appropriate,

— time limits for completion of individual processing steps and the total process, where appropriate,

— expected yield ranges at appropriate phases of processing or time,

— where appropriate, special notations and precautions to be followed, or cross references to these,

— the instructions for storage of the active substance or intermediate thereof to assure its suitability for use, including the labelling and packaging materials and special storage conditions with time limits, where appropriate.

Article 26

Batch production and control records

1. Batch production records shall be prepared for each active substance and intermediate thereof. Those batch production records shall:

(a) for each batch include the complete information referred to in paragraph 2;

(b) be checked before issuance of the record to assure that it is the correct version and a legible accurate reproduction of the appropriate master production instruction;

(c) include a reference to the master production instructions being used, in case that batch production record is produced from a separate part of the master production instruction;

(d) be numbered with a unique batch or identification number and dated and signed when issued. In continuous production, the product code together with the date and time may serve as the unique identifier until the final number is allocated.

2. Batch production and control records shall include:

(a) dates and, where appropriate, times of production and control;

(b) identification of major equipment (e.g. reactors, dryers, mills, etc.) used;

(c) specific identification of each batch, including weights, measures, and batch numbers of raw materials, intermediates, or any reprocessed materials used during manufacturing;

(d) results recorded for critical process parameters;

(e) samplings performed;

(f) signatures of the persons performing and directly supervising or checking each critical step in the operation;

(g) in-process and laboratory test results;

(h) yield at appropriate phases or times;

(i) description of packaging and labelling of the active substance or the intermediate thereof;

(j) the representative label of active substance or intermediate thereof, if made commercially available;

(k) any deviation from procedures and instructions or any unusual occurrence which could impact the manufacture or testing of the active substance, its evaluation, investigation conducted (if appropriate) or reference to that investigation if stored separately;

(l) results of the release testing.

3. Written procedures shall be established and followed for investigating critical deviations from procedures and instructions or any unusual occurrence which could impact the manufacture or testing of the active substance or the failure of a batch of active substance or intermediate thereof to meet specifications. The investigation shall be extended to other batches that may have been associated with that deviation or failure.

Article 27

Laboratory control records

1. Laboratory control records shall be prepared for each active substance. Those laboratory control records shall include complete data derived from all tests conducted to ensure compliance with established specifications and standards, including examinations and assays and in particular, the following aspects:

(a) a description of samples received for testing, including the material name or source, batch number or other distinctive code, date of sampling, and, where appropriate, the quantity and date the sample was received for testing;

(b) a description of or reference to each test method used;

(c) a statement of the weight or measure of the sample used for each test as described by the method; data on or cross-reference to the preparation and testing of reference standards, reagents and standard solutions;

(d) a complete record of all raw data generated during each test, in addition to graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific material and batch tested;

(e) a record of all calculations performed in connection with the test, including, for example, units of measure, conversion factors, and equivalency factors;

(f) a statement of the test results and how they compare with established acceptance criteria;

(g) the signature of the person who performed each test and the dates when the tests were performed;

(h) the date and signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.

2. Laboratory control records shall also include complete records on:

(a) all modifications to an established analytical method;

(b) periodic calibration of laboratory instruments, apparatus, gauges, and recording devices;

(c) all stability testing performed on active substances;

(d) out-of-specification investigations.

Article 28

Batch production and laboratory control records review

1. Written procedures shall be established and followed for review and approval of batch production records referred to in Article 26 and laboratory control records referred to in Article 27, to ensure compliance of the active substance or intermediate thereof with established specifications before a batch is released.

2. Production and laboratory control records of non-critical process steps may be reviewed by qualified production personnel or other units following procedures approved by the quality unit.

3. All deviation, investigation, and out-of-specification reports shall be reviewed, as part of the batch record review, before the batch is released.

4. The quality unit can delegate the responsibility and authority for release of intermediates to the production unit, except for those intermediates dispatched outside the control of the manufacturer.

CHAPTER VII

MATERIALS MANAGEMENT

Article 29

Handling of materials

1. Handling of materials including aspects related to the receipt, identification, quarantine, storage, handling, sampling, testing and approval or rejection, shall be done in accordance with written procedures or instructions and recorded as appropriate.

2. Suppliers of materials used in the manufacturing of the active substance shall be approved by the quality unit after verifying the suitability thereof. In case of critical materials, qualification of the suppliers is required. The level of supervision shall be proportionate to the risks posed by the individual materials.

3. All materials shall be purchased in compliance with the relevant specification.

4. Where the supplier of a critical material is not the manufacturer of that material, the name and address of that manufacturer shall be known by the intermediate or active substance manufacturer.

5. Changes in the source of supply of critical raw materials shall be treated according to Chapter XIII.

Article 30

Receipt and quarantine for incoming materials

1. Upon receipt, each container or grouping of containers of materials shall be examined visually for correct labelling, including for correlation between the name used by the supplier and the name used by the manufacturer, if these are different.

2. Damage to containers and any other problem (e.g. evidence of seal tampering or evidence of breaches of package integrity) that may adversely affect the quality of a material shall be investigated.

3. Incoming materials shall be physically or administratively quarantined immediately after receipt, until their release is authorised by a responsible person, after verification of compliance with the relevant specifications.

4. Before incoming materials are mixed with existing stocks (e.g. solvents or stocks in silos), they shall be identified as correct, tested, if appropriate, and released. Procedures shall be available to prevent discharging materials erroneously into the existing stock.

5. Whenever bulk deliveries are made in non-dedicated tankers, the absence of cross-contamination from the tanker shall be assured. Such assurance can be provided by means of one or more of the following elements:

— a certificate of cleaning,

— testing for trace impurities,

— audit of the supplier.

6. Large storage containers, and their attendant manifolds, filling and discharge lines shall be appropriately identified.

7. Each container or grouping of containers with incoming materials shall be assigned and identified with a distinctive code, batch, or receipt number. That number shall be used in recording the disposition of each batch.

8. A system shall be in place to identify the status of each batch during receipt and quarantine.

Article 31

Testing of incoming materials

1. At least one test shall be performed to verify the identity of each batch of incoming material. A supplier's certificate of analysis may be used in place of performing tests, provided that the manufacturer has a system in place to evaluate suppliers.

2. Supplier approval shall include an evaluation that provides adequate evidence (e.g. compliance history), that the manufacturer consistently provides material meeting the relevant specifications.

3. A full analysis shall be conducted on at least three batches of incoming material before reducing in-house testing of that material. That full analysis shall be performed at appropriate intervals and compared with the supplier's certificates of analysis.

4. The reliability of certificates of analysis shall be checked at regular intervals.

5. By way of derogation from paragraph 1, processing aids, hazardous or highly toxic raw materials, other special materials, or materials transferred to another unit within the manufacturer's control do not need to be tested if the supplier's certificate of analysis is obtained, showing that those materials conform to established specifications. Visual examination of containers, labels, and recording of batch numbers shall contribute to establish the identity of those materials. The lack of on-site testing for those materials shall be justified and documented.

Article 32

Sampling of incoming materials

1. Personnel in charge of taking samples shall receive training on the techniques and equipment for sampling, the risks of cross-contamination, precautions to be taken with regard to unstable or sterile substances, the need to record any unexpected or unusual circumstance as well as other aspects relevant to the implementation of the sampling procedures.

2. Samples shall be representative of the batch of material from which they are taken. The taking of samples shall be done in accordance with written procedures that describe at least the following:

(a) the number of containers to be sampled;

(b) which part of the container to sample;

(c) the amount of sample to be taken from each container.

3. The number of containers to sample and the sample size shall be based upon a sampling plan that takes into consideration the following:

(a) the criticality of the incoming material;

(b) material variability;

(c) compliance history of the supplier;

(d) the amount of sample needed for analysis.

4. Sampling shall be conducted at defined locations and by procedures designed to prevent contamination of the material sampled and contamination of other materials.

5. Containers from which samples are collected shall be opened carefully and subsequently reclosed. They shall be marked to indicate that a sample has been taken.

6. Sample containers shall bear a label indicating the content, batch number, date of sampling and containers from which the samples have been taken.

Article 33

Re-evaluation of materials

All materials shall be re-evaluated as appropriate to determine their suitability for use (e.g. after prolonged storage or exposure to heat or humidity).

CHAPTER VIII

PRODUCTION AND IN-PROCESS CONTROLS

Article 34

Production operations

1. Raw materials for manufacture of active substances or intermediates thereof shall be weighed or measured under appropriate conditions that do not affect their suitability for use.

2. Balances and measuring equipment shall be of an appropriate range and precision to ensure the accuracy of weighing operations.

3. Whenever a material is subdivided for later use in production operations, the container receiving the material shall be suitable and shall be identified so that the following information is available:

(a) material name or item code;

(b) receiving or control number;

(c) weight or measure of material in the new container;

(d) re-evaluation or retest date if appropriate.

4. Critical activities, including the critical weighing, measuring, or subdividing operations shall be verified or subjected to an equivalent control. Prior to use, the manufacturer shall ensure that its production personnel verifies that the materials are those specified in the batch record for the intended active substance or intermediate thereof.

5. Actual yields shall be compared with expected yields at designated steps in the production process. Expected yields with appropriate ranges shall be established based on previous laboratory, pilot scale or manufacturing data. Deviations in yield associated with critical process steps shall be investigated to determine their impact or potential impact on the resulting quality of the affected batches.

6. Any deviation in yield shall be documented and explained. Any critical deviation shall be investigated.

7. The processing status of major units of equipment shall be indicated either on the individual units of equipment or by appropriate documentation, computer control systems, or alternative means.

8. Materials to be reprocessed or reworked shall be appropriately controlled to prevent unauthorised use.

Article 35

Time limits

Whenever time limits are specified in the master production instructions, those time limits shall be met to ensure the quality of active substances and intermediates thereof. Time limit deviations shall be documented and evaluated.

Article 36

In-process controls and in-process sampling

1. Written procedures shall be established to monitor the progress and control the performance of processing steps that cause variability in the quality of active substances and intermediates thereof. In-process controls and their acceptance criteria shall be defined based on the information gained during the development stage or historical data.

2. The acceptance criteria and the type and extent of testing may depend on:

(a) the nature of the intermediate or active substance being manufactured;

(b) the reaction or process step being conducted;

(c) the degree to which the process introduces variability in the quality of the active substance or the intermediate thereof.

3. Less stringent in-process controls may be appropriate in early processing steps, whereas more stringent controls may be appropriate for later processing steps (e.g. isolation and purification steps).

4. Critical in-process controls and critical process monitoring, including the control points and methods, shall be stated in writing and approved by the quality unit.

5. In-process controls may be performed by qualified personnel of the production department. The process may be adjusted without prior quality unit approval in case those adjustments are made within established limits approved by the quality unit. All tests and results shall be fully documented as part of the batch record.

6. Written procedures shall describe the sampling methods for in-process materials, intermediates and active substances. These procedures shall be designed to prevent contamination of the sampled material and of other intermediates or active substances. Procedures shall be established to ensure the integrity of samples after collection.

7. Out-of-specification investigations shall be performed.

8. By way of derogation from paragraph 7, out-of-specification investigations are not required for in-process tests that are performed for the purpose of monitoring or adjusting the process.

Article 37

Blending batches of intermediates or active substances

1. Out-of-specification batches shall not be blended with other batches for the purpose of meeting specifications.

2. Each batch incorporated into the blend shall:

(a) have been manufactured using an established process; and

(b) have been individually tested and found to meet appropriate specifications prior to blending.

3. Acceptable blending operations include:

(a) blending of small batches to increase batch size;

(b) blending of tailings (e.g. relatively small quantities of isolated material) from batches of the same intermediate or active substance to form a single batch.

4. Blending processes shall be adequately controlled and documented and the blended batch shall be tested for conformity to established specifications, where appropriate.

5. The batch record of the blending process shall allow traceability back to the individual batches that compose the blend.

6. Where physical attributes of the active substance are critical (e.g. active substances intended for use in solid oral dosage forms or suspensions), blending operations shall be validated to show homogeneity of the combined batch. Validation shall include testing of critical attributes (e.g. particle size distribution, bulk density, and tap density) that may be affected by the blending process.

7. Where the blending may adversely affect stability, stability testing of the final blended batches shall be performed.

8. The expiry or retest date of the blended batch shall be based on the manufacturing date of the oldest tailings or batch in the blend.

Article 38

Contamination control

1. Carryover of residual materials into successive batches shall not result in the carryover of degradants or microbial contamination that may adversely alter the established active substance's impurity profile.

2. Production operations shall be conducted in a manner that prevents contamination of active substances or intermediates thereof by other materials.

3. Precautions to avoid contamination shall be taken for the handling of active substances after purification.

CHAPTER IX

PACKAGING AND LABELLING

Article 39

General requirements concerning packaging and labelling

1. Written procedures shall be put in place to describe the receipt, identification, quarantine, sampling, examination or testing, release, and handling of packaging and labelling materials.

2. Packaging and labelling materials shall conform to established specifications. Packaging and labelling materials that do not comply with the specifications shall be rejected to avoid their use in operations for which they are unsuitable.

Article 40

Containers

1. Containers shall provide adequate protection against deterioration or contamination of the active substances or intermediates thereof that may occur during transportation and storage.

2. Containers shall be clean and, where indicated by the nature of the active substances or intermediates thereof, sanitised to ensure that they are suitable for their intended use. Those containers shall not be reactive, additive, or absorptive so as to alter the quality of the active substances or intermediates thereof beyond the specified limits.

3. Whenever containers are re-used, they shall be cleaned in accordance with documented procedures and all previous labels shall be removed or defaced.

Article 41

Label issuance and control

1. Access to the areas where labels are stored shall be limited to authorised personnel.

2. Procedures shall be used to reconcile the quantities of labels issued, used and returned, and to identify discrepancies between the number of containers labelled and the number of labels issued. Such discrepancies shall be investigated, and the investigation shall be approved by the quality unit.

3. All excess labels bearing batch numbers or other batch-related printing shall be destroyed. Returned labels shall be maintained and stored in a manner that provides proper identification and prevents mix-ups of labels.

4. Obsolete and outdated labels shall be destroyed, and such disposal be recorded.

5. Printing devices used to print labels for packaging operations shall be controlled to ensure that all imprinting conforms to the print specified in the batch production record.

6. Printed labels issued for a batch shall be carefully examined for proper identity and conformity with specifications in the master production record. The results of this examination shall be documented.

7. A printed label as used for the batch concerned shall be included in the batch production record.

Article 42

Packaging and labelling operations

1. Documented procedures shall be put in place to ensure that correct packaging materials and labels are used.

2. Appropriate measures shall be implemented to avoid mix ups of packaging materials or labels. There shall be physical or spatial separation from operations involving other intermediates or active substances.

3. Labels used on containers of intermediates or active substances shall indicate the name or identifying code, the batch number of the product, and storage conditions, when that information is critical to assure the quality of the active substance or intermediates thereof.

4. Whenever the intermediate or the active substance is intended to be transferred outside the control of the manufacturer, the label shall also include the name and address of the manufacturer, quantity of contents, special transport conditions and any special legal requirements. For intermediates or active substances with an expiry date, the expiry date shall be indicated on the label and on the certificate of analysis. For intermediates or active substances with a retest date, the retest date shall be indicated on the label and on the certificate of analysis.

5. Packaging and labelling premises shall be inspected immediately before use to ensure that all materials not needed for the next packaging operation have been removed. This inspection shall be documented in the batch production records, the facility log, or other documentation system.

6. Packaged and labelled intermediates or active substances shall be examined to ensure that containers and packages in the batch have the correct label. That examination shall be part of the packaging operation. Results of those examinations shall be recorded in the batch production or control records.

7. Intermediate or active substance containers that are transported outside of the manufacturer's control shall be sealed in a manner such that, if the seal is breached or missing, the recipient will be alerted to the possibility that the contents may have been altered.

CHAPTER X

STORAGE AND DISTRIBUTION

Article 43

Storage conditions and warehousing procedures

1. All materials used for the manufacturing of active substances shall be stored and handled under appropriate conditions (e.g. controlled temperature and humidity, where necessary) to ensure their quality and prevent degradation, contamination, and cross-contamination.

2. Whenever storage conditions are critical for the maintenance of material characteristics, records of those conditions shall be maintained.

3. Materials stored in fiber drums, bags or boxes shall be stored off the floor and, where appropriate, suitably spaced to permit cleaning and inspection.

4. Materials shall be stored for a period of time that has no adverse effect on their quality. Materials shall be controlled so that the oldest stock is used first.

5. Certain materials in suitable containers may be stored outdoors, provided identifying labels remain legible and containers are appropriately cleaned before opening and use.

6. Rejected materials shall be identified and controlled under a quarantine system designed to prevent their unauthorised use in manufacturing.

7. Separated areas shall be provided for the storage of quarantined, rejected, returned, or recalled materials.

Article 44

Distribution procedures

1. Active substances and intermediates thereof shall only be released for distribution to third parties after they have been released by the quality unit.

2. Active substances and intermediates thereof can be transferred under quarantine to another unit under the manufacturer's control when authorised by the quality unit and if appropriate controls and documentation are in place.

3. Active substances and intermediates thereof shall be transported in a manner that does not adversely affect their quality.

4. Special transport or storage conditions for an active substance or intermediate shall be stated on the label.

5. In case of outsourced activities as referred to in Chapter XVI, the manufacturer ('contract giver') shall ensure that adequate information is transmitted to the contractor ('contract acceptor') for the performance of the outsourced activities and that the contract acceptor follows the appropriate transport and storage conditions.

6. A system shall be in place by which the distribution of each batch of intermediate or active substance can be traceable to permit its recall.

CHAPTER XI

LABORATORY CONTROLS

Article 45

General controls

1. All specifications, sampling plans and test procedures shall be scientifically justified and appropriate to ensure that raw materials, intermediates, active substances and labels and packaging materials conform to established standards of quality and purity.

2. Specifications and test procedures shall be in compliance with the terms of the marketing authorisation. There can be specifications in addition to those in the terms of the marketing authorisation.

3. Specifications, sampling plans and test procedures, including changes to them, shall be drafted by the appropriate organisational unit and reviewed and approved by the quality unit.

4. Appropriate specifications shall be established for active substances in accordance with accepted standards and consistent with the manufacturing process.

5. The specifications for the active substance shall include a control of the impurities (e.g. organic impurities, inorganic impurities and residual solvents). If the active substance has a specification for microbiological purity, appropriate action limits for total microbial counts and objectionable organisms shall be established and met. If the active substance has a specification for endotoxins, appropriate action limits shall be established and met.

6. Laboratory controls shall be monitored and documented at the time of performance.

7. Procedures shall be established for the investigation and documentation of out-of-specification results. Those procedures shall require analysis of the data, assessment of the criticality of the out-of-specification result, allocation of the tasks for corrective actions and conclusions. Any re-sampling or retesting after out-of-specification results shall be performed according to a documented procedure.

8. Procedures shall be established for the preparation of reagents and standard solutions and the labelling thereof. Expiry dates shall be applied as appropriate for analytical reagents or standard solutions.

9. Primary reference standards shall be suitable for their intended use. The source of each primary reference standard shall be documented. Records shall be maintained of each primary reference standard's storage and use in accordance with the supplier's recommendations.

10. Primary reference standards obtained from an officially recognised source may be used without testing if stored under conditions consistent with the supplier's recommendations.

11. Where a primary reference standard is not available from an officially recognised source, an "in-house primary reference standard" shall be established. Appropriate testing shall be performed to establish fully the identity and purity of the in-house primary reference standard. Appropriate documentation of that testing shall be maintained.

12. Secondary reference standards shall be appropriately prepared, identified, tested, approved, and stored. The suitability of each batch of secondary reference standard shall be determined prior to first use by comparing against a primary reference standard. Each batch of secondary reference standard shall be periodically requalified in accordance with a written protocol.

Article 46

Testing

1. Appropriate laboratory tests to determine conformity to specifications shall be conducted for each batch of active substance and intermediates thereof.

2. An impurity profile describing the identified and unidentified impurities present in a typical batch produced by a specific controlled production process shall be established for each active substance. The impurity profile shall include:

(a) the identity of the impurity or some qualitative analytical designation (e.g. retention time);

(b) the range of each identified impurity;

(c) a classification of each identified impurity (e.g. inorganic, organic, solvent).

3. By way of derogation from paragraph 2, impurity profiles are not necessary for active substances from herbal or animal tissue origin.

4. The impurity profile shall be compared at appropriate intervals against the impurity profile in the terms of the marketing authorisation or compared against historical data in order to detect changes to the active substance resulting from modifications in raw materials, equipment operating parameters, or the production process.

5. Appropriate microbiological tests shall be conducted on each batch of intermediate and active substance where microbial quality is specified.

Article 47

Certificates of analysis

1. Upon request, certificates of analysis shall be issued for each batch of intermediate or active substance.

2. The certificate of analysis shall contain at least:

(a) the name of the intermediate or active substance including, where appropriate, its grade;

(b) the batch number;

(c) the date of release;

(d) the expiry date for intermediates or active substances with an expiry date;

(e) the retest date for intermediates or active substances with a retest date;

(f) each test performed in accordance with compendial or customer requirements, including the acceptance limits, and the numerical results obtained, if appropriate.

3. Certificates shall be dated and signed by authorised personnel of the quality unit and shall include the name, address and telephone number of the original manufacturer.

4. Where the analysis has been carried out by entities involved in repackaging or reprocessing, the certificate of analysis shall include the name, address and telephone number of the entity involved in repackaging or reprocessing and a reference to the name of the original manufacturer.

5. Whenever new certificates are issued by or on behalf of entities involved in repackaging or reprocessing, those certificates shall include the name, address and telephone number of the laboratory that performed the analysis. They shall also contain a reference to the name and address of the original manufacturer and to the original batch certificate, a copy of which shall be attached.

Article 48

On-going stability monitoring programme

1. Manufacturers shall put in place a documented, on-going stability programme to monitor the stability data of active substances. The results shall be used to confirm appropriate storage conditions and retest or expiry dates.

2. The test procedures used in stability studies shall be appropriate for the active substance and validated.

3. Stability samples shall be stored in containers that simulate the market container.

4. The first three production scale batches shall be placed on the on-going stability programme to confirm the retest or expiry date.

5. By way of derogation from paragraph 4, where data from previous studies show that the active substance is expected to remain stable for at least two years, fewer than three batches may be used.

6. After the first three production scale batches being placed on the on-going stability programme, at least one batch per year of the active substance manufactured shall be included into the on-going stability programme, unless none are produced in a given year or a different frequency is otherwise justified.

7. In case of active substances with short shelf life, stability testing shall be done more frequently. When data exist confirming that the stability of the active substance is not compromised, elimination of specific test intervals may be considered.

8. Where appropriate, the stability testing of active substances shall be performed in accordance with the conditions set out in the Guideline on stability: stability testing of new veterinary drug substances and medicinal products ([5]).

Article 49

Expiry and retest dating

1. Where an intermediate is intended to be transferred outside the control of the manufacturer and an expiry or retest date is assigned, supporting stability information shall be available (e.g. published data, test results).

2. The expiry or retest date of an active substance shall be based on an evaluation of data derived from stability studies.

3. Preliminary active substance expiry or retest dates may be based on pilot scale batches where the following conditions are fulfilled:

(a) the pilot batches employ a method of manufacture and procedure that simulates the final process to be used on a production scale;

(b) the quality of the active substance represents the material to be made on a production scale.

Article 50

Retention of samples

1. Reference samples shall be kept for the purpose of potential future evaluation of the quality of batches of active substance and not for future stability testing purposes.

2. Reference samples of each active substance batch shall be retained for one year after the expiry date of the batch, or for three years after distribution of the batch, whichever is the longest.

3. For active substances with retest dates, reference samples shall be retained for three years after the batch is completely distributed by the manufacturer.

4. Reference samples shall be stored in the same packaging system in which the active substance is stored or in one that is equivalent to or more protective than the marketed packaging system.

5. Sufficient quantities shall be retained to conduct at least two full compendial analyses or, when there is no pharmacopoeial monograph, two full specification analyses.

([5]) European Medicines Agency Guideline on Stability: stability testing of new veterinary drug substances and medicinal products (EMEA/CVMP/VICH/899/99).

CHAPTER XII

VALIDATION

Article 51

Validation policy and methodology

1. The manufacturers' overall policy and methodology for validation, including the validation of production processes, cleaning procedures, analytical methods, in- process control test procedures, computerised systems and the appointment of persons responsible for design, review, approval and documentation of each validation phase, shall be established and documented.

2. The critical process parameters or attributes of the active substances shall be identified during its development stage or from historical data, and the ranges necessary for the reproducible operation shall be defined, including:

(a) critical product attributes of the active substance;

(b) process parameters that may affect the critical quality attributes of the active substance;

(c) the range for each critical process parameter expected to be used during routine manufacturing and process control.

3. Validation shall extend to those operations determined to be critical to the quality and purity of the active substance.

Article 52

Validation documentation

1. A written validation protocol, specifying how validation of a particular process will be conducted, shall be established. The protocol shall be reviewed and approved by the quality unit and other designated units.

2. The validation protocol shall specify:

(a) the critical process steps and acceptance criteria;

(b) the type of validation to be conducted (e.g. prospective, concurrent);

(c) the number of process runs.

3. A validation report that refers to the validation protocol shall be prepared. That validation report shall contain:

(a) a summary of the results obtained;

(b) any deviations from the validation protocol observed;

(c) comments and conclusions on the deviations under point (b);

(d) recommendations for change to correct deficiencies.

4. Any deviations from the validation protocol shall be documented with appropriate justification.

Article 53

Qualification

1. Before starting the process validation, appropriate qualification of critical equipment and ancillary systems shall be completed.

2. Qualification may be carried out by conducting the following activities, individually or combined:

(a) design qualification: documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose;

(b) installation qualification: documented verification that the equipment or systems, as installed or modified, comply with the approved design, the manufacturer's recommendations and/or user requirements;

(c) operational qualification: documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges;

(d) performance qualification: documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications.

Article 54

Process validation

1. Prospective validation shall be used for all active substance processes.

2. Prospective validation performed on an active substance process shall be completed before the commercial distribution of the veterinary medicinal product manufactured from that active substance.

3. By way of derogation from paragraph 1, concurrent validation may be conducted in the following cases:

(a) data from replicate production runs are unavailable because only a limited number of active substance batches have been produced;

(b) active substance batches are produced infrequently; or

(c) active substance batches are produced by means of a validated process that has been modified.

4. Prior to the completion of concurrent validation, batches may be released and used in the manufacturing of a veterinary medicinal product based on thorough monitoring and testing of the active substance batches.

5. By further way of derogation from paragraph 1, retrospective validation may be performed for well-established processes that have been used without significant changes to active substance quality due to changes in raw materials, equipment, systems, premises or the production process. That validation approach may be used if all the following conditions are met:

(a) critical quality attributes and critical process parameters have been identified;

(b) appropriate in-process acceptance criteria and controls have been established;

(c) there have not been significant process or product failures attributable to cause other than operator error or equipment failures unrelated to equipment suitability;

(d) impurity profiles have been established for the existing active substance.

6. Batches selected for retrospective validation shall be:

(a) representative of all batches made during the review period, including any batches that failed to meet specifications;

(b) sufficient in number to demonstrate process consistency.

7. Retained samples may be used for retrospective validation testing.

Article 55

Process validation programme

1. The number of process runs for validation shall depend on the complexity of the process or on the criticality of the process change being considered.

2. A minimum of three consecutive successful production batches shall be used for prospective and concurrent validation. In situations where additional process runs are warranted to prove consistency of the process (e.g. complex active substance processes or active substance processes with prolonged completion times), this number shall be increased.

3. For retrospective validation, data from ten to thirty consecutive batches shall be examined to assess process consistency.

4. By way of derogation from paragraph 3, fewer batches can be examined for retrospective validation, if justified.

5. Critical process parameters shall be controlled and monitored during process validation studies. Process parameters unrelated to quality, such as variables controlled to minimise energy consumption or equipment use, may be excluded from the process validation.

6. Process validation shall confirm that the impurity profile for each active substance is within the specified limits. The impurity profile shall be comparable to or better than historical data and, where applicable, comparable to or better than the profile determined during process development or for batches used for pivotal clinical and toxicological studies.

Article 56

Periodic review of validated systems

1. Validated systems and processes shall be periodically reviewed.

2. Where no significant changes have been made to the system or process, and a quality review confirms that the system or process is consistently producing material meeting its specifications, no revalidation is required.

Article 57

Cleaning validation

1. Cleaning procedures shall be validated. Cleaning validation shall be directed to situations or process steps where contamination or carryover of materials poses the greatest risk to active substance quality.

2. Validation of cleaning procedures shall reflect actual equipment usage patterns. Where various active substances or intermediates are manufactured in the same equipment and the equipment is cleaned by the same process, a representative intermediate or active substance may be selected for cleaning validation. This selection shall be based on:

(a) the solubility of the intermediate or active substance;

(b) the difficulty of cleaning;

(c) the calculation of residue limits based on potency, toxicity, and stability.

3. The cleaning validation protocol shall describe:

(a) the equipment to be cleaned;

(b) the procedures;

(c) the materials;

(d) the acceptable cleaning levels;

(e) the parameters to be monitored and controlled;

(f) the analytical methods to be applied;

(g) the type of samples to be obtained and how they are collected and labelled.

4. Sampling shall include swabbing, rinsing or alternative methods (e.g. direct extraction), as appropriate, to detect both insoluble and soluble residues. The sampling methods used shall allow the quantitative measurement of the levels of residues remaining on the equipment surfaces after cleaning.

5. Validated analytical methods sensitive to detect residues or contaminants shall be applied. The detection limit for each analytical method shall be sufficiently sensitive to detect the established acceptable level of the residue or contaminant. The method's attainable recovery level shall be established. Residue limits shall be practical, achievable, verifiable and based on the most deleterious residue. Limits may be established based on the minimum known pharmacological, toxicological, or physiological activity of the active substance or its most deleterious component.

6. Equipment cleaning or sanitisation tests shall address microbiological and endotoxin contamination for those processes where there is a need to reduce total microbiological count or endotoxins in the active substance, or for other processes where such contamination could be of concern (e.g. non-sterile active substances used to manufacture sterile products).

7. Cleaning procedures shall be monitored at appropriate intervals after validation to ensure that those procedures are effective when applied during routine production. Equipment cleanliness may be monitored by analytical testing and visual examination, where feasible. Visual inspection may allow detection of gross contamination concentrated in small areas that could otherwise go undetected by sampling or analysis.

Article 58

Validation of analytical methods

1. Analytical methods shall be validated unless the method employed is included in the relevant pharmacopoeia or other recognised standard reference. The suitability of all testing methods used shall be verified under actual conditions of use and this verification of suitability shall be documented.

2. The validation of the analytical methods shall be performed in accordance with the requirements set out in the guideline on validation of analytical procedures: methodology ([6]). The degree of analytical validation performed shall reflect the purpose of the analysis and the stage of the active substance production process.

3. Complete records shall be maintained of any modification of a validated analytical method. Such records shall include the reason for the modification and appropriate data to verify that the modification produces results that are as accurate and reliable as the established method.

CHAPTER XIII

CHANGE CONTROL

Article 59

General requirements for change control

1. A formal change control system shall be established to evaluate all changes that may affect the production and control of the intermediate or active substance.

([6]) European Medicines Agency Guideline on validation of analytical procedures: methodology (EMEA/CVMP/VICH/591/98).

2. Written procedures shall describe the identification, documentation, appropriate review and approval of changes in raw materials, specifications, analytical methods, premises, support systems, equipment (including computer hard- and software), processing steps, labelling and packaging materials.

3. Any proposals for changes relevant to the good manufacturing practices shall be drafted, reviewed and approved by the appropriate organisational unit, and reviewed and approved by the quality unit.

4. The potential impact of proposed changes on the quality of the active substances or intermediates thereof shall be evaluated. A classification procedure may contribute to determine the level of testing, validation and documentation needed to justify changes to a validated process. Changes shall be classified (e.g. as minor or major) depending on the nature and extent of the changes and the effects those changes may have on the process.

5. A scientific assessment shall be carried out to determine which additional testing and validation studies are appropriate to justify a change in a validated process.

6. All documents affected by the changes shall be revised and updated where approved changes are implemented.

7. After implementation of the change, an evaluation of the first batches produced or tested under the change shall be performed.

8. The potential for critical changes to affect established retest or expiry dates shall be evaluated. Where necessary, samples of the active substances or intermediates thereof produced by the modified process shall be placed on an accelerated stability programme and added to the on-going stability programme.

9. Manufacturers of the veterinary medicinal product shall be notified of changes from established production and process control procedures that may impact the quality of the active substance used in the veterinary medicinal product.

CHAPTER XIV

REJECTION AND RE-USE OF MATERIALS

Article 60

Rejection

Active substances and intermediates thereof failing to meet established specifications shall be identified as such and quarantined. The final disposal of rejected materials shall be recorded.

Article 61

Reprocessing

1. An intermediate or an active substance, including one that does not comply with standards or specifications, may be introduced back into the manufacturing process and reprocessing by repeating a crystallisation step or other appropriate chemical or physical manipulation steps (e.g. distillation, filtration, chromatography, milling) that are part of the established manufacturing process. Whenever such reprocessing is used for the majority of batches, that reprocessing shall be included as part of the standard manufacturing process.

2. Introducing unreacted material back into a process and repeating a chemical reaction is considered to be reprocessing unless it is part of the established process. Such reprocessing shall be preceded by careful evaluation to ensure that the quality of the active substance or intermediates thereof is not adversely impacted due to the potential formation of by-products and over-reacted materials.

Article 62

Reworking

1. Batches that do not conform to established standards or specifications shall not be reworked unless an investigation into the reason for non-conformity has been performed.

2. Batches that have been reworked shall be subject to appropriate evaluation, testing, stability testing if warranted, and documentation to show that the reworked product is of equivalent quality to that produced by the original process.

3. Concurrent validation may be used as a validation approach for rework procedures. In case only one batch shall be reworked, a report may be written, and the batch may be released once it is proved to be acceptable.

4. Procedures shall provide for comparing the impurity profile of each reworked batch against batches manufactured by the established process. Where routine analytical methods are inadequate to characterise the reworked batch, additional methods shall be used.

Article 63

Recovery of materials and solvents

1. Reactants, intermediates or the active substance may be recovered (e.g. from mother liquor or filtrates), provided that approved procedures exist for the recovery and the recovered materials meet the required specifications.

2. Solvents may be recovered and re-used in the same processes or in different processes, provided that the recovery procedures are controlled and monitored to ensure that solvents meet established standards before re-use or co-mingling with other approved materials.

3. Fresh and recovered solvents and reagents may be combined provided that adequate testing has shown their suitability for the intended use.

4. The use of recovered solvents, mother liquors and other recovered materials shall be adequately documented.

Article 64

Returns

1. Returned intermediates or active substances shall be clearly labelled as such and quarantined.

2. If the conditions under which returned intermediates or active substances have been stored or shipped before or during their return or the condition of their containers casts doubt on their quality, the returned intermediates or active substances shall be reprocessed, reworked or destroyed, as appropriate.

3. Records of returned intermediates or active substances shall be maintained in accordance with the provisions of Article 21(4) of Commission Implementing Regulation (EU) 2021/1280 ([7]).

([7]) Commission Implementing Regulation (EU) 2021/1280 of 2 August 2021 as regards measures on good distribution practice for active substances used as starting materials in veterinary medicinal products in accordance with Regulation (EU) 2019/6 of the European Parliament and of the Council (OJ L 279, 3.8.2021, p. 1, ELI: http://data.europa.eu/eli/reg_impl/2021/1280/oj).

CHAPTER XV

COMPLAINTS AND RECALLS

Article 65

Procedures for complaints and recalls for manufacturers

1. A system shall be put in place to ensure that all quality-related complaints, whether received orally or in writing, are recorded and thoroughly investigated and that appropriate actions are implemented, including the recall of the active substance where appropriate. Operating procedures shall be developed describing the actions to be taken upon the receipt of a quality-related complaint.

2. Complaint records shall include the following:

(a) name or company name and permanent address or registered place of business of complainant;

(b) name, title, where appropriate, and contact details of the person submitting the complaint;

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

(d) date the complaint is received;

(e) action initially taken, including dates and identity of person taking that action;

(f) any follow-up action taken;

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

(h) final decision on the intermediate or active substance batch concerned.

3. When a quality defect is discovered or suspected in a batch, consideration shall be given whether it is necessary to check other batches or, as appropriate, other products to determine if they are also affected. Batches that may contain portions of the defective batch or components shall be investigated.

4. The priority during an investigation shall be to ensure that appropriate risk-minimisation measures are taken. All decisions and measures adopted shall reflect the level of risk and shall be documented. The effectiveness of the corrective and preventive measures implemented shall be monitored.

5. Procedures for the recall of active substances shall be established, which shall include how a recall is to be initiated, who is to be informed in the event of a recall (including relevant authorities) and how the recalled material is to be treated.

CHAPTER XVI

OUTSOURCED ACTIVITIES

Article 66

Requirements for outsourced activities

1. The outsourcing of operations related to the manufacturing or control of active substances shall be made by means of a written contract that provides for clear delineation of the responsibilities of each party.

2. The following additional aspects shall be covered in the contract:

(a) the contract acceptor shall comply with good manufacturing practice for active substances;

(b) the contract acceptor shall permit audits by the contract giver in connection with the outsourced activities;

(c) all records related to the outsourced activities shall be kept at the site where the activity occurs and be easily accessible;

(d) the contract acceptor shall not subcontract any of the work entrusted to him or her under the contract without written authorisation from the contract giver;

(e) the contract acceptor shall not make changes in the process, equipment, test methods, specifications or other contractual requirements without written authorisation from the contract giver.

3. All outsourced manufacturing or control operations shall comply with the good manufacturing practices for active substances used as starting materials in veterinary medicinal products. Special consideration shall be given to prevent cross-contamination and to ensure traceability.

4. Contract acceptors shall be audited by the contract giver to ensure compliance with good manufacturing practices for active substances used as starting materials in veterinary medicinal products as regards the specific operations occurring at the contract sites.

CHAPTER XVII

ENTITIES INVOLVED IN REPACKAGING AND RELABELLING

Article 67

Traceability of active substances and intermediates

Entities involved in repackaging or relabelling of active substances and intermediates thereof shall ensure complete traceability of the active substances and intermediates by keeping records in accordance with Article 13(3) of Implementing Regulation (EU) 2021/1280 on good distribution practice for active substances used as starting material in veterinary medicinal products.

Article 68

Quality management

1. Repackaging, relabelling and holding of active substances and intermediates thereof shall be performed under appropriate good manufacturing controls, to avoid mix-ups and loss of active substance or intermediate identity or purity.

2. Repackaging shall be conducted under appropriate environmental conditions to avoid contamination and cross-contamination.

Article 69

Stability studies

Whenever the active substance or intermediate is repackaged in a different type of container than that used originally by the active substance or intermediate manufacturer, stability studies shall be performed to justify assigned expiration or retest dates.

Article 70

Transfer of information

Entities involved in repackaging or relabelling shall:

(a) transfer relevant information to their customers and competent authorities in accordance with the provisions of Article 19 of Implementing Regulation (EU) 2021/1280 on good distribution practice for active substances used as starting material in veterinary medicinal products;

(b) ensure compliance with Article 47 with regards to the certificates of analysis.

CHAPTER XVIII

SPECIFIC REQUIREMENTS FOR ACTIVE SUBSTANCES MANUFACTURED BY CELL CULTURE OR FERMENTATION

Article 71

General

1. This chapter applies to active substances or intermediates thereof manufactured by cell culture or fermentation using natural or recombinant organisms.

2. This Chapter applies as from the point at which a vial of the cell bank is retrieved for use in the manufacturing of an active substance or intermediates thereof.

3. For active substances or intermediates manufactured by means of cell culture or fermentation, the control of bioburden, viral contamination and endotoxins during the manufacture as well as monitoring of the process at appropriate stages may be necessary depending on the source, method of preparation and the intended use of the active substance or intermediate thereof.

4. Appropriate equipment and environmental controls shall be used to minimise the risk of contamination. The acceptance criteria for environmental quality and the frequency of monitoring shall depend on the step in the production and the production conditions (open, closed or contained systems).

5. Process controls shall take into account:

(a) maintenance of the working cell bank, where appropriate;

(b) proper inoculation and expansion of the culture;

(c) control of the critical operating parameters during fermentation or cell culture;

(d) monitoring of the process for cell growth, viability (for most cell culture processes) and productivity, where appropriate;

(e) harvest and purification procedures that remove cells, cellular debris and media components while protecting the active substances or intermediates thereof from contamination (particularly of a microbiological nature) and from loss of quality;

(f) monitoring of bioburden and, where needed, endotoxin levels at appropriate stages of production;

(g) viral safety concerns as described in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q5A Guideline ([8]), where appropriate.

6. Where appropriate, the removal of media components, host cell proteins, other process-related impurities, product-related impurities or contaminants shall be demonstrated.

Article 72

Cell bank maintenance and record keeping

1. Access to cell banks shall be limited to authorised personnel.

2. Cell banks shall be maintained under storage conditions designed to maintain cell viability and prevent contamination. The international guideline ICH Q5A Guideline shall be taken into account.

3. Records of the use of the vials from the cell banks and storage conditions shall be maintained.

4. Where appropriate, cell banks shall be periodically monitored to determine suitability for use.

([8]) ICH Q5A Guideline on viral safety evaluation of biotechnology products derived from cell lines of human or animal origin.

Article 73

Cell culture or fermentation

1. Where aseptic addition of cell substrates, media, buffers and gases is needed, closed or contained systems shall be used where possible. If the inoculation of the initial vessel or subsequent transfers or additions (media, buffers) are performed in open vessels, there shall be controls and procedures in place to minimise the risk of contamination.

2. Where the quality of the active substance can be affected by microbial contamination, manipulations using open vessels shall be performed in a biosafety cabinet or similarly controlled environment.

3. Personnel shall be appropriately gowned and take special precautions handling the cultures.

4. Critical operating parameters (e.g. temperature, pH, agitation rates, addition of gases, pressure) shall be monitored to ensure compliance with the established process. Cell growth, viability (for most cell culture processes), and where appropriate, productivity shall also be monitored. Critical parameters will vary from one process to another, and for classical fermentation, certain parameters (e.g. cell viability) may not need to be monitored.

5. Cell culture equipment shall be cleaned and sterilised after use. As appropriate, fermentation equipment shall be cleaned and sanitised or sterilised.

6. Culture media shall be sterilised before use where appropriate to protect the quality of the active substance.

7. Appropriate procedures shall be in place to detect contamination and to determine the course of action to be taken. Those procedures shall include instructions on how to determine the impact of the contamination on the product and to decontaminate the equipment and return it to a condition to be used in subsequent batches. Foreign organisms observed during fermentation processes shall be identified as appropriate and the effect of their presence on product quality shall be assessed, if necessary. The results of those assessments shall be taken into consideration in the disposition of the material produced.

8. Records of contamination events shall be maintained.

9. Use of shared (multi-product) equipment shall be based on a risk assessment and may warrant additional testing after cleaning between product campaigns, as appropriate, to prevent the risk of cross-contamination.

Article 74

Harvesting, isolation and purification

1. Harvesting steps, either to remove cells or cellular components or to collect cellular components after disruption, shall be performed in equipment and areas designed to minimise the risk of contamination.

2. Harvest and purification procedures to remove or inactivate the producing organism, cellular debris and media components (while minimising degradation, contamination, and loss of quality) shall be adequate to ensure that the intermediate or active substance is recovered with consistent quality.

3. All equipment shall be properly cleaned and, as appropriate, sanitised after use. Multiple successive batching without cleaning may be used if intermediate or active substance quality is not compromised.

4. If open systems are used, purification shall be performed under environmental conditions appropriate for ensuring product quality.

5. Additional controls, such as the use of dedicated chromatography resins or additional testing, may be appropriate if equipment is to be used for multiple products. Introduction of those methods is subject to risk assessment.

Article 75

Viral removal and inactivation steps

1. Viral removal and viral inactivation steps shall be performed within their validated parameters.

2. Appropriate precautions shall be taken to prevent potential viral contamination from pre-viral to post-viral removal or inactivation steps. Open processing shall be performed in areas that are separate from other processing activities and have separate air handling unit.

3. The same equipment shall normally not be used for different purification steps. In those cases where the same equipment is used, the equipment shall be appropriately cleaned and sanitised before re-use.

4. Appropriate precautions shall be taken to prevent potential virus carry-over (e.g. through equipment or environment) from previous steps.

CHAPTER XIX

SPECIFIC REQUIREMENTS FOR ACTIVE SUBSTANCE GASES

Article 76

Active substance gases

1. The production of active substance gases through a continuous process (e.g. air separation) shall be continuously monitored for quality. The results of this monitoring shall be kept in a manner permitting trend evaluation.

2. Transfers and deliveries of cryogenic and liquefied gas and the filling and labelling of cylinders and mobile cryogenic vessels shall comply with the requirements laid down in Sections V.6.1 and V.6.2 of Annex III to Implementing Regulation (EU) 2025/2091 on good manufacturing practice for veterinary medicinal products.

CHAPTER XX

FINAL PROVISIONS

Article 77

Entry into force and application

This Regulation shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Union*.

It shall apply from 16 July 2026.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels, 17 October 2025.

For the Commission
The President
Ursula VON DER LEYEN

ANNEX

Starting point of manufacture of active substances

The point at which the active substance starting material is normally introduced into the manufacturing process is indicated in the table below

Type of manufacturing	Manufacturing steps of active substances				
Chemical manufacturing	Production of the active substance starting material	Introduction of the active substance starting material into the process	Production of intermediate(s)	Isolation and purification	Physical processing, and packaging
Active substance derived from animal sources	Collection of organ, fluid, or tissue	Cutting, mixing, and/or initial processing	Introduction of the of the active substance starting material into the process	Isolation and purification	Physical processing, and packaging
Active substance extracted from plants	Collection of plants	Cutting and initial extraction(s)	Introduction of the of the active substance starting material into the process	Isolation and purification	Physical processing, and packaging
Herbal extracts used as active substance	Collection of plants	Cutting and initial extraction(s)		Further extraction	Physical processing, and packaging
Active substance consisting of comminuted or powdered herbs	Collection of plants and/or cultivation and harvesting	Cutting/comminuting			Physical processing, and packaging
Biotechnology: fermentation/cell culture	Establishment of master cell bank and working cell bank	Maintenance of working cell bank	Cell culture and/ or fermentation	Isolation and purification	Physical processing, and packaging
'classical' fermentation to produce an active substance	Establishment of cell bank	Maintenance of cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing, and packaging

Manufacturing steps of active substances to which this Regulation applies are marked in grey.