Official Journal
of the European Union

EN
L series

2025/2091

27.10.2025

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

(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, holders of a manufacturing authorisation ('manufacturers') are required to comply with good manufacturing practice. Compliance with good manufacturing practice is required for the manufacture of veterinary medicinal products in the Union, including the manufacture of veterinary medicinal products intended for export, as well as for imports of veterinary medicinal products into the Union.

(2) The Commission is to adopt good manufacturing practice for veterinary medicinal products applicable in the Union. The good manufacturing practice for veterinary medicinal products applicable in the Union should continue to be aligned with relevant international standards.

(3) The manufacture of certain types of veterinary medicinal products warrants specific consideration. Additional requirements should be implemented in the manufacture of sterile veterinary medicinal products and for aseptic manufacturing. An end-product test for sterility is limited in its ability to detect contamination. In contrast, data derived from in-process controls and by monitoring relevant sterilisation parameters can provide more accurate and relevant information to support the sterility assurance of the product. Accordingly, sole reliance on end testing for the demonstration of sterility should not be possible.

(4) Additional requirements should also be implemented in the manufacture of biological and immunological veterinary medicinal products, including measures to protect workers and the environment, as well as specific quality and traceability requirements regarding the use of materials of biological origin. In cases 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 (e.g. veterinary medicinal products that consist of cells, viral-based vaccines or phages), the requirements of good manufacturing practice for active substances should not apply; instead the requirements laid down in this Regulation should apply to the entire manufacturing process. However, this Regulation should not apply to the manufacture of inactivated immunological veterinary medicinal products which are manufactured from pathogens and antigens obtained from an animal or animals in an epidemiological unit and used for the treatment of that animal or those animals in the same epidemiological unit or for the treatment of an animal or animals in a unit having a confirmed epidemiological link.

(5) The manufacture of herbal veterinary medicinal products, veterinary medicinal products intended for incorporation into medicated feedingstuffs, ectoparasitic veterinary medicinal products for external application, liquids creams and ointments, medicinal gases and pressurised metered dose aerosol veterinary medicinal products for inhalation warrants specific consideration. It is therefore necessary to set out certain adjustments to the good manufacturing practice requirements or, where appropriate, additional requirements for those products.

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

(6) The manufacture of homeopathic veterinary medicinal products subject to a registration procedure pursuant to Article 86(1) of Regulation (EU) 2019/6 is to comply with good manufacturing practice. The requirements set out in this Regulation should apply adapted to the fact that such products do not have a marketing authorisation. Accordingly, references to the terms of the marketing authorisation should, for these products, be understood as referring to the terms of the registration.

(7) In accordance with Regulation (EU) 2019/6, certificates of good manufacturing practice are to be issued when compliance with the requirements set out in this Regulation is demonstrated. To avoid placing any restraint upon the development of any new concepts or new technologies, manufacturers 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, safety and efficacy of the veterinary medicinal product as well as its compliance with the terms of the marketing authorisation is ensured.

(8) Good manufacturing practice should apply throughout the lifecycle of the veterinary medicinal product, including technology transfer and up to the discontinuation of production.

(9) For the manufacturer to be able to comply with good manufacturing practice, cooperation between the manufacturer and the marketing authorisation holder is necessary. Where the manufacturer and the marketing authorisation holder are different legal entities, the obligations of the manufacturer and marketing authorisation holder vis-à-vis each other should be specified in a technical agreement between them.

(10) Manufacturers should ensure that the products are fit for their intended use, comply with the requirements of the marketing authorisation and do not create risks for the treated animals or the user due to inadequate quality. To achieve this objective, manufacturers should implement a comprehensive pharmaceutical quality 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. Regular self-inspections should also be conducted to verify the effectiveness of the pharmaceutical quality system.

(12) In order to ensure the quality of veterinary medicinal products, 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.

(13) In order to ensure the quality of veterinary medicinal products, manufacturers should have suitable premises and equipment for the manufacture and control of the veterinary medicinal products 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 the manufacture of veterinary medicinal products, should be set out as a basic requirement of good manufacturing practice.

(14) In order to ensure the quality of veterinary medicinal products, manufacturers should ensure that appropriate hygiene standards are maintained at all times during the manufacturing process.

(15) A comprehensive documentation system should be set out as a key component of the pharmaceutical quality 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 veterinary medicinal products and compliance with the terms of the marketing authorisation. Additionally, the documentation system should ensure that all the activities that, directly or indirectly, may affect the quality of veterinary medicinal products are duly recorded and that the integrity of the data is maintained throughout the relevant retention period.

(16) Through process validation, the manufacturers should ensure that the critical aspects of the manufacturing process are duly controlled and that a consistent production is ensured in accordance with the quality requirements set out in the marketing authorisation.

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

(18) Quality 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, quality control should encompass sampling, specifications and testing, as well as organisational measures, documentation and release procedures.

(19) Correct sampling is essential to ensure the quality of veterinary medicinal products. Reference samples and retention samples should be kept as a record of the batch of finished product or of batches of materials used in the manufacture of the veterinary medicinal product and for assessment in the case of quality investigations.

(20) In order to ensure the quality of veterinary medicinal products and compliance with the terms of the marketing authorisation, manufacturers should perform batch release tests and in-process controls. An on-going stability programme should be implemented also.

(21) Real time testing and parametric release testing should be acceptable under certain conditions.

(22) Details on the process of certification by the qualified person and batch release should be laid down. In the case of veterinary medicinal products manufactured outside the Union, the certification process should be regarded as the final step in the manufacturing process which precedes the actual placing on the market.

(23) In order to ensure that the use of computerised systems does not increase the risks to the quality of veterinary medicinal products, certain requirements for the use of such systems should be laid down.

(24) In order to ensure that the outsourcing of activities related to the manufacture and control of veterinary medicinal products does not increase the risks to the quality of the product, 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.

(25) 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.

(26) Specific requirements for the use of ionising radiation in the manufacture of veterinary medicinal products should be laid down.

(27) 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 ([2]), 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.

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

([2]) 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).

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 veterinary medicinal products.

2. The manufacture of sterile veterinary medicinal products and aseptic manufacturing shall comply with the additional requirements set out in Annex I.

3. The manufacture of biological and immunological veterinary medicinal products shall comply with the additional requirements set out in Annex II. However, this Regulation shall not apply to inactivated immunological veterinary medicinal products which are manufactured from pathogens and antigens obtained from an animal or animals in an epidemiological unit and used for the treatment of that animal or those animals in the same epidemiological unit or for the treatment of an animal or animals in a unit having a confirmed epidemiological link.

4. Additional requirements and specific adaptations to the requirements laid down in this Regulation are set out in Annex III for the following veterinary medicinal products:

(a) herbal veterinary medicinal products;

(b) veterinary medicinal products intended for incorporation into medicated feeding stuffs;

(c) ectoparasitic veterinary medicinal products for external application;

(d) liquids creams and ointments;

(e) medicinal gases;

(f) pressurised metered dose aerosol products for inhalation.

5. Whilst meeting the requirements laid down in this Regulation demonstrates compliance with good manufacturing practice for veterinary medicinal products, alternative approaches to the requirements provided for in this Regulation may be implemented where it is duly justified that the alternative approach is capable of meeting the same objectives and that the quality, safety and efficacy of the veterinary medicinal product concerned and compliance with the terms of the marketing authorisation is ensured.

Article 2

Definitions

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

(1) ‘pharmaceutical quality system’ means the total sum of the measures implemented as part of the manufacturing process to ensure that medicinal products are of the quality required for their intended use;

(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 veterinary medicinal product across the product’s lifecycle;

(3) ‘manufacturing site’ means a site that is engaged in any of the activities for which a manufacturing authorisation is required in accordance with Article 88(1) of Regulation (EU) 2019/6;

(4) ‘batch’ means a defined quantity of materials or product that undergo the same process(es) so that it can be expected to be homogeneous. For the control of the finished product, a batch of a veterinary medicinal product comprises all the units of a pharmaceutical form which are made from the same initial mass of materials and have undergone a single series of manufacturing operations or a single sterilisation operation or, in the case of a continuous production process, all the units manufactured in a given period of time. In the case of continuous manufacturing, a batch corresponds to a defined fraction of the production, characterised by its intended homogeneity;

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

(6) ‘intermediate product’ means a partly processed material which must undergo further manufacturing steps before it becomes a bulk product;

(7) ‘finished product’ means a veterinary medicinal product that has undergone all the stages of production, including packaging in its final container;

(8) ‘packaging’ means all operations, including filling (with the exception of sterile filling) and labelling, which a bulk product has to undergo in order to become a finished product;

(9) ‘packaging material’ means any material employed in the packaging of a veterinary medicinal product, excluding any outer packaging used for transportation or shipment. Packaging material can relate to immediate packaging or outer packaging;

(10) ‘in-process controls’ means the checks performed during production in order to monitor and, if necessary, adjust the process to ensure that the product conforms to the required specifications. Environmental monitoring and equipment controls are part of in-process controls;

(11) ‘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;

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

(13) ‘reference sample’ means a sample of a batch of materials used in the manufacture of a veterinary medicinal product or finished product which is stored for the purpose of being analysed should the need arise during the shelf life of the batch concerned;

(14) ‘retention sample’ means a sample of a fully packaged unit from a batch of finished product which is stored for identification purposes;

(15) ‘reprocessing’ means the treatment of all or part of a batch of product of an unacceptable quality from a defined stage of production so that its quality may be rendered acceptable by one or more additional operations;

(16) ‘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;

(17) ‘clean area’ means an area designed, maintained, and controlled to prevent particle and microbiological contamination;

(18) ‘contained area’ means an area that is designed (including air handling and filtration), maintained and controlled so as to prevent contamination of the external environment by biological or other agents;

(19) ‘segregated area’ means an area within a manufacturing site that has separate storage, separate production suite with separate HVAC (heat, ventilation and air conditioning), dedicated equipment reserved solely for the production of one type of product with a specific risk profile and restrictions on the movement of personnel and equipment;

(20) 'airlock' means an enclosed space with interlocked doors, constructed to maintain air pressure control between adjoining rooms (generally with different air cleanliness standards). The intent of an airlock is to preclude ingress of particle matter and microorganism contamination from a lesser controlled area. A pass-through hatch has the same meaning as 'airlock' but is typically of a smaller size;

(21) 'closed system' means a system designed and operated so as to avoid exposure of the product or material to the room environment. Materials may be introduced to a closed system, but the addition must be done in such a way so as to avoid exposure of the product to the room environment (e.g. by means of sterile connectors or fusion systems). A closed system may need to be opened (e.g. to install a filter or make a connection) but it is returned to a closed state through a sanitisation or sterilisation step prior to process use;

(22) 'cross-contamination' means the contamination of a material or a product with another material or product;

(23) 'isolator' means an enclosure capable of being subject to reproducible interior bio-decontamination, with an internal work zone meeting grade A conditions that provides uncompromised, continuous isolation of its interior from the external environment (e.g. surrounding cleanroom air and personnel). There are two major types of isolators:

(a) closed isolator systems, which exclude external contamination of the isolator's interior by accomplishing material transfer via aseptic connection to auxiliary equipment, rather than use of openings to the surrounding environment. Closed systems remain sealed throughout operations;

(b) open isolator systems, which are designed to allow for the continuous or semi-continuous ingress or egress of materials during operations through one or more openings. Openings are engineered (e.g. using continuous overpressure) to exclude the entry of external contaminant into the isolator;

(24) '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;

(25) 'aseptic processing/manufacturing' means processing or manufacturing activities performed under conditions which prevent contamination;

(26) 'quarantine' means the isolation – physically or by other effective means – of materials, intermediate, bulk or finished products whilst awaiting a decision on their release or refusal;

(27) 'reconciliation' means a comparison, having due regard for normal variation, between the amount of product or materials theoretically and actually produced or used;

(28) 'bracketing' means an approach such that only the extremes of certain predetermined factors are tested or validated. The design assumes that validation of any intermediate levels is covered by the tests or validation of the extremes;

(29) 'matrix' means an approach where a subset of the total number of possible samples for all factor combinations is tested at a specified time point and another subset of samples is tested for all factor combinations at a subsequent time point. The results of each subset of samples is assumed to be representative for all samples at a given time point;

(30) '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 ([3]).

([3]) 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).

Article 3

Role of the marketing authorisation holder regarding good manufacturing practice

1. The marketing authorisation holder shall ensure that the specifications and instructions submitted to the manufacturer are in accordance with the terms of the marketing authorisation. Changes to the specifications or instructions required to comply with a variation to the terms of the marketing authorisation shall be notified immediately to the manufacturer.

2. The marketing authorisation holder shall communicate swiftly to the manufacturer any information that is relevant to the manufacturing process, as well as any relevant information that may have an impact on the quality, safety and efficacy of the veterinary medicinal product. In turn, the manufacturer shall inform the marketing authorisation holder of any information that is gathered in the context of the manufacturing activities and that is relevant for the quality, safety or efficacy of the veterinary medicinal product.

3. Where the marketing authorisation holder is a different entity than the manufacturer, he or she shall evaluate the results of the product quality review referred to in Article 6 and assess if any appropriate measure should be implemented.

4. The obligations of the marketing authorisation holder and the manufacturer and vis-à-vis each other shall be defined in writing.

CHAPTER II

PHARMACEUTICAL QUALITY SYSTEM

Article 4

Implementation of a pharmaceutical quality system

1. Manufacturers shall have in place a comprehensive pharmaceutical quality system designed to ensure the quality of the veterinary medicinal products.

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

Article 5

Requirements of the pharmaceutical quality system

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

(a) the evaluation of the risks 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. While some aspects may be company-wide, the pharmaceutical quality system shall be developed and implemented at site level.

3. The size of the company and complexity of the relevant activities shall be taken into consideration in developing a pharmaceutical quality system or modifying an existing one. Senior management shall have the ultimate responsibility to ensure the effectiveness of the pharmaceutical quality system and, to that end, shall ensure that appropriate resources are allocated.

4. The pharmaceutical quality system shall be duly documented and the effectiveness thereof shall be monitored.

5. The pharmaceutical quality 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) the premises and equipment are suitable for the intended use and they are appropriately maintained;

(c) there is an adequate documentation system that ensures that appropriate specifications are laid down for materials used in the manufacture of the veterinary medicinal product, intermediate product, bulk product and finished product, that the production and quality control procedures are clearly defined, and that appropriate records are kept;

(d) arrangements are put in place for the selection and monitoring of suppliers;

(e) 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 and the terms of the marketing authorisation;

(f) appropriate controls on intermediate products and any other in-process controls and validations are carried out;

(g) veterinary medicinal products are not sold or supplied before a qualified person has certified that each production batch has been produced and controlled in accordance with the requirements of the marketing authorisation and in compliance with good manufacturing practice;

(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 veterinary medicinal product are identified as soon as possible, the causes investigated, and appropriate corrective and/or preventive measures are taken. The effectiveness of such measures shall be monitored and assessed;

(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) processes are implemented to ensure adequate management of outsourced activities;

(l) knowledge related to the product and the manufacturing thereof is duly managed throughout the life-cycle of the veterinary medicinal product and in particular in the context of the transfer of activities and the implementation of changes to the manufacturing process or control procedures;

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

Article 6

Product quality reviews

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

(a) materials used in the manufacturing process, especially those from new sources;

(b) the supply chain traceability of active substances;

(c) critical in-process controls and finished product results;

(d) all batches that failed to meet established specification(s) and the investigation thereof;

(e) significant deviations or non-conformances, the investigation thereof, and the effectiveness of resultant corrective and preventive actions taken;

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

(g) variations to the terms of the marketing authorisation affecting quality that have been submitted, granted or refused, as well as a review of post-marketing obligations affecting quality, including those relevant for veterinary medicinal products intended only for export;

(h) the results of the stability monitoring programme and any adverse trends;

(i) quality-related returns, complaints and recalls and the investigations performed at the time;

(j) adequacy of any other previous product, process or equipment corrective actions;

(k) the qualification status of relevant equipment and utilities, such as HVAC, water or compressed gases;

(l) any contractual arrangements for outsourced activities to ensure that they are up to date.

2. Procedures shall be set for the conduct and evaluation of the product quality reviews and the effectiveness thereof shall be verified during the self-inspections referred to in Article 7. Product quality reviews may be grouped by product type (e.g. solid dosage forms, liquid dosage forms, sterile products), where scientifically justified.

3. The results of the product quality review shall be evaluated and it shall be assessed whether corrective and/or preventive actions or any revalidation is required. Where appropriate, opportunities for quality improvements shall be considered.

Article 7

Self-inspection

1. Self-inspections shall be conducted to monitor the implementation of the arrangements regarding personnel, premises, equipment, documentation, production, quality control, batch release and arrangements to deal with quality-related complaints and recalls with the aim of verifying the suitability thereof to ensure that the veterinary medicinal products meet the required quality standards, and comply with the terms of the marketing authorisation and with good manufacturing practice.

2. Self-inspections shall be conducted at pre-defined intervals by individuals not involved in the audited activities.

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.

Article 8

Management review

There shall be a periodic review of the operation of the pharmaceutical quality system with the involvement of senior management to identify opportunities for the improvement of the veterinary medicinal products, the manufacturing process and of the system itself.

CHAPTER III

PERSONNEL

Article 9

General requirements for personnel

1. At each manufacturing site there shall be a 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. Key personnel, including the qualified persons referred to in Article 97 of Regulation (EU) 2019/6, the head of production, the head of quality control and, where applicable, the head of quality assurance or the head of the quality unit shall be appointed by senior management. They shall be given sufficient resources to fulfil their duties.

3. The duties of the key personnel shall be clearly defined in job descriptions. The hierarchical relationships shall be set out in an organisation chart. There shall be no gaps or unexplained overlaps. The head of production shall assume responsibility for the activities set out in Chapter VI, as well as for the training of personnel and the qualification and maintenance of equipment and premises used for production. The head of quality control shall be responsible for the quality control operations set out in and for the training of personnel.

4. The heads of production and quality control shall be independent from each other. In large organisations, it may be necessary to delegate some of their tasks. However, such delegation of tasks shall not imply a delegation of responsibility. Additionally, depending on the size and organisational structure of the company, a separate head of quality assurance or head of the quality unit may be appointed. In that case, the responsibilities of the heads of production and quality control may be shared with the head of quality assurance or the head of the quality unit.

5. 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 consultants shall be kept.

Article 10

Training

1. All personnel shall receive initial and continuous training relevant to the tasks assigned. Training on the pharmaceutical quality system and good manufacturing practice shall be provided for personnel whose duties take them into production and storage areas or into control laboratories, and for other personnel whose activities may have an impact on the quality of the product. 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 11.

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

Article 11

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. Personnel shall be offered a medical examination upon recruitment and subsequent health monitoring proportionate to the risks arising from the specific characteristics of the manufactured product and the tasks of the personnel. Personnel shall be encouraged to declare health conditions that can be of relevance to the quality of products to the manufacturer.

3. As far as possible, no person affected by an infectious disease or having open lesions on the exposed surface of the body shall be involved in the manufacture of veterinary medicinal products.

4. 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 operator and the product from the risk of contamination.

5. Direct contact between the operator's hands and the exposed product as well as with any part of the equipment that comes into contact with the product shall be avoided.

6. Eating, drinking, chewing or smoking, or the storage of food, drink, smoking materials or personal medication in the production and storage areas shall be prohibited. Any unhygienic practice within the manufacturing area or in any other area where the product might be adversely affected shall also be prohibited.

7. Visitors or untrained personnel shall generally not be taken into the production or quality control areas. If this is unavoidable, visitors or untrained personnel shall be given information in advance, particularly about personal hygiene and the prescribed protective clothing, and they shall be closely supervised.

CHAPTER IV

PREMISES AND EQUIPMENT

Article 12

General requirements for premises

1. Premises used for the manufacture or import of veterinary medicinal products 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 products.

2. Premises shall be designed and equipped so as to afford maximum protection against the entry of insects or other animals. Measures to prevent the entry of unauthorised people shall be implemented.

3. Production, storage and quality control areas shall not be used as a right of way by personnel not working in those areas.

Article 13

Production areas

1. Cross-contamination shall be prevented by the appropriate design and operation of the premises. The measures to prevent cross-contamination shall be commensurate with the risks. Quality risk management principles shall be used to assess and control the risks.

2. Depending on the level of risk and based on the outcome of a quality risk management assessment, it may be necessary to dedicate premises and equipment for manufacturing or packaging operations to a particular product or product class. Dedicated premises shall be required when a risk cannot be adequately controlled by operational or technical measures.

3. The layout of the premises shall permit the production to take place in areas connected in a logical order corresponding to the sequence of the operations and the required level of cleanliness.

4. The arrangement of the working and in-process storage space shall be adequate to minimise the risk of confusion between different products or their components, to avoid cross-contamination, and to minimise the risk of omission or the wrong application of any of the manufacturing or control steps.

5. Where the materials used in the production of a veterinary medicinal product, an intermediate product or bulk product are exposed to the environment, the interior surfaces of the area (walls, floors and ceilings) shall be smooth, free from cracks and open joints, shall not shed particulate matter, and shall permit easy and effective cleaning and, if necessary, disinfection.

6. Pipework, light fittings, ventilation points and other services shall be designed and sited so as to avoid the creation of recesses that are difficult to clean. As far as possible, for maintenance purposes, they shall be accessible from outside the manufacturing areas.

7. Drains shall be of adequate size and have trapped gullies. Open channels shall be avoided where possible but, where they are necessary, they shall be shallow to facilitate cleaning and disinfection.

8. Production areas shall be effectively ventilated, with air control facilities (including temperature and, where necessary, humidity and filtration) appropriate to the products handled, to the operations undertaken within them, and to the external environment.

9. In cases where dust is generated, such as during sampling, weighing, mixing and processing operations, or packaging of dry products, specific measures shall be implemented to avoid cross-contamination and to facilitate cleaning.

Article 14

Quality control areas

1. Quality control areas shall generally be separated from production areas. Laboratories for the control of biologicals, microbiologicals and radioisotopes shall also be separated from each other. However, in-process controls may be carried out within the production area provided that they do not carry any risk for the products.

2. Quality control areas shall be designed to suit the operations to be carried out in those areas. Sufficient space shall be given to avoid mix-ups and cross-contamination during testing. Adequate storage space for samples and records shall be available. Separate rooms may also be required to protect sensitive instruments from vibration, electrical interference, humidity, or any other condition that may have a negative impact on their performance.

3. Special precautions shall be taken in quality control areas handling hazardous substances, such as biological samples.

Article 15

Storage areas

1. Storage areas shall be of sufficient capacity to allow the orderly storage of the various categories of materials and products, including products in quarantine, and products released, rejected, returned or recalled.

2. Receiving and dispatch bays shall protect materials and products from the weather. Reception areas shall be designed and equipped to allow containers of incoming materials to be cleaned where necessary before storage.

3. Materials or products that present a specific risk shall be stored in safe and secure areas.

4. Where quarantine status is ensured by storage in separate areas, those areas shall be clearly marked and their access restricted to authorised personnel. Any system replacing a physical quarantine shall provide equivalent security.

5. Separate areas shall be provided for the storage of rejected, recalled or returned materials or products. Where sampling is conducted in the storage area, it shall be conducted in such a way as to prevent contamination or cross-contamination.

Article 16

Ancillary areas

1. Rest and refreshment rooms shall be separate from production, storage and quality control areas. Toilets shall not directly communicate with production, storage or quality control areas.

2. Maintenance workshops shall -as far as possible- be separated from production areas. Whenever parts and tools are stored in the production area, they shall be kept in rooms or lockers reserved for that use.

3. Animals shall be kept in separated areas, with a separate entrance and air handling facilities.

Article 17

Temperature and environmental controls

1. Lighting, temperature, humidity and ventilation conditions shall be appropriate and such that they do not adversely affect, directly or indirectly, the veterinary medicinal products during their manufacture and storage, or the accurate functioning of equipment. Where special conditions are required (e.g. temperature, humidity), these shall be specified and monitored.

2. Appropriate measures to monitor key environmental parameters shall be applied at the manufacturing site.

Article 18

Equipment

1. Equipment used in production or control operations shall be suitable for its intended purpose and shall not present any hazard to the product. The parts of production equipment that come into contact with the product shall not have any unwanted reactive, additive, adsorptive or absorptive properties that may affect the quality of the product.

2. Equipment that is critical to the quality of the products shall be subject to appropriate qualification.

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

4. Equipment shall be operated and maintained in such a way as to minimise the risk of error and to avoid contamination, cross-contamination and, in general, any adverse effect on the quality of the product.

5. Equipment shall be calibrated, inspected or checked, as appropriate, at defined intervals to ensure an adequate performance. In the case of computerised systems, the checks shall include an evaluation of the ability of the system to ensure data integrity. Appropriate records of those checks shall be maintained. Additional requirements relevant to the use of computerised systems are laid down in Annex IV.

6. Equipment shall be adequately cleaned to avoid the risk of contamination for the products. The cleaning or decontamination procedures shall be detailed in writing, ensuring that the cleaning equipment does not become a source of contamination. Equipment shall only be stored in a clean and dry condition.

7. The location and installation of the equipment shall be adequate to minimise risks of errors or contamination. In general, equipment, including laboratory equipment, shall not be moved between high-risk areas. If equipment is moved between high-risk areas, appropriate measures shall be applied to avoid the risk of cross-contamination. Where appropriate, the qualification status of the equipment moved shall also be reconsidered.

8. Fixed pipework shall be clearly labelled to indicate the content and, where applicable, the direction of flow.

9. Water for pharmaceutical use and, where appropriate, other water pipes shall be sanitised according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.

10. Defective equipment shall be removed from production and quality control areas or, if the removal thereof is not possible, it shall be clearly labelled as defective.

Article 19

Qualification of premises and equipment

1. Premises and equipment used in the manufacture of veterinary medicinal products, including utilities and systems, shall be qualified as appropriate to ensure that they are adequate for the intended operations. The qualification shall be performed in accordance with the requirements laid down in Annex V.

2. Decisions on the scope and extent of the qualification shall be based on a risk-assessment, which shall be documented.

3. Before starting the manufacture of a new type of veterinary medicinal product in premises that have already been qualified, the manufacturer shall assess if there is a need for re-qualification having regard to the specific risks and characteristics of the new manufacturing process or new product.

4. Premises and equipment shall be re-evaluated at appropriate intervals to confirm that they remain suitable for the intended operations.

CHAPTER V

DOCUMENTATION

Article 20

Documentation system

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

2. The documentation system shall cover in a comprehensive matter the instructions and specifications as well as other documentation relevant to the pharmaceutical quality system and shall ensure that records of the activities which may, directly or indirectly, affect the quality of the veterinary medicinal products are kept.

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

4. Documentation may be kept in a variety of forms and the requirements set out in this Chapter are applicable irrespective of the 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.

Article 21

Specifications and instructions

1. Specifications and instructions shall be laid down in an orderly fashion and shall be clearly drafted.

2. The specifications for the materials used in the production of veterinary medicinal products and for the finished product, as well as the manufacturing instructions shall be adequate to ensure compliance with the terms of the marketing authorisation and the required level of quality. In particular, the following shall be duly documented:

(a) specifications for active substances and other substances used in the manufacture of the veterinary medicinal product and for immediate packaging materials, including the following:

— a description of the active substances or other substances used, including any relevant information required to avoid risk of error (e.g. use of internal codes), and identification of the approved supplier(s). Where relevant, reference to a pharmacopeial monograph shall be provided;

— the quality and quantitative requirements as well as acceptance criteria, as appropriate;

— instructions for sampling and testing, as appropriate;

— storage conditions and, where applicable, any special handling precautions;

— the maximum period of storage;

(b) specifications for intermediate products and bulk products, including release criteria and the maximum period of storage, shall be set out for critical stages and when those products are purchased or dispatched;

(c) specifications for finished products, in particular:

— the name or identification of the product and, where applicable, the reference code;

— a description of the pharmaceutical form and packaging;

— instructions for sampling and testing;

— the qualitative and quantitative requirements with acceptance limits;

— storage conditions and, where applicable, any special handling precautions;

— the shelf-life;

(d) manufacturing instructions (including a description of the principal equipment to be used) and in-process controls, including the following:

— the name of the product, with a product reference code relating to its specification;

— a description of the pharmaceutical form, strength of the product and batch size;

— a list of all materials to be used and the relevant amounts of each;

— an indication of the expected final yield with the acceptable limits and, where applicable, of relevant intermediate yields;

— an indication of the location where the relevant step should take place and the principal equipment to be used;

— an indication of or reference to the methods to be used for preparing the critical equipment (e.g. cleaning, assembling, calibrating, sterilising);

— detailed stepwise instructions to be followed (e.g. verification that equipment and workstation is clear of previous products, checks on materials, pre-treatments, sequence for adding materials, critical process parameters such as time, temperature, etc.);

— instructions for any in-process controls, together with their limits;

— where necessary, the requirements for bulk storage of the products, including the container, labelling and, where applicable, special storage conditions;

— any special precautions to be observed;

(e) packaging instructions for each veterinary medicinal product and pack size, including:

— the name of the product as well as the batch number of the bulk product and finished product;

— a description of its pharmaceutical form, and strength where applicable;

— the pack size expressed in terms of the number, weight or volume of the product in the final container;

— a complete list of all the packaging materials required, including quantities, sizes and types, with the code or reference number relating to the specification of each packaging material;

— relevant instructions with an indication of the equipment to be used, and relevant precautions, including the need for a careful examination of the area and equipment in order to ascertain the line clearance before operations begin;

— details of in-process controls with instructions for sampling and acceptance limits.

3. Documents containing specifications and instructions, including any changes thereto, shall be approved, signed and dated by authorised persons and the date of entry into operation shall be defined. Steps shall be taken to ensure that only the current version of a document is used.

Article 22

Records

1. Adequate records shall be kept to enable the entire history of a batch to be traced. As a minimum, the following shall be documented:

(a) receipt records for each delivery of materials used in the manufacture of the veterinary medicinal products including bulk products, intermediate products, and packaging materials. The receipt records shall include:

— the name of the material on the delivery note and the containers as well as any in-house name or internal code, if appropriate;

— the name of the supplier and manufacturer;

— the supplier's batch or reference number;

— the total quantity and number of containers received;

— the date of receipt;

— the batch number assigned after receipt;

— any relevant comment;

(b) a batch processing record which shall contain the following information:

— the name of the product and batch number;

— the dates and times of commencement, of critical intermediate stages, and of completion of production;

— the batch number or analytical control number and quantities actually weighed of each material used;

— an identification (e.g. by means of initials or another suitable system) of the operator who performed each significant step and, where appropriate, of the person that checked these operations;

— a record of the in-process controls and the initials of the operator who carried them out;

— details of the manufacturing operations carried out and identification of major equipment used;

— the product yield obtained at relevant stages of manufacture;

— notes on any problems or unusual events that may impact on the quality of the product, including relevant details, with signed authorisation for any deviation from the manufacturing instructions;

— the approval of the batch processing record by the person responsible for the processing operations.

Where a validated process is continuously monitored and controlled, the batch record may be limited to automatically generated reports with compliance summaries and exception or out-of- specification data reports;

(c) a batch packaging record which shall contain the following information:

— the name of the product and batch number;

— the dates and times of the packaging operations;

— an identification (e.g. by means of initials or another suitable system) of the operator who performed each significant step and, where appropriate, of the person who checked those operations;

— records of checks regarding the conformity with the packaging instructions, including the results of in-process controls;

— details of the packaging operations carried out and identification of major equipment and the packaging lines used;

— whenever possible, samples of printed packaging materials used, including the batch coding, expiry date and any additional overprinting;

— notes on any problems or unusual events that may have an impact on the quality of the product including details, with signed authorisation for any deviation from the packaging instructions;

— the quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of obtained product, in order to provide for an adequate reconciliation. This information may be omitted where electronic controls are in place;

— the approval of the batch packaging record by the person responsible for the packaging operations.

2. Records shall be made or completed at the time each action is taken and in such a way that all significant activities concerning the manufacture of veterinary medicinal products are traceable.

3. Logbooks shall be kept for major or critical analytical testing, for production equipment and for areas where a product has been processed. They shall be used to record in chronological order, as appropriate, any use of the area, equipment or method, calibrations, maintenance, cleaning or repair operations, including the dates and identity of people who carried out such operations.

4. Relevant records shall form the basis for assessment of the suitability for certification and release of a particular batch.

Article 23

Other documentation

1. Policies and procedures applied to safeguard the quality of the product shall be duly documented, including the following:

(a) training;

(b) validation of manufacturing process and relevant analytical methods;

(c) qualification of premises and equipment (including utilities and systems);

(d) procedures or instructions for the handling of materials and products;

(e) release and rejection procedures for materials and products;

(f) cleaning procedures and the validation thereof, which shall be in accordance with the requirements laid down in Annex V;

(g) procedures relating to quality control;

(h) maintenance and calibration of equipment;

(i) environmental monitoring;

(j) investigations into deviations and non-conformances;

(k) procedures for handling of quality-related complaints and recall or return of products;

(l) procedures for handling changes to the manufacturing process (change control);

(m) internal audits as well as audits of suppliers and sub-contractors;

(n) technology transfer, where applicable.

2. Clear operating procedures shall be available for main manufacturing and test equipment.

3. A site master file shall be prepared for every manufacturing site involved in the manufacture of veterinary medicinal products, which shall provide a high-level description of the premises, of the activities conducted at the manufacturing site and of the quality system implemented. A model template is set out in Annex VI.

Article 24

Retention periods

1. Batch documentation shall be kept for one year after the expiry of the batch to which it relates or at least five years after certification of the batch by the qualified person, whichever is longer.

2. Critical documentation that supports information in the marketing authorisation shall be retained whilst the authorisation remains in force, including relevant raw data such as data related to validation or stability. It may be considered acceptable to retire certain documentation, such as raw data supporting validation reports or stability reports, where the data has been superseded by a full set of new data. Justification for this shall be documented and shall take into account the requirements for retention of batch documentation. In the case of process validation data, the accompanying raw data shall be retained for a period at least as long as the records for all batches whose release has been supported on the basis of that validation exercise.

3. For other types of documentation, the retention period shall depend on the business activity which the documentation supports.

Article 25

Data integrity

1. Suitable measures shall be implemented to ensure data integrity from the moment when data is generated and throughout the relevant retention period, including:

(a) implementation of measures to protect data against accidental loss or damage by appropriate methods such as duplication or back-up and transfer to another storage system;

(b) implementation of measures to protect data against tampering or unauthorised manipulation. In the case of computerised systems, suitable controls shall be put in place to limit access to authorised persons, such as the use of keys, pass cards, personal codes with passwords, biometrics or restricted access to computer equipment and data storage areas. The type of security controls shall be adapted to the criticality of the computerised system;

(c) implementation of measures to ensure the accuracy, completeness, availability and legibility of documents throughout the retention period. Handwritten entries shall be made in a clear, legible and indelible way.

The implemented measures shall be commensurate to the risks and the criticality of the data.

2. The issuance, revision, superseding and withdrawal of all documents shall be controlled by keeping a record of all revisions (revision histories).

3. Any alteration made to the entry on a document shall be signed and dated. The alteration shall permit the reading of the original information. Where appropriate, the reason for the alteration shall be recorded.

CHAPTER VI

PRODUCTION

Article 26

General requirements for production

1. Manufacturing operations (including packaging operations) and controls shall follow clearly defined procedures designed to ensure the quality of the product and compliance with the requirements set in the relevant manufacturing authorisation and marketing authorisation.

2. Manufacturing steps that may have an impact on the quality or reproducibility of the production, including significant changes thereto, shall be validated. Periodic re-validation shall be required to ensure that such manufacturing processes remain capable of achieving the intended results. Process validation shall comply with the requirements laid down in Annex V.

3. Manufacturing processes shall be duly documented and reviewed regularly, and they shall be improved as appropriate. The effects of changes to the manufacturing process on the quality of the finished product and in relation to the need to ensure consistent production shall be considered prior to the implementation of any changes. No change from the specifications and processes described in the dossier supporting the marketing authorisation shall be implemented before the relevant approval is obtained from the competent authorities, with the exception of variations not requiring assessment in accordance with Article 61 of Regulation (EU) 2019/6.

4. Adequate and sufficient resources shall be made available for the in-process controls.

5. Any deviation from instructions or procedures shall be avoided as far as possible. If a deviation occurs, it shall be approved in writing by a responsible person after having assessed the impact thereof on quality, safety and efficacy with the involvement of the qualified person as appropriate. Deviations shall be investigated to identify the root cause and to implement corrective and preventive measures as appropriate.

6. The manufacturer shall report to the marketing authorisation holder any constraints in manufacturing operations that may result in an abnormal restriction in the supply of the veterinary medicinal product.

Article 27

Handling of materials and products

1. Handling of materials and products, including aspects related to the receipt, quarantine, sampling, storage, labelling and packaging, shall be done in accordance with written procedures or instructions and recorded as appropriate.

2. All incoming materials shall be checked to ensure that the consignment corresponds to the order.

3. Containers shall be cleaned where necessary. 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 the material shall be investigated, recorded and reported to the department responsible for quality control.

4. Transport conditions for bulk products, intermediate products and samples shall be verified to ensure compliance with any specified conditions.

5. 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. If one material delivery is made up of different batches, each batch shall be considered separately for the purposes of sampling, testing and release.

6. All materials shall be stored under appropriate conditions to ensure the quality and in an orderly fashion to permit batch segregation (physical or electronic) and stock rotation.

7. Containers shall be labelled appropriately, including:

(a) the designated name of the product and internal code reference, where applicable;

(b) the batch number given at receipt;

(c) where appropriate, the status of the content (e.g. in quarantine, on test, released, rejected);

(d) where appropriate, an expiry date beyond which retesting is necessary.

Where fully computerised storage systems are used, all the information referred to in points (a) to (d) does not need to appear in a legible form on the label.

8. At all times during the manufacturing process, all materials, bulk containers, major items of equipment and, where appropriate, rooms used shall be labelled or otherwise identified with an indication of the product or material being processed, its strength (where applicable), and batch number. Where applicable, this indication shall also mention the stage of production.

9. Special precautions shall be taken when handling dry materials or products to prevent the generation and dissemination of dust, particularly for highly active or sensitising materials.

Article 28

Qualification of suppliers and compliance with specifications

1. Suppliers of materials used in the manufacture of the veterinary medicinal product shall be approved after verifying the suitability thereof. In the case of critical materials, the qualification of the suppliers shall be required. The level of supervision of the suppliers shall be proportionate to the risks to the quality of the product posed by the individual materials.

2. The quality requirements (specifications) for the materials used in the manufacture of veterinary medicinal products shall be agreed with the supplier and documented.

3. Compliance with the requirements set out in the marketing authorisation shall be verified by means of appropriate testing. The level of supervision and further testing required shall be proportionate to the risks. The testing strategy shall be justified and, as a minimum, an identity check of each batch shall be performed by means of tests performed on samples taken from all the containers. Sampling a proportion of the containers shall only be acceptable when validated procedures based on quality risk management principles are in place to ensure the correct labelling of containers, and potential risks to the quality are addressed, for example through the qualification of the supplier.

At appropriate intervals, having regard to the risks, a full analysis of the active substances and other critical materials shall be performed and the results shall be compared with the manufacturer or supplier's certificate of analysis in order to check the reliability of the latter. The testing may be outsourced. If that testing identifies any discrepancy, an investigation shall be performed and appropriate measures taken. The acceptance of certificates of analysis from the material manufacturer or supplier shall be discontinued until those measures are implemented.

4. Sufficient experience with the relevant supplier or manufacturer of active substances, including assessment of batches previously received and the history of compliance, shall be required before reducing the in-house testing. Any significant change in the manufacturing or testing processes of the active substances shall also be considered as a relevant factor.

5. Audits at the sites of manufacturers and distributors of active substances shall be conducted at appropriate intervals following a risk-based approach to confirm that they comply with good manufacturing practice and good distribution practice and with the specifications provided. Specific consideration shall be given to potential cross-contamination from other materials on site. Deficiencies shall be clearly identified and corrective and preventive actions shall be implemented as appropriate.

Article 29

Prevention of cross-contamination

1. The production of non-medicinal products shall generally be avoided in areas and with equipment destined for the production of veterinary medicinal products, unless measures to prevent cross-contamination are applied in an effective manner. In particular, the production or storage of chemical substances used in biocides and plant protection products shall be avoided in areas used for the manufacture or storage of veterinary medicinal products, except where the same substance and its grade is also used for manufacture of veterinary medicinal products.

2. Where veterinary medicinal products are produced in an area shared with non-medicinal products, good manufacturing practice for medicinal products shall be implemented in the area.

3. Operations on different products shall not be carried out simultaneously or consecutively in the same room unless there is no risk of mix-up or cross-contamination.

4. Before any manufacturing operation starts, steps shall be taken to ensure that the work area and the equipment are clean and free from any materials, products, product residues or documents not required for the current operation. Mix-ups of materials shall be prevented.

5. At every stage of production, products and materials shall be protected from microbial and other contamination. The risk of cross-contamination shall be assessed having regard to the characteristics of the product and the manufacturing process. The risk of accidental cross-contamination resulting from the uncontrolled release of dust, gases, vapours, aerosols, genetic material or organisms from active substances or other materials used in the production, from residues on equipment and from operators' clothing shall be assessed.

6. Measures to prevent cross-contamination identified on the basis of quality risk management principles shall be put in place. Measures that may be considered to prevent cross-contamination include:

(a) the dedication of a whole manufacturing site or a self-contained production area on a campaign basis (separation in time) followed by a cleaning process of validated effectiveness;

(b) the use of segregated areas;

(c) the use of closed systems for processing and for material or product transfer;

(d) the use of airlocks and pressure cascade to confine potential airborne contaminants within a specified area;

(e) the use of physical barrier systems, including isolators, as containment measures;

(f) the dedication of specific equipment or certain parts thereof (e.g. filters) to a given type of product with a specific risk profile;

(g) the utilisation of single use disposable technologies;

(h) the implementation of validated cleaning or decontamination procedures adapted to the specific characteristics of the product and of the manufacturing process. The cleaning or decontamination procedures that are necessary, including the frequency thereof, shall be determined on the basis of a risk-assessment;

(i) other suitable organisational measures, such as keeping specific protective clothing inside areas where products at high-risk of contamination are processed, implementing adequate measures for the handling of waste, contaminated rinsing water and soiled gowning, or imposing restrictions on the movement of personnel.

7. The control strategy shall address all the potential risks, including measures at the level of the premises, equipment and personnel, controls on materials used in the manufacture, implementation of effective sterilisation and sanitisations procedures, and adequate monitoring systems. The totality of the measures applied shall ensure the absence of contamination of the products manufactured within the manufacturing site. Sole reliance shall not be placed on any terminal process or finished product test.

8. The effectiveness of the measures implemented shall be reviewed periodically according to set procedures. This assessment shall lead to the implementation of corrective and preventive actions where necessary.

Article 30

Packaging operations

1. The name and batch number of the product being handled shall be displayed at each packaging station or line.

2. Containers for filling shall be clean before being filled. Filling and sealing shall be followed as quickly as possible by labelling. If it is not possible, appropriate procedures shall be applied to avoid mix-ups or mislabelling.

3. The correct performance of printing operations (for example code numbers, expiry dates) shall be checked and recorded. Printed and embossed information on packaging materials shall be clear and resistant to fade or erasure.

4. Checks shall be made to ensure that any electronic code readers, label counters or similar devices are operating correctly.

5. Appropriate measures shall be implemented to avoid mix ups, such as storing and transporting cut labels and other loose printed materials in separate closed containers. Special care shall be taken when using cut-labels and when over-printing is carried out off-line. To avoid mix-ups, roll-feed labels are generally preferable to cut-labels.

6. The following controls shall be performed on the product during packaging operations:

(a) general appearance of the packages;

(b) whether the packages are complete;

(c) whether the correct products and packaging materials are used;

(d) whether any over-printing is correct;

(e) correct functioning of line monitors.

Samples taken away from the packaging line shall not be returned.

7. Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and packaging materials and the number of units produced shall be investigated and resolved before the release of the product.

8. Outdated or obsolete immediate packaging material or printed packaging material shall be destroyed and such disposal recorded. A documented procedure shall be followed if un-coded printed materials are returned to stock.

Article 31

Rejected, recovered and returned materials

1. Rejected materials shall be clearly marked as such and stored separately in restricted areas. They shall either be returned to the suppliers or, where appropriate, reprocessed or destroyed. Whatever action is taken, it shall be approved and recorded by authorised personnel.

2. The reprocessing of rejected materials can only be accepted exceptionally and provided that the quality of the final product is not affected and that the specifications set out in the marketing authorisation are met. The recovery of materials conforming to the required specifications from a distinct batch is only possible after an evaluation of the risks, including any possible effect on the shelf-life. Records shall be kept.

3. The need for additional testing of any finished product which has been reprocessed, or into which a reprocessed material has been incorporated, shall be evaluated by the quality control department.

4. Returned products, which have left the control of the manufacturer, shall be destroyed, unless their quality is confirmed by the quality control department. The nature of the product, its condition and history, any special storage conditions, and the time elapsed since it was issued shall be taken into account in that assessment. Where any doubt arises over the quality of the product, it shall not be considered suitable for re-issue or re-use. Any action taken shall be recorded.

Article 32

Use of ionising radiation

The use of ionising radiation in the manufacture of veterinary medicinal products shall comply with the additional requirements set out in Annex VII.

CHAPTER VII

QUALITY CONTROL

Article 33

General requirements for quality control

1. A quality control department independent from other departments shall be established and maintained.

2. The quality control department shall be allocated adequate resources, including regarding personnel, premises and equipment, to ensure that quality control can be effectively carried out having regard to the nature and size of the manufacturing operations.

3. The quality control department shall ensure that relevant tests are carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory. The quality control department is at least responsible for the following:

(a) establishing, validating and implementing quality control procedures;

(b) overseeing the control of the reference and retention samples of materials and products, where applicable;

(c) ensuring the correct labelling of containers of materials and products;

(d) ensuring the monitoring of the stability of the products;

(e) participating in the investigation of complaints related to the quality of the product.

All the activities referred to in the first subparagraph, points (a) to (e) shall be carried out in accordance with written procedures and, where necessary, recorded.

4. The head of quality control supervises all quality control procedures. In particular, it shall be responsible for the following tasks:

(a) approval of specifications, sampling instructions, test methods and other quality control procedures;

(b) ensuring that required testing is carried out and the associated records evaluated;

(c) ensuring that the appropriate validations are done;

(d) approval or rejection of materials used in production, intermediate products, bulk products and finished products;

(e) ensuring the qualification and maintenance of the premises and equipment used for quality control;

(f) approval and monitoring of any contract analysts.

5. Personnel involved in quality control shall have access to production areas and to all documents that are needed for the assessment of quality control, including:

(a) specifications;

(b) procedures describing sampling and testing;

(c) testing reports and certificates of analysis;

(d) procedures for calibration and qualification of instruments and maintenance of equipment and relevant records;

(e) validation records of test methods, where applicable;

(f) environmental monitoring data for air, water and other utilities, where required;

(g) procedures for the investigation of out of specification and out of trend results.

6. Relevant quality control data, such as tests results, yields and environmental data, shall be assessed in a manner permitting trend evaluation. In the case of out of specifications or significant atypical trends, their possible impact on the batches on the market shall be assessed. Where following that assessment it is concluded that the quality of the marketed veterinary medicinal product may be impacted or that shortages of supply can be expected, the competent authorities shall be informed.

7. A quality control check shall be conducted before a finished veterinary medicinal product is released for sale or distribution. That check shall cover all relevant factors, including production conditions, results of in-process testing, a review of manufacturing (including packaging) documentation, compliance with the finished product specifications and examination of the final finished pack.

8. Quality control activities can be outsourced provided that the requirements set out in Article 43 are respected. Where tests on materials used in the manufacture of the veterinary medicinal products are outsourced, audits shall be performed by the manufacturer or via a third party to ensure compliance with relevant requirements of good manufacturing practice and the specifications or methods provided.

Article 34

Sampling

1. A sampling plan shall be established, which shall take into account the risks to the quality of the veterinary medicinal product and address the different materials used in the manufacturing process as well as the various stages of production.

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

(a) the amount of sample to be taken;

(b) equipment and containers to be used;

(c) precautions to be observed to prevent contamination;

(d) other precautions to be observed, in particular in the case of sterile or noxious materials;

(e) storage conditions for the samples taken;

(f) the cleaning instructions for the equipment used.

3. Personnel in charge of taking samples shall receive training on the following:

(a) techniques and equipment for sampling;

(b) the risks of cross-contamination;

(c) precautions to be taken with regard to unstable or sterile substances;

(d) the need to record any unexpected or unusual circumstance;

(e) other aspects relevant to the implementation of the sampling procedures.

4. Sample containers shall bear a label indicating the content, batch number, date of sampling and containers from which the samples have been taken. When containers are too small, the use of bar-codes or other means that permit access to that information may be considered.

Sample containers shall be handled and stored in a way that minimises the risk of mix-up or the deterioration of their content. The storage conditions set out in the marketing authorisation shall be applied.

5. Samples shall be kept at the disposal of the competent authorities for the following periods:

(a) Reference samples and/or retention samples from each batch of finished product shall be retained for at least one year after the expiry date. The reference sample shall be contained in its finished immediate packaging.

However, in the case of large volume presentations, where it is not feasible to retain samples from each batch in its final packaging, the manufacturer shall ensure that sufficient representative samples of each batch are retained and that the container used for storage is composed of the same material as the immediate container in which the product is marketed.

(b) Reference samples of materials used in the manufacture of veterinary medicinal products, other than solvents, gases or water, shall be kept for at least two years after the release of the product. That period may be shortened if the period of stability of the material, as indicated in the relevant specification, is shorter.

(c) Samples of packaging materials shall be kept for the duration of the shelf-life of the finished product concerned. For this purpose, retention of printed materials as part of the reference and/or retention samples is also acceptable.

For finished products, reference and retention samples may be regarded as interchangeable.

6. Reference samples shall be of sufficient size to permit the carrying out on at least two occasions of the full analytical controls on the batch in accordance with the marketing authorisation.

7. In cases when the marketing authorisation holder is not the entity responsible for batch release or when several sites are responsible for the manufacture or batch release, the responsibility for the taking and storing of reference and retention samples shall be defined in writing.

8. The ability to do relevant testing throughout the shelf-life of the veterinary medicinal product shall be ensured.

Article 35

Testing

1. Tests shall be performed to ensure that each batch of the finished product meets the relevant specifications and is in accordance with the terms of the marketing authorisation. Tests shall be performed at appropriate stages of production to control those conditions that are important for the quality of the product. Testing methods shall be validated.

2. The following records shall be kept in connection with the tests performed:

(a) name of the material or product and, where applicable, dosage form;

(b) batch number and, where appropriate, the manufacturer or supplier;

(c) references to the relevant specifications and testing procedures;

(d) test results, including observations and calculations, and reference to any certificates of analysis;

(e) dates of testing;

(f) identification of the persons who performed the testing;

(g) identification of the persons who verified the testing and the calculations, where appropriate;

(h) a clear statement of approval or rejection (or other status decision) and the dated signature of the responsible person;

(i) reference to the equipment used.

3. Reference standards shall be suitable for their intended use. Their qualification or certification status shall be documented. Whenever compendial reference standards from an officially recognised source exist, these shall preferably be used as primary reference standards, unless duly justified. The use of secondary standards shall be documented and their traceability to primary standards shall be demonstrated. Compendial materials shall be used for the purpose described in the appropriate monograph unless otherwise authorised by the relevant competent authority.

4. Materials used for quality control tests, such as reagents, culture media, glassware, and reference standards shall be of appropriate quality and used according to the instructions of the manufacturer unless scientifically justified. The expiry date of reagents and culture media shall be indicated on the label, together with specific storage conditions. Where necessary, identity verification or testing shall be considered upon receipt or before use.

5. Where appropriate, animals used for testing components, materials or products shall be quarantined before use. They shall be maintained and controlled in a manner that assures their suitability for the intended use. In addition, they shall be identified and adequate records kept showing the history of their use.

6. Used microbiological media and strains shall be decontaminated in accordance with a standard procedure and disposed of in a manner to prevent cross-contamination.

Article 36

On-going stability programme

1. After the marketing authorisation is granted, a programme shall be implemented to verify that, under the relevant storage conditions specified in the marketing authorisation and in the packaging as intended for marketing, the veterinary medicinal product remains within the specifications during the shelf-life ('on-going stability programme').

2. The on-going stability programme shall be described in a written protocol which shall detail, among others, the number of batches, the test methods to be used, the acceptance criteria and the testing intervals. The methodology in the on-going stability programme can differ from the approach followed to obtain the stability data submitted in the marketing authorisation application (e.g. different frequency of testing), provided that it is justified.

3. The on-going stability studies shall generally be performed on the finished product as released by the manufacturer, unless a different approach is duly justified. When intermediate products or bulk products are stored for extended periods of time, consideration shall be given to include in the on-going stability programme those batches that have been manufactured from materials stored for longer periods of time. Stability studies on the reconstituted product need not be conducted as part of the on-going stability programme.

4. The number of batches and frequency of testing shall be adequate to allow for trend analysis and shall take into account the risks, such as significant changes in production, significant deviations, reworking or reprocessing operations. At least one batch of the product per strength and packaging type shall be included per year in the on-going stability programme, unless none are produced in a given year or a different frequency is otherwise justified. In particular, where the on-going stability monitoring requires testing using animals and no appropriate alternative techniques are available, the frequency of testing may be adapted. Bracketing and matrixing approaches may be applied if scientifically justified in the protocol.

5. Results of on-going stability studies shall be subject to periodic review and be made available to key personnel and, in particular, to the qualified person. A summary of all the data generated shall be kept.

Article 37

Technical transfer of testing methods

1. Prior to transferring a test method, the transferring site shall verify that the test method complies with the terms of the marketing authorisation and relevant regulatory requirements.

2. The transfer of testing methods from one laboratory (transferring laboratory) to another laboratory (receiving laboratory) shall be described in a detailed protocol.

3. The protocol shall include, among others, the following elements:

(a) identification of the testing to be performed and the relevant test method undergoing transfer;

(b) identification of any specific training requirements;

(c) identification of standards and samples to be tested;

(d) identification of any special transport and storage conditions of test items;

(e) the acceptance criteria.

4. Deviations from the protocol shall be investigated prior to the closure of the technical transfer process. The technical transfer report shall document the comparative outcome of the process and shall identify areas requiring further test method revalidation, if applicable.

CHAPTER VIII

CERTIFICATION AND BATCH RELEASE

Article 38

Qualified person

1. Each manufacturing site of veterinary medicinal products in the Union shall have at least one qualified person.

2. To comply with the obligation set out under Article 97(6) of Regulation (EU) 2019/6, the qualified person shall, as a minimum, verify the following aspects:

(a) the source and specifications for the materials used in the manufacture of veterinary medicinal products and the packaging materials comply with the terms of the marketing authorisation;

(b) the active substances have been manufactured in accordance with good manufacturing practices and distributed in accordance with good distribution practice;

(c) where applicable, the viral and microbial safety and TSE (transmissible spongiform encephalopathies) status of all materials used the manufacture is compliant with the terms of the marketing authorisation;

(d) all manufacturing steps, including controls and testing, have been done in accordance with the marketing authorisation and at a manufacturing site authorised therein and in compliance with good manufacturing practice;

(e) all required in-process controls and checks, including environmental monitoring, have been made and appropriate records exists;

(f) finished product quality control test data shows compliance with the relevant specifications or, where applicable, the real time release testing programme;

(g) on-going stability data continues to support certification;

(h) the impact of any deviation to the manufacturing process or testing has been evaluated and any additional checks and tests are complete;

(i) the impact of any change to the manufacturing process or testing has been evaluated and any additional checks and tests have been completed;

(j) audits of manufacturing sites and sites involved in the manufacture or testing of the active substances support the certification of the batch;

(k) measures related to the implementation of outsourced manufacture or testing, as provided for in the subcontracting arrangements, are in place;

(l) all investigations on matters that may impact the quality of the batch being certified have been completed to a sufficient degree to support the certification of the batch;

(m) the self-inspection programme is active.

The qualified person, while being responsible for ensuring that the verifications set out in the first subparagraph are done, may delegate those tasks to appropriately trained personnel or third parties.

3. The qualified person shall have access to any documentation relevant to the steps for which he or she assumes responsibility, including details of the marketing authorisation necessary to assess if the relevant requirements have been complied with and relevant data about the entire manufacturing process of the veterinary medicinal product, including importation activities, if any.

4. Where more than one qualified person is involved in the assessment of one batch of a veterinary medicinal product, the division of responsibilities amongst them, including details on the responsibility for assessment of any deviations, shall be clearly laid down in writing.

5. The qualified person may rely on audits conducted by third parties attesting the compliance with good manufacturing practice in specific manufacturing sites. In such cases, the requirements in Article 43 shall apply. The qualified person shall have access to any documentation that is relevant to the review of the audit outcome.

For the approval of the audit report, the qualified person shall take into consideration the following:

(a) whether the audit report addresses general requirements of good manufacturing practice, such as the quality management system and production and quality control procedures related to the supplied product, with sufficient level of detail so as to allow a conclusion that the relevant activities covered by the audit comply with the marketing authorisation and good manufacturing practice;

(b) in the case of outsourced activities, whether there has been verification of the compliance with the marketing authorisation and good manufacturing practice.

Article 39

Certification and batch release

1. Batches of veterinary medicinal products can only be released for sale or supply to the market after a qualified person certifies – by means of a control report– that each batch of a veterinary medicinal product has been manufactured and tested in accordance with the requirements of the marketing authorisation and good manufacturing practice. Certification can only be performed by the qualified person of a manufacturer described in the marketing authorisation. A model template for batch release certificate is provided in Annex VIII.

2. Reliance by the qualified person on real time release testing or parametric release is only possible if the conditions and requirements laid down in Annex IX are met.

3. Evidence of the certification referred to in paragraph 1 shall be recorded by the qualified person in a register or equivalent document provided for that purpose. That register or equivalent document shall be kept up to date and shall remain at the disposal of the competent authority for one year after the expiry of the batch to which it relates or at least five years after certification of the batch by the qualified person, whichever is longer.

4. The qualified person who performs the certification of the batch of a veterinary medicinal product may assume full responsibility for all stages of manufacture of the batch or may share this responsibility with other qualified persons who have confirmed compliance of specific steps in the manufacture and control of a batch.

If a manufacturing site only undertakes partial manufacturing operations, the qualified person at that site shall, at least, confirm that the operations undertaken at that manufacturing site have been performed in accordance with good manufacturing practice and the terms of the written agreement detailing the operations for which the manufacturing site is responsible. Partial manufacturing shall only occur in a manufacturing site authorised in accordance with the terms of the marketing authorisation. A model template for confirmation of partial manufacturing is provided in Annex VIII.

5. Where various batches of finished product originate from the same batch of bulk product, certification of the different batches of finished product may be based on the quality control testing of a previously certified batch provided that this is justified based on quality risk management principles. The following elements shall at least be verified by the qualified person:

(a) the relevant requirements for storage of the bulk product prior to packaging have been complied with;

(b) the batch of the finished product has been stored and, where applicable, transported under the required conditions;

(c) the consignment has remained secure and there is no evidence of tampering during storage or transportation;

(d) the identification of the product has been established;

(e) the samples tested are representative of all finished product batches derived from the batch of bulk product.

6. Where the qualified person certifies a batch of a veterinary medicinal product in accordance with paragraph 1, he or she shall assign the release status to that batch by means of a formal and unambiguous notification to the manufacturing site releasing the product.

7. Pending the assignment of the release status referred to in paragraph 6, the batch shall remain at the manufacturing site or be shipped under quarantine to another manufacturing site authorised for that purpose. Safeguards to ensure that uncertified batches are not released shall be put in place. Those safeguards may be physical (by using segregation and labelling) or electronic (by using validated computerised systems). When uncertified batches are moved from one authorised manufacturing site to another, the safeguards to prevent premature release shall remain.

Article 40

Additional considerations for imports of veterinary medicinal products

1. To comply with the obligation set out under Article 97(7) of Regulation (EU) 2019/6, the certification by the qualified person can only occur after a physical importation has taken place. The site of physical importation and the site of the qualified person responsible for the certification/confirmation shall be authorised in accordance with Article 88(1) of Regulation (EU) 2019/6.

2. Sampling of the imported product shall be fully representative of the batch. Samples required for the testing of the imported batch as well as reference and/or retention samples may either be taken after arrival in the Union or at the manufacturing site in the third country in accordance with a documented procedure. Responsibilities in relation to the sampling shall be defined in a written agreement between the manufacturing sites. Any samples taken outside the Union shall be shipped under equivalent transport conditions as the batch that they represent.

3. Where sampling is performed in a third country manufacturing site, the documented procedure referred to in paragraph 2 shall be justified in accordance with quality risk management principles and shall include at least the following elements:

(a) audits of the manufacturing activities, including sampling, at the third country manufacturing site and evaluation of subsequent transportation steps of both the batch and samples to ensure that the samples are representative of the imported batch;

(b) a comprehensive analysis supporting the conclusion that samples taken in the third country are representative of the batch after importation, including at least the following:

— a description of the sampling process;

— a description of the transport conditions of the sample and the imported batch; any differences shall be justified;

— comparative analysis of samples taken in the third country and samples taken after importation. In case of discrepancies or out of trends, these shall be documented and investigated;

— consideration of the time interval between sampling and importation of the batch and generation of data to support appropriate defined limits;

(c) a random periodic analysis of samples taken after importation shall be performed to justify ongoing reliance on samples taken in a third country;

(d) the conditions of storage and transport of the finished product and the samples, shall be checked before certifying any batch;

(e) batch documentation supplied by the third country manufacturing site shall be in a format and language that is understandable for the importer;

(f) relevant ordering and delivery documentation shall be available for inspection at the manufacturing site responsible for certification;

(g) where batches are subdivided and partial quantities are imported separately, reconciliation of the quantities shall be verified and documented. Any discrepancy shall be investigated under the responsibility of the qualified person responsible for the certification of the batch;

(h) the manufacturing site responsible for certification shall ensure that an ongoing stability programme is in place and that reference and retention samples have been taken. The ongoing stability programme may be carried out at the third country manufacturing site.

4. The manufacturing site responsible for certification shall qualify the third country manufacturer and conduct periodic monitoring, including by means of on-site audits, to ensure compliance with good manufacturing practice and the terms of the marketing authorisation.

Article 41

Repackaging operations

The qualified person of a manufacturing site that is only involved in repackaging operations shall certify that the repackaging has been done in compliance with relevant good manufacturing practice requirements.

Article 42

Handling of unplanned deviations

Where an unplanned deviation related to the manufacturing process or the analytical control methods has occurred, a qualified person may confirm compliance or certify the batch only if the following conditions are met:

(a) the specifications for active substances, excipients, packaging materials and finished product are complied with;

(b) there is an in-depth assessment of the impact of the deviation which supports a conclusion that the occurrence does not have a negative effect on quality, safety or efficacy of the product;

(c) where appropriate, the need for inclusion of the affected batch/batches in the on-going stability programme has been evaluated.

CHAPTER IX

OUTSOURCED ACTIVITIES

Article 43

Requirements for outsourced activities

1. The outsourcing of operations related to the manufacture or control of veterinary medicinal products shall be made by means of a written contract that provides for clear delineation of the responsibilities of each party.

2. The manufacturer ('contract giver') shall assess the suitability of the contractor ('contract acceptor') to carry out the outsourced activities.

3. The contract giver shall ensure that adequate information is transmitted to the contract acceptor for the performance of the outsourced activities and that the contract acceptor is aware of any problems associated with the product or the work that might pose a hazard to the premises, equipment, personnel, other materials or other products.

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

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

(b) the contract acceptor shall permit audits or inspections by the contract giver and the competent authorities in connection with the outsourced activities;

(c) all records related to the outsourced activities as well as the reference samples shall either be transferred to the contract giver or, in the alternative, the contract giver shall be granted access to them;

(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.

5. The contract giver shall review and assess the records and the results related to the outsourced activities and take relevant measures where appropriate.

CHAPTER X

QUALITY DEFECTS AND RECALL OF PRODUCTS

Article 44

Quality defects

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 veterinary medicinal products where appropriate.

2. Personnel responsible for managing quality-related complaints and quality defect investigations shall be independent from marketing and sales departments unless otherwise justified. If the qualified person involved in the certification of the concerned batches does not participate in the investigation, it shall be informed in a timely manner.

3. Operating procedures shall be developed describing the actions to be taken upon the receipt of a quality-related complaint. Those operating procedures shall address at least the following:

(a) the determination of the extent of quality defect;

(b) the assessment of the risks posed by the quality defect;

(c) the identification of the potential root causes of the quality defect or, where such route cause cannot be ascertained, the most probable reason;

(d) the need for appropriate risk minimisation measures;

(e) the need for corrective or preventive measures;

(f) the assessment of the impact that any recall action may have on the availability of the veterinary medicinal product;

(g) the internal and external communications to be made.

4. If the handling of quality-related complaints and suspected quality defects is managed centrally within an organisation, the relative roles and responsibilities of the parties concerned shall be documented.

5. If the veterinary medicinal product is manufactured by an entity that is not the marketing authorisation holder, the role and responsibilities of the manufacturer, the marketing authorisation holder and any other relevant third party shall be laid down in writing.

6. 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.

7. Quality defect investigations shall include a review of previous quality defect reports or any other relevant information that is indicative of specific or recurring problems.

8. The priority during an investigation shall be to ensure that appropriate risk-minimisations 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.

9. Quality defects shall be reported in a timely manner to the marketing authorisation holder. Competent authorities shall also be informed in the case of a confirmed quality defect that may result in the recall of the product or an abnormal restriction in the supply. Unplanned deviations as described in Article 42 need not be notified.

10. Measures to address quality defects shall be proportionate to the risks and the priority shall be the protection of treated animals and user safety. Wherever possible, the actions to be taken shall be discussed with the competent authorities concerned in advance.

Article 45

Product recalls

1. Procedures for the recall of products 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. The respective role and tasks of the manufacturer and marketing authorisation holder regarding the initiation and organisation of recalls shall be clearly established.

2. It shall be ensured that recall operations can be initiated promptly and at any time. In certain cases, and with a view to protect the health of consumers or animals, it may be necessary to recall products prior to establishing the root cause or the full extent of the quality defect.

3. The effectiveness of the procedure for recalls shall be periodically evaluated, including during office hours and out-of-office hours. The possibility of performing mock-recall actions shall be considered and the outcome of this evaluation shall be documented.

4. Recalled products shall be identified and stored separately in a secure area while awaiting a decision on their fate. The progress of the recall shall be recorded until the recall procedure is closed and a final report is issued, including a reconciliation between the delivered and recovered quantities of the concerned products or batches.

5. All competent authorities concerned shall be informed prior to the initiation of a recall unless urgent action is required to protect the health of consumers or animals. The competent authorities shall also be informed in situations in which no recall action is being proposed for a defective batch because the batch has expired.

6. In addition to recalls, there are other risk-reducing actions that may be considered to manage the risks presented by quality defects, such as the transmission of appropriate information to healthcare professionals. Such course of action shall be discussed with and agreed by the competent authorities.

CHAPTER XI

FINAL PROVISIONS

Article 46

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 I

STERILE PRODUCTS AND ASEPTIC MANUFACTURING

SECTION I

SCOPE

The additional requirements set out in this Annex shall apply to the manufacture of sterile products and products where aseptic manufacturing is required.

SECTION II

GENERAL PRINCIPLES

II.1. The manufacture of sterile products is subject to special requirements in order to minimise risks of microbial, particulate and endotoxin/pyrogen contamination. The following aspects shall be specifically considered:

(a) premises, equipment and processes shall be appropriately designed, qualified and/or validated and, where applicable, subjected to ongoing verification. The use of appropriate technologies (e.g. restricted access barriers systems, isolators, robotic systems, rapid/alternative methods and continuous monitoring systems) shall be considered to increase the protection of the product from potential extraneous sources of endotoxin/pyrogen, particulate and microbial contamination, and assist in the rapid detection of potential contaminants in the environment and in the product;

(b) personnel shall have adequate qualifications and experience and training with a specific focus on the principles involved in the protection of sterile products;

(c) processes and monitoring systems for the manufacture of sterile products shall be designed, commissioned, qualified, monitored and regularly reviewed by personnel with appropriate knowledge (including on aspects related to the process and relevant engineering and microbiological knowledge);

(d) raw materials and packaging materials shall be adequately controlled and tested to ensure that the level of bioburden and endotoxin/pyrogen are suitable for use;

(e) processes associated with the finishing and storage of sterile products shall not compromise the sterility of the product. Aspects to be considered in this regard include container integrity and maintenance of adequate storage conditions;

(f) all non-conformities, such as sterility test failures, environmental monitoring excursions or deviations from established procedures shall be adequately investigated before certification/release of the batch. The investigation shall determine the potential impact on the process and product quality and whether any other processes or batches are potentially impacted. The reason for including or excluding a product or batch from the scope of the investigation shall be clearly justified and recorded.

II.2. Processes, equipment, premises and manufacturing activities shall be managed in accordance with quality risk management principles so as to proactively identify, evaluate and control potential risks to quality. Monitoring or testing alone are not considered sufficient – on their own – to ensure sterility.

II.3. A contamination control strategy shall be developed by the manufacturer and be implemented in the site. The contamination control strategy shall aim at avoiding contamination by identifying all the critical control points and assessing the effectiveness of all the controls (design, procedural, technical and organisational) and monitoring measures implemented to manage the risks. The effectiveness of the contamination control strategy shall be periodically reviewed and, where appropriate, updated and shall also drive continual improvement of the manufacturing and control methods.

II.4. While the contamination control strategy includes a series of interrelated measures that are typically assessed, controlled and monitored individually, the effectiveness of the implemented measures shall be assessed altogether.

II.5. The development of the contamination control strategy requires detailed technical and process knowledge. Potential sources of contamination are attributable to microbial and cellular debris (e.g. pyrogen, endotoxin) as well as particulate (e.g. glass and other visible and sub-visible particles). Elements to be considered within a contamination control strategy include but are not limited to:

— plant and processes design, including the associated documentation;

— premises and equipment;

— personnel;

— utilities;

— raw material controls, including in-process controls;

— product containers and closures;

— approval of key component suppliers and critical service providers;

— management of outsourced activities and availability/transfer of critical information between parties;

— process validation, including validation of sterilisation processes;

— preventive maintenance: maintaining equipment, utilities and premises (planned and unplanned maintenance) so as to minimise the risk of contamination;

— cleaning and disinfection;

— monitoring systems, including an assessment of the feasibility of the introduction of scientifically sound, alternative methods that optimise the detection of environmental contamination;

— prevention mechanisms: trend analysis, detailed investigation, root cause determination, corrective and preventive actions and the need for comprehensive investigational tools;

— continuous improvement based on information derived from the above.

II.6. Changes to the systems in place shall be assessed for any impact on the contamination control strategy before and after implementation.

II.7. The manufacturer shall take all the steps and precautions necessary to ensure the sterility of the products manufactured within its facilities. Sole reliance shall not be placed on any terminal process or finished product test.

SECTION III

PREMISES

III.1. **General requirements**

III.1.1. The manufacture of sterile products shall be carried out in appropriate cleanrooms, entry to which shall be through change rooms that act as airlocks for personnel and airlocks for equipment and materials.

III.1.2. Cleanrooms and change rooms shall be maintained to an appropriate cleanliness standard and supplied with air that has passed through filters of an appropriate efficiency. Controls and monitoring shall be scientifically justified and shall effectively evaluate the state of environmental conditions of cleanrooms, airlocks and pass-through hatches.

III.1.3. The various operations of component preparation, product preparation and filling shall be carried out with appropriate technical and operational separation measures within the cleanroom or the premises to prevent mix up and contamination.

III.1.4. Restricted Access Barrier Systems (RABS) ([1]) or isolators can minimise microbial contamination associated with direct human interventions in the critical zone ([2]). Their use shall therefore be considered as part of the contamination control strategy; the use of alternative approaches shall be justified.

III.1.5. The following grades of cleanroom/zone shall be used:

(a) Grade A: for high-risk operations, such as aseptic processing line, filling zone, stopper bowl, open primary packaging or for making aseptic connections under the protection of first air ([3]).

Grade A conditions are usually provided by a localised airflow protection, such as unidirectional airflow ([4]) workstations within RABS or isolators. The maintenance of unidirectional airflow shall be demonstrated and qualified across the whole of the grade A area. Direct intervention (e.g. without the protection of barrier and glove port technology) into the grade A area by operators shall be minimised.

(b) Grade B: this is the background cleanroom for grade A for aseptic preparation and filling (except for isolators). Air pressure differences shall be continuously monitored. Cleanrooms of lower grade than grade B may be considered where isolator technology is used (see Section III.3.3 of this Annex).

(c) Grade C and D: for less critical stages in the manufacture of aseptically filled sterile products or as a background for isolators. They may also be used for the preparation/filling of terminally sterilised products.

III.1.6. In cleanrooms and critical zones, all exposed surfaces shall be smooth, impervious and unbroken in order to minimise the shedding or accumulation of particles or micro-organisms.

III.1.7. To reduce the accumulation of dust and to facilitate cleaning there shall be no recesses that are difficult to clean effectively. Therefore, projecting ledges, shelves, cupboards and equipment shall be kept to a minimum. Doors shall be designed to avoid recesses that cannot be cleaned. Sliding doors are generally undesirable for this reason.

III.1.8. Materials used in cleanrooms, both in the construction of the room and for items used within the room, shall be selected to minimise generation of particles and to permit the repeated application of cleaning, disinfectant and sporicidal agents as appropriate.

III.1.9. Ceilings shall be designed and sealed to prevent contamination from the space above them.

III.1.10. Sinks and drains are not allowed in the grade A and grade B areas. In other grades, air breaks shall be fitted between the machine or sink and the drains. Floor drains in lower grade cleanrooms shall be fitted with traps or water seals designed to prevent back flow and shall be regularly cleaned, disinfected and maintained.

([1]) For the purposes of this Annex, 'restricted access barrier system' means a system that provides an enclosed, but not fully sealed, environment meeting defined air quality conditions, and using a rigid-wall enclosure and integrated gloves to separate its interior from the surrounding cleanroom environment. The inner surfaces of the RABS are disinfected and decontaminated with a sporicidal agent. Operators use gloves, half suits, rapid transfer system/ports and other integrated transfer ports to perform manipulations or convey materials to the interior of the RABS. Depending on the design, doors are rarely opened, and only under strictly pre-defined conditions.

([2]) For the purposes of this Annex, 'critical zone' means a space within the aseptic processing area in which product and critical surfaces are exposed to the environment.

([3]) For the purposes of this Annex, 'first air' means filtered air that has not been interrupted prior to contacting the exposed product and product contact surfaces.

([4]) For the purposes of this Annex, 'unidirectional airflow' means an airflow moving in a single direction, in a robust and uniform manner, and at sufficient speed, to reproducibly sweep particles away from the critical processing or testing area.

III.1.11. Cleanrooms shall be supplied with a filtered air supply that maintains a positive pressure and/or an airflow relative to the background environment of a lower grade under all operational conditions and shall flush the area effectively. Adjacent rooms of different grades shall have an air pressure difference of a minimum of 10 Pascals (guidance value). Particular attention shall be paid to the protection of the critical zone.

III.1.12. The above-referred requirements regarding air supplies and pressures may be modified where necessary to contain certain materials (e.g. pathogenic, highly toxic or radioactive products or live viral or bacterial materials). The modification may include positively or negatively pressurised airlocks that prevent the hazardous material from contaminating the surrounding areas. Where for reasons of containment, it is necessary for the air to flow into a critical zone, the source of the air shall be from an area of the same or higher grade.

III.1.13. Decontamination of facilities (e.g. the cleanrooms and the heating, ventilation, and air-conditioning (HVAC) systems) and the treatment of air leaving a clean area, may be necessary for some operations based on a risk assessment (e.g. in the context of production involving pathogenic, highly toxic or radioactive materials or live viral or bacterial materials, when there is a risk of spreading to the environment, or when contamination has been detected).

III.1.14. Airflow patterns within cleanrooms and zones shall be visualised and it shall be demonstrated that there is no ingress from lower grade to higher grade areas and that air does not travel from less clean areas (such as the floor), operators or equipment so that contamination may be transferred to the higher-grade areas. In particular, the following applies:

(a) Where unidirectional airflow is required, visualisation studies shall be performed to determine compliance.

(b) Where filled, closed products are transferred to an adjacent cleanroom of a lower grade via a small egress point, airflow visualisation studies shall demonstrate that air does not ingress from the lower grade cleanrooms to the grade B area.

(c) Where air movement is shown to be a contamination risk to the clean area or critical zone, corrective actions, such as design improvement, shall be implemented.

(d) Airflow pattern studies shall be performed both at rest and in operation (e.g. simulating operator interventions). Video recordings of the airflow patterns shall be retained. The outcome of the air visualisation studies shall be documented and be duly considered when establishing the facility's environmental monitoring programme.

III.1.15. Indicators of air pressure differences shall be installed between cleanrooms and/or between isolators and their background. Set points and the criticality of air pressure differences shall be addressed as part of the contamination control strategy. Air pressure differences identified as critical shall be continuously monitored and recorded. A warning system shall be in place to instantly indicate and warn operators of any failure in the air supply or reduction of air pressure differences (below set limits for those identified as critical). The warning signal shall not be overridden without an assessment and a procedure shall be available to outline the steps to be taken when a warning signal is given. Where alarm delays are set, these shall be assessed and justified. Other air pressure differences shall be monitored and recorded at regular intervals.

III.1.16. Facilities shall be designed to permit observation of production activities from outside the grade A and B areas (e.g. through the provision of windows or remote cameras with a full view of the area and processes to allow observation and supervision without entry). This requirement shall be implemented when designing new facilities or during refurbishment of existing facilities.

III.2. **Transfer of equipment and materials and movement of personnel**

III.2.1. The transfer of equipment and materials into and out of the cleanrooms and critical zones is one of the greatest potential sources of contamination and appropriate controls shall be therefore implemented. In particular, the transfer of materials, equipment, and components into the grade A or B areas shall be carried out via a unidirectional process. Where possible, items shall be sterilised and passed into these areas through double-ended sterilisers (e.g. through a double-door autoclave or a depyrogenation oven/tunnel) sealed into the wall. Where sterilisation upon transfer of the items is not possible, a validated procedure which achieves the same objective of not introducing contamination shall be implemented (e.g. using an effective transfer disinfection process, rapid transfer systems for isolators or, for gaseous or liquid materials, a bacteria-retentive filter). The removal of items from the grade A and B areas (e.g. materials, waste, environmental samples) shall be carried out via a separate unidirectional process. If this is not possible, a time-based separation of movement (incoming/exiting material) shall be considered and adequate controls shall be applied to avoid potential contamination.

III.2.2. Only materials and equipment that have been included on an approved list, which is developed on the basis of an assessment during the validation of the transfer process, shall be transferred into the grade A or grade B areas via an airlock or pass-through hatches. Any unapproved items that require transfer shall be pre-approved as an exception.

III.2.3. The movement of material or equipment from a lower grade or unclassified area to a higher-grade clean area shall be subject to cleaning and disinfection commensurate with the risks. Equipment and materials (intended for use in the grade A area) shall be protected when transiting through the grade B area. Appropriate risk assessment and mitigation measures shall be applied and recorded, including a specific disinfection and monitoring programme approved by the department responsible for quality assurance.

III.2.4. Airlocks shall be designed and used to provide physical separation and to minimise microbial and particle contamination of the different areas and shall be used for material and personnel moving between different grades. Wherever possible, airlocks used for personnel movement shall be separated from those used for material movement. Where this is not possible, time-based separation of movement (personnel/material) shall be considered. Airlocks shall be flushed effectively with filtered air to ensure that the grade of the cleanroom is maintained. The final stage of the airlock shall, in the 'at rest' state, be of the same cleanliness grade (viable and total particle) as the cleanroom into which it leads. The use of separate change rooms for entering and leaving the grade B area is desirable. Where this is not possible, time-based separation of activities (ingress/egress) shall be considered. Where the risk of contamination is high, separate change rooms for entering and leaving production areas shall be used.

III.2.5. The following aspects shall be considered in the design of airlocks:

— Personnel airlocks ([5]): In general, hand-washing facilities shall be provided only in the first stage of the changing room and not be present in changing rooms directly accessing the grade B area.

— Material airlocks ([6]): Airlock and pass-through hatches shall be designed to protect the higher-grade environment, for example by effective flushing with an active filtered air supply.

For pass-through hatches and airlocks (for material and personnel), the entry and exit doors shall not be opened simultaneously. For airlocks leading to the grade A and grade B areas, an interlocking system shall be used. For airlocks leading to grade C and D areas, at least a visual and/or audible warning system shall be implemented. Where required to maintain the segregation of the area, a time delay between the closing and opening of interlocked doors shall be implemented.

([5]) For the purposes of this Annex, 'personnel airlock' means an area of increasing cleanliness used for entry of personnel (e.g. from the grade D area to the grade C area, or from the C area to the grade B area).

([6]) For the purposes of this Annex, 'material airlock' means an area used for transfer of materials and equipment.

III.3. **Barrier technologies**

III.3.1. Isolators and RABS and associated processes shall be designed to provide protection through the separation of the grade A environment from the environment of the surrounding room. The hazards introduced from the entry or removal of items during processing shall be minimised by the implementation of appropriate technologies or validated systems.

III.3.2. The design of the technology and processes used shall ensure that appropriate conditions are maintained in the critical zone to protect the exposed product during the operations.

(a) Requirements for isolators:

— The design of open isolators shall ensure grade A conditions with first air protection in the critical zone and unidirectional airflow that sweeps over and away from the exposed products during processing.

— The design of closed isolators shall ensure grade A conditions with adequate protection for the exposed products during processing. Airflow may not be fully unidirectional in closed isolators where simple operations are conducted. However, any turbulent airflow ([7]) shall not increase the risk of contamination of the exposed product. Where processing lines are included in closed isolators, grade A conditions shall be ensured with first air protection in the critical zone and unidirectional airflow that sweeps over and away from the exposed products during processing.

— Negative pressure isolators shall only be used when containment of the product is considered essential (e.g. radiopharmaceutical products) and specialised risk control measures shall be applied to ensure that the critical zone is not compromised.

(b) Requirements for RABS: The design of RABS shall ensure grade A conditions with unidirectional airflow and first air protection in the critical zone. A positive airflow from the critical zone to the supporting background environment shall be maintained.

III.3.3. The background environment for isolators or RABS shall ensure that the risk of transfer of contamination is minimised.

(a) Requirements for isolators:

— The background classification applied shall be based on a risk assessment and justified as part of the contamination control strategy. The background environment for open isolators shall generally correspond to a minimum of grade C, while the background for closed isolators shall correspond to a minimum of grade D.

— Key considerations when performing the risk assessment for the contamination control strategy of an isolator include the bio-decontamination programme, the extent of automation, the impact of glove manipulations that may potentially compromise ‘first air’ protection of the critical process points, the impact of potential loss of barrier/glove integrity, transfer mechanisms used and activities such as set-up or maintenance that may require the doors to be opened prior to the final bio-decontamination of the isolator. Where additional process risks are identified, a higher grade of background shall be implemented unless appropriately justified in the contamination control strategy.

— Airflow pattern studies shall be performed at the interfaces of open isolators to demonstrate the absence of air ingress.

([7]) For the purposes of this Annex, ‘turbulent airflow’ means air that is not unidirectional. Turbulent air in cleanrooms shall flush the cleanroom via mixed flow distribution and ensure maintenance of an acceptable air quality.

(b) Requirements for RABS: The background environment for RABS used for aseptic processing shall correspond to a minimum of grade B and airflow pattern studies shall be performed to demonstrate the absence of air ingress during interventions, including door openings if applicable.

III.3.4. The materials used for glove systems (for both isolators and RABS) shall have appropriate mechanical and chemical resistance. The frequency of glove replacement shall be defined as part of the contamination control strategy.

(a) Requirements for Isolators:

— Leak testing of the glove system shall be performed using a suitable methodology having regard to the intended use and the risks involved. The testing shall be performed at defined intervals. In general, glove integrity testing shall be performed at least at the beginning and at the end of each batch or campaign. Additional glove integrity testing may be necessary depending on the campaign length.

Glove integrity monitoring shall include a visual inspection associated with each use and following any manipulation that may affect the integrity of the system.

For manual aseptic processing activities (i.e. the operator manually compounds, fills, places and/or seals an open container with sterile product) where a single unit or a small-size batch is produced, the frequency of integrity verification may be based on other criteria, such as the beginning and end of each manufacturing session.

— Integrity/leak testing of the isolator system shall be performed at defined intervals.

(b) Requirements for RABS: Gloves used in the grade A area shall be sterilised before installation and sterilised or effectively bio-decontaminated by a validated method prior to each manufacturing campaign. If during operation there is exposure to the background environment, there shall be disinfection using an approved methodology after each exposure. Gloves shall be visually examined with each use, and integrity testing shall be performed at periodic intervals.

III.3.5. Decontamination methods (cleaning and bio-decontamination, and – where applicable – inactivation for biological materials) shall be duly documented. The cleaning process prior to the bio-decontamination step is essential as any residues that remain may inhibit the effectiveness of the decontamination process. It shall be demonstrated that the cleaning and bio-decontamination agents used do not have an adverse impact on the product produced within the RABS or isolator.

(a) Requirements for isolators: The bio-decontamination process of the interior shall be automated, validated and controlled within defined cycle parameters and shall include a sporicidal agent in a suitable form (e.g. gaseous or vaporised form). Gloves shall be appropriately extended with fingers separated to ensure contact with the agent. Methods used (cleaning and sporicidal bio-decontamination) shall render the interior surfaces and critical zone of the isolator free from viable microorganisms.

(b) Requirements for RABS: The sporicidal disinfection shall include the routine application of a sporicidal agent using a method that has been validated and demonstrated to cover all areas of the interior surfaces and ensure a suitable environment for aseptic processing.

III.4. **Cleanroom and clean air equipment qualification**

III.4.1. Cleanrooms and clean air equipment such as unidirectional airflow units ([8]), RABS and isolators, used for the manufacture of sterile products/aseptic manufacturing, shall be qualified according to the required characteristics of the environment. Each manufacturing operation requires an appropriate environmental cleanliness level in the operational state in order to minimise the risk of contamination of the product or materials being handled. Appropriate cleanliness levels in the 'at rest' and 'operational' states shall also be maintained.

III.4.2. Cleanrooms and clean air equipment shall be qualified in accordance with Annex V. Through the qualification of cleanrooms and clean air equipment, the level of compliance of a classified cleanroom or clean air equipment with the relevant requirements having regard to the intended use is assessed ([9]). The following is part of the qualification requirements (where relevant to the design/operation of the installation):

— installed filter system leakage and integrity testing;

— airflow tests – volume and velocity;

— air pressure difference test;

— airflow direction test and visualisation;

— microbial airborne and surface contamination;

— temperature measurement test;

— relative humidity test;

— recovery test;

— containment leak test.

III.4.3. Cleanroom classification is part of the cleanroom qualification. Through the cleanroom classification the level of air cleanliness is assessed by measuring the total particle concentration. Classification activities shall be scheduled and performed so as to avoid any impact on process or product quality. For example, initial classification shall be performed during simulated operations and reclassification performed during simulated operations or during aseptic process simulation.

III.4.4. For cleanroom classification, the total amount of particles equal to or greater than 0,5 and 5 μm shall be measured. This measurement shall be performed both at rest and in simulated operations in accordance with the limits specified in Table 1:

— 'at rest' state is the condition whereby the installation of all the utilities is complete including any functioning HVAC, with the main manufacturing equipment installed as specified but not operating and without personnel present in the room.

— The total particle limits given in Table 1 for the 'at rest' state shall be achieved after a 'clean up' period on completion of operations and line clearance/cleaning activities. The 'clean up' period (guidance value of less than 20 minutes) shall be determined during the qualification of the rooms, documented and adhered to in procedures to reinstate a qualified state of cleanliness if disrupted during operation.

([8]) For the purposes of this Annex, 'unidirectional airflow unit' means a cabinet supplied with filtered unidirectional airflow. The concept is interchangeable with 'laminar airflow unit'.

([9]) It is noted that qualification of cleanrooms is a different process than environmental monitoring.

— ‘in operation’ state is the condition where the installation of the cleanroom is complete, the HVAC system fully operational, equipment installed and functioning in the manufacturer’s defined operating mode with the maximum number of personnel present performing or simulating routine operational work.

Table 1

Maximum permitted total particle concentration for classification

	Maximum limits for total particle ≥ 0,5 μm/m³		Maximum limits for total particle ≥ 5 μm/m³	
Grade	at rest	in operation	at rest	in operation
A	3 520	3 520	Not specified (1)	Not specified (1)
B	3 520	352 000	Not specified (1)	2 930
C	352 000	3 520 000	2 930	29 300
D	3 520 000	Not pre-defined (2)	29 300	Not pre-defined (2)

(1) Classification including 5μm particles may be considered where relevant in accordance with the contamination control strategy or historical trends.

(2) For grade D, in operation limits are not pre-defined. The manufacturer shall establish relevant in operation limits based on a risk assessment and routine data where applicable.

III.4.5. For classification of the cleanroom, the minimum number of sampling locations and their positioning as set out in ISO 14644 Part 1 shall be followed. For the aseptic processing area and the background environment (the grade A and grade B areas, respectively), additional sample locations shall be considered as appropriate having regard to the risks, and all critical processing areas such as the point of fill and container closure feeder bowls shall be evaluated. Critical processing locations shall be determined on the basis of a documented risk assessment and knowledge of the process and operations to be performed in the area.

III.4.6. The speed of air supplied by unidirectional airflow systems shall be clearly justified in the qualification protocol including the location for air speed measurement. Air speed shall be designed, measured and maintained to ensure that appropriate unidirectional air movement provides protection for the product and open components at the working position (e.g. where high-risk operations occur and where product and/or components are exposed). Unidirectional airflow systems shall provide a homogeneous air speed in a range of 0,36–0,54 m/s (guidance value) at the working position, unless otherwise scientifically justified in the contamination control strategy. Airflow visualisation studies shall correlate with the air speed measurement.

III.4.7. The microbial contamination level of the cleanrooms shall be determined as part of the cleanroom qualification. The number of sampling locations shall be based on a documented risk assessment and the results obtained from room classification, air visualisation studies and knowledge of the process and operations to be performed in the area. The maximum limits for microbial contamination during qualification for each grade are given in Table 2. Qualification shall include both ‘at rest’ and ‘in operation’ states.

Table 2

Maximum permitted microbial contamination level during qualification

Grade	Air sample CFU ([2])/ m^3	Settle plates (diameter 90 mm) CFU/4 hours ([2])	Contact plates (diameter 55 mm) CFU/plate
A	No growth		
B	10	5	5
C	100	50	25
D	200	100	50

([1]) For the purposes of this Annex, 'colony forming unit' or 'CFU' means a single detectable colony that originates from one or more microorganisms. Colony forming units are typically expressed as CFU per ml for liquid samples, CFU per m^3 for air sample and CFU per sample for samples captured on solid medium such as settle or contact plates.

([2]) Settle plates shall be exposed for the duration of operations and changed as required after a maximum of 4 hours. Exposure time shall be based on recovery studies and shall not allow desiccation of the media used.

Note 1: All methods indicated for a specific grade in the table shall be used for qualifying the area of that specific grade. If one of the methods tabulated is not used, or alternative methods are used, the approach taken shall be appropriately justified.

Note 2: Limits are applied using CFU throughout the document. If different or new technologies are used that present results in a manner different from CFU, the manufacturer shall scientifically justify the limits applied and where possible correlate them to CFU.

Note 3: For the qualification of personnel gowning, the limits given for contact plates and glove prints in Table 6 shall apply.

Note 4: Sampling methods shall not pose a risk of contamination to the manufacturing operations.

III.4.8. The requalification of cleanrooms and clean air equipment shall be carried out periodically following defined procedures. The requalification shall include at least the following:

— cleanroom classification (total particle concentration);

— integrity test of final filters;

— airflow volume measurement;

— verification of air pressure difference between rooms;

— air velocity test: this test is required for filling zones supplied with unidirectional airflow (e.g. when filling terminally sterilised products or background to grade A and RABS). In the case of grade B, C and D areas, the conduct of the air velocity test shall be based on a risk assessment, which shall be documented as part of the contamination control strategy. Finally, for grades with non-unidirectional airflow, the air velocity test shall be replaced by a measurement of recovery testing.

III.4.9. The maximum time interval for requalification of grade A and B areas is 6 months, while for grade C and D areas the maximum time interval for requalification is 12 months.

In addition, appropriate requalification consisting of at least the above tests shall also be carried out following completion of a remedial action implemented to rectify an out of compliance in the equipment or premises or, as appropriate, after changes to equipment, premises or processes. Examples of changes requiring requalification include the interruption of air movement which affects the operation of the installation, a change in the design of the cleanroom or of the operational setting parameters of the HVAC system, or maintenance activities affecting the operation of the installation (e.g. change of final filters).

III.5. **Disinfection**

III.5.1. Particular attention shall be paid to the disinfection of cleanrooms. Specifically, cleanrooms shall be cleaned and disinfected thoroughly in accordance with a written programme. More than one type of disinfecting agent shall be used to ensure that, where they have different modes of action, their combined usage is effective against bacteria and fungi. Disinfection shall include the periodic use of a sporicidal agent. Monitoring to assess the effectiveness of the disinfection programme and to detect changes in types of microbial flora (e.g. organisms resistant to the disinfection regime currently in use) shall be undertaken regularly.

For disinfection to be effective, it is necessary to previously clean to remove surface contamination. Additionally, in some cases, a cleaning process shall be implemented to effectively remove disinfectant residues.

III.5.2. The disinfection process shall be validated. Validation studies shall demonstrate the suitability and effectiveness of the disinfectants in the specific manner in which they are used and on the type of surface material, or representative material if justified, and shall support the in-use expiry periods of prepared solutions.

III.5.3. Disinfectants and detergents used in grade A and grade B areas shall be sterile prior to use. Disinfectants used in grade C and D may also have to be sterile when this is considered appropriate in the contamination control strategy. Where the disinfectants and detergents are diluted/prepared by the sterile product manufacturer, this shall be done in a manner to prevent contamination and there shall be monitoring for microbial contamination. Dilutions shall be kept in previously cleaned containers (and sterilised where applicable) and shall only be stored for the relevant defined period. If the disinfectants and detergents are supplied 'ready-made', the results from certificates of analysis or conformance may be accepted subject to successful completion of the appropriate vendor qualification.

III.5.4. Where fumigation or vapour disinfection (e.g. Vapour-phase Hydrogen Peroxide) of cleanrooms and associated surfaces are used, the effectiveness of the fumigation agent and of the dispersion system used shall be understood and validated.

SECTION IV

EQUIPMENT

IV.1. A written, detailed description of the equipment shall be available (including process and instrumentation diagrams as appropriate). This shall form part of the initial qualification package and shall be kept up to date.

IV.2 Equipment monitoring requirements shall be established as part of the qualification. Process and equipment alarm events shall be acknowledged and evaluated for trends. The frequency at which alarms are assessed shall be based on their criticality (critical alarms shall be reviewed immediately).

IV.3. As far as possible, equipment, fittings and services shall be designed and installed so that operations, maintenance and repairs can be performed outside the cleanroom. If maintenance has to be performed in the cleanroom and the required standards of cleanliness and/or asepsis cannot be maintained, precautions such as restricting access to the work area to specified personnel or the generation of clearly defined work protocols and maintenance procedures shall be considered. Additional cleaning, disinfection and environmental monitoring shall also be considered. If sterilisation of equipment is required, it shall be carried out, wherever possible, after complete reassembly.

IV.4. The cleaning process shall be validated as being able to remove any residue or debris that would detrimentally impact the effectiveness of the disinfecting agent used, and to minimise the chemical, microbial and particulate contamination of the product during the process and prior to disinfection.

IV.5. For aseptic processes, direct and indirect product contact parts shall be sterilised. For the purpose of complying with this requirement, 'direct product contact parts' are those parts of the equipment that the product passes through, such as filling needles or pump, while 'indirect product contact parts' are those parts of the equipment that are not in contact with the product but may come into contact with other sterilised surfaces that are critical to the overall product sterility (e.g. sterilised items such as stopper bowls and guides, and sterilised components).

IV.6. All equipment such as sterilisers, air handling systems (including air filtration) and water systems shall be subject to qualification, monitoring and planned maintenance. Upon completion of maintenance, their return to use shall be approved.

IV.7. Where unplanned maintenance of equipment critical to the sterility of the product is to be carried out, an assessment of the potential impact to the sterility of the product shall be performed and recorded.

IV.8. A conveyor belt shall not pass through a partition between a grade A or B area and a processing area of lower air cleanliness, unless the belt itself is continually sterilised (e.g. in a sterilising tunnel).

IV.9. Particle counters, including sampling tubing, shall be qualified. The manufacturer's recommended specifications shall be considered for tube diameter and bend radii. Tube length shall typically be no longer than 1 m unless justified and the number of bends shall be minimised. Portable particle counters with a short length of sample tubing shall be used for classification purposes. Isokinetic sampling heads ([10]) shall be used in unidirectional airflow systems. They shall be oriented appropriately and positioned as close as possible to the critical location to ensure that samples are representative.

SECTION V

UTILITIES

V.1. **General requirements**

V.1.1. The nature and extent of controls applied to utility systems shall be commensurate with the risk to the quality of the product associated with the utility. The impact of the utility on the quality of the product is to be determined via a risk assessment and documented as part of the contamination control strategy.

The following utilities can generally be considered associated with a higher risk:

— utilities that are in direct contact with the product, e.g. water for washing and rinsing, gases and steam for sterilisation;

— contact materials that will ultimately become part of the product;

— contact surfaces that come into contact with the product;

— utilities that otherwise directly impact the product.

V.1.2. Utilities shall be designed, installed, qualified, operated, maintained and monitored in a manner that ensures that the utility system functions as expected.

V.1.3. Results for critical parameters and critical quality attributes of high-risk utilities shall be subject to regular trend analysis to ensure that the system capabilities remain appropriate.

([10]) For the purposes of this Annex, 'isokinetic sampling head' means a sampling head designed to disturb the air as little as possible so that the same particles go into the nozzle as would have passed the area if the nozzle had not been there (i.e. the sampling condition in which the mean velocity of the air entering the sample probe inlet is nearly the same (± 20 percent) as the mean velocity of the airflow at that location).

V.1.4. Records of the utility system installation shall be kept throughout the utility system's life-cycle, including drawings and schematic diagrams, construction materials and system specifications. Important information that shall be kept includes:

— pipeline flow direction, slopes, diameter and length;

— tank and vessel details;

— valves, filters, drains, sampling and user points.

V.1.5. Pipes, ducts and other utilities shall not be present in cleanrooms. If unavoidable, then they shall be installed so that they do not create recesses, unsealed openings or surfaces that are difficult to clean. In addition, the installation shall allow the cleaning and disinfection of the outer surface of the pipes.

V.2. **Water systems** ([11])

V.2.1. Water treatment plants and distribution systems shall be designed, constructed, installed, commissioned, qualified, monitored and maintained so as to prevent microbiological contamination and ensure a reliable source of water of an appropriate quality. In particular, measures shall be taken to minimise the risk of presence of particulates, microbial contamination/proliferation and endotoxin/pyrogen (e.g. sloping of piping to provide complete drainage and the avoidance of dead legs ([12])). Where filters are included in the system, special attention shall be paid to their monitoring and maintenance.

V.2.2. Water systems shall be qualified and validated to maintain the appropriate levels of physical, chemical and microbial control, taking the effect of seasonal variations into account.

V.2.3. Water flow shall remain turbulent through the pipes in water distribution systems to minimise the risk of microbial adhesion, and subsequent biofilm formation. The flow rate shall be established during the qualification and be routinely monitored.

V.2.4. Water for injections shall be produced from water that meets the specifications defined during the qualification process and it shall be stored and distributed in a manner that minimises the risk of microbial growth (e.g. by constant circulation at a temperature above 70 °C). Moreover, water for injections shall be produced by distillation or by a purification process that is equivalent to distillation, such as reverse osmosis coupled with other appropriate techniques such as electrodeionisation (EDI), ultrafiltration or nanofiltration.

V.2.5. Where water for injection storage tanks are equipped with hydrophobic bacteria retentive vent filters, the filters shall not be a source of contamination and the integrity of the filter shall be tested before installation and after use. Controls shall be put in place to prevent condensation formation on the filter (e.g. by heating).

V.2.6. To minimise the risk of biofilm formation, sterilisation, disinfection or regeneration of water systems shall be carried out according to a predetermined schedule and also as a remedial action following out-of-limit or specification results. When chemicals are used to disinfect a water system, a validated rinsing/flushing procedure shall be subsequently performed. Additionally, water shall be tested after disinfection/regeneration. Chemical testing results shall be checked before the water system is returned to use and it shall be verified that microbiological/endotoxin results are within specification before batches manufactured using water from the system are considered for certification/release.

([11]) For the purposes of this Annex, 'water system' means a system for producing, storing and distributing water, usually compliant to a specific pharmacopeia grade (e.g. purified water and water for injection).

([12]) For the purposes of this Annex, 'dead leg' means a length of a non-circulating pipe (where fluid may remain static) that is greater than 3 internal pipe diameters.

V.2.7. Regular ongoing chemical and microbial monitoring of water systems shall be performed to ensure that the water continues to meet compendial requirements. Alert levels shall be set on the basis of the initial qualification data and thereafter be periodically reassessed on the basis of data obtained during subsequent re-qualifications, routine monitoring and investigations. Review of ongoing monitoring data shall be carried out to identify any adverse trend in the performance of the system. Sampling programmes shall be based on the qualification data and shall consider the potential worst case sampling locations ensuring that at least one representative sample of the water that is used for manufacturing processes is included every day as well as any other additional requirement that may be necessary in accordance with the contamination control strategy. To ensure that representative water samples are obtained for analysis on a regular basis, sampling programmes shall address all outlets and points of use at a specified interval.

V.2.8. Alert level excursions shall be documented and reviewed and include an investigation to determine whether the excursion is a single (isolated) event or if the results are indicative of an adverse trend or of the deterioration of the system. Each action limit excursion shall be investigated to determine the probable root cause(s) and any potential impact on the product quality and manufacturing processes.

V.2.9. Water for injection systems shall include continuous monitoring systems such as Total Organic Carbon (TOC) and conductivity, as these may give a better indication of overall system performance than discrete sampling. Sensor locations shall be based on risk.

V.2.10. Water used in production shall comply with the current monograph of the relevant Pharmacopeia.

V.3. **Steam used as a direct sterilising agent**

V.3.1. Feed water to a pure steam (clean steam) generator shall be appropriately purified. Pure steam generators shall be designed, qualified and operated in a manner to ensure that the quality of the steam produced meets the defined chemical and endotoxin levels.

V.3.2. Steam used as a direct sterilising agent shall be of a suitable quality and shall not contain additives at a level that could cause contamination to the product or the equipment. In the case of generators supplying pure steam for the direct sterilisation of materials or product-contact surfaces (e.g. porous hard-good autoclave loads), the steam condensate shall meet the requirements of the current monograph for water for injections of the relevant Pharmacopeia (microbial testing is not mandatory for steam condensate). A suitable sampling schedule shall also be in place to ensure that representative pure steam is obtained for analysis on a regular basis. Other aspects of the quality of the pure steam used for sterilisation shall be assessed periodically against validated parameters, including – unless otherwise justified – non-condensable gases, dryness value (dryness fraction) and superheat.

V.4. **Gases and vacuum systems**

V.4.1. Gases that come in direct contact with the product or primary container surfaces shall be of appropriate chemical, particulate and microbial quality. All relevant parameters, including oil and water content, shall be specified taking into account the use and type of the gas, the design of the gas generation system and, where applicable, comply with the current monograph of the relevant Pharmacopeia or the product quality requirement.

V.4.2. Gases used in aseptic processes shall be filtered through a sterilising grade filter ([13]) (with a nominal pore size of a maximum of 0,22 µm) at the point of use. Where the filter is used on a batch basis (e.g. for filtration of gas used for overlay of aseptically filled products) or as product vessel vent filter, the results of the integrity test shall be reviewed as part of the batch certification/release process. Any transfer pipework or tubing that is located after the final sterilising grade filter shall be sterilised. When gases are used in the process, microbial monitoring of the gas shall be performed periodically at the point of use.

V.4.3. Where backflow from vacuum or pressure systems poses a potential risk to the product, mechanism(s) shall be put in place to prevent backflow when the vacuum or pressure system is shut off.

V.5. **Heating and cooling and hydraulic systems**

V.5.1. Major items of equipment associated with hydraulic, heating and cooling systems shall, where possible, be located outside the filling room. Appropriate controls shall be implemented to contain any spillage or cross contamination associated with the system fluids.

V.5.2. Appropriate systems shall be put in place to ensure that any leak from these systems that could present a risk to the product are detected (e.g. an indication system for leakage).

SECTION VI

PERSONNEL

VI.1. The manufacturer shall ensure that there are sufficient personnel, suitably qualified, trained and experienced in the manufacture and testing of sterile products and any of the specific manufacturing technologies used in the site's manufacturing operations.

VI.2. Only the minimum number of personnel required shall be present in cleanrooms. The maximum number of operators in cleanrooms shall be determined and documented. During activities such as initial qualification and the aseptic process simulation the maximum number of operators that can be present in the cleanroom shall be duly considered so as not to compromise sterility assurance.

VI.3. All personnel including those performing cleaning, maintenance, monitoring and those that access cleanrooms shall receive regular training on aspects relevant to the manufacture of sterile products/aseptic manufacturing, including on gowning, the basic elements of microbiology and hygiene, with a specific focus on cleanroom practices, contamination control, aseptic techniques and the protection of sterile products (for those operators entering the grade B cleanrooms and/or intervening into grade A) and the potential consequences to the treated animals if the product is not sterile / fails to meet the required quality specifications. The level of training shall be based on the criticality of the function and the area where the personnel are working.

VI.4. Personnel accessing grade A and B areas shall be trained for aseptic gowning and aseptic behaviour. Compliance with aseptic gowning procedures is to be confirmed by means of an assessment prior to starting their functions and shall be periodically reassessed (at least annually). The assessment process shall involve both visual and microbial assessment (using monitoring locations such as gloved fingers, forearms, chest and hood (facemask/forehead).

([13]) For the purposes of this Annex, 'sterilising grade filter' means a filter that, when appropriately validated, is able to remove a defined microbial challenge from a fluid or gas producing a sterile effluent. Usually, such filters have a pore size equal or less than 0,22 µm.

VI.5. Unsupervised access to the grade A and grade B areas where aseptic operations are or will be conducted shall be restricted to appropriately qualified personnel, who have passed the gowning assessment and have participated in a successful aseptic process simulation.

Unqualified personnel shall not enter grade B cleanrooms or grade A in operation. If needed in exceptional cases, manufacturers shall establish written procedures outlining the process by which unqualified personnel can be brought into the grade B and A areas. An authorised person from the manufacturer shall supervise the unqualified personnel during their activities and assess the impact of these activities on the cleanliness of the area. Access by these persons shall be assessed and recorded.

VI.6. A process shall be put in place for the disqualification of personnel based on aspects of ongoing assessment and/or identification of an adverse trend from the personnel monitoring programme and/or after being implicated in a failed aseptic process simulation. Once disqualified, retraining and requalification shall be completed before permitting the operator to have any further involvement in aseptic practices. For operators entering grade B cleanrooms or performing intervention into grade A, it is advised that the requalification includes participation in a successful aseptic process simulation.

VI.7. High standards of personal hygiene and cleanness are essential. When a heath condition that may introduce an undue microbial hazard is declared by the relevant personnel or otherwise becomes apparent, access to the cleanroom shall be barred. Health conditions and actions to be taken with regard to personnel that can introduce an undue microbial hazard shall be documented in relevant procedures.

VI.8. Personnel involved in the handling/processing of materials of human/animal origin or of cultures of micro-organisms, other than those used in the current manufacturing process, or in other activities that may have a negative impact to quality (e.g. microbial contamination), shall not enter clean areas unless clearly defined and effective decontamination and entry procedures have been followed and documented.

VI.9. Wristwatches, make-up, jewellery, other personal items such as mobile phones and any other non-essential items shall not be allowed in clean areas. Electronic devices used in cleanrooms, e.g. mobile phones and tablets, that are supplied by the manufacturer solely for use in the cleanrooms, may be acceptable if suitably designed to permit cleaning and disinfection commensurate with the grade in which they are used. The use and disinfection of such equipment shall be included in the contamination control strategy.

VI.10. Cleanroom gowning and hand washing shall be done in accordance with written procedures designed to minimise the contamination of cleanroom clothing and/or the transfer of contaminants to the clean areas.

VI.11. 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 contamination. When the required type of clothing needs to protect the operator from the product, it shall also be ensured that the protection of the product from contamination is not compromised.

Garments shall be visually checked for cleanliness and integrity immediately prior to and after gowning. Gown integrity shall also be checked upon exit. Prior to the use of sterilised garments and eye coverings, it shall be checked that they have been subject to the sterilisation process, that they are within their specified hold time and that the packaging has not been tampered. Reusable garments (including eye coverings) are to be replaced if damage is identified, or at a set frequency that is determined during qualification studies. The qualification of garments shall consider any necessary garment testing requirements, including damage to garments that may not be identified by visual inspection alone.

VI.12. A description of clothing typically required for each cleanliness grade is given below:

(a) Grade B (including access/interventions into grade A):

— appropriate garments that are dedicated for use under a sterilised suit shall be worn before gowning;

— appropriately sterilised, non-powdered, rubber or plastic gloves shall be worn while donning the sterilised garments;

— sterile headgear shall enclose all hair (including facial hair) and, where separate from the rest of the gown, it shall be tucked into the neck of the sterile suit;

— a sterile facemask and sterile eye coverings (e.g. goggles) shall be worn to cover and enclose all facial skin and prevent the shedding of droplets and particles;

— appropriate sterilised footwear (e.g. over-boots) shall be worn;

— trouser legs shall be tucked inside the footwear and garment sleeves shall be tucked into a second pair of sterile gloves worn over the pair worn while donning the gown;

— the protective clothing shall minimise shedding of fibres or particles and retain particles shed by the body. The particle shedding and the particle retention efficiencies of the garments is to be assessed during the garment qualification;

— garments shall be packed and folded in such a way as to allow operators to don the gown without contacting the outer surface of the garment and to prevent the garment from touching the floor.

(b) Grade C:

— hair, beards and moustaches shall be covered;

— a single or two-piece trouser suit gathered at the wrists and with high neck and appropriately disinfected shoes or overshoes shall be worn; they shall minimise the shedding of fibres and particles;

— additional gowning, including gloves and facemask, may be required in grade C areas when performing activities that pose a risk of contamination.

(c) Grade D:

— hair, beards and moustaches shall be covered;

— a general protective suit and appropriately disinfected shoes or overshoes shall be worn;

— appropriate measures shall be taken to avoid any ingress of contaminants from outside the clean area;

— additional gowning including gloves and facemask may be required in grade D areas when performing activities that pose a risk of contamination.

VI.13. Cleanroom gowning shall take place in change rooms of an appropriate cleanliness grade to ensure that gown cleanliness is maintained. Outdoor clothing including socks (other than personal underwear) shall not be brought into changing rooms leading directly to grade B and C areas. In addition, a single or two-piece facility trouser suit, covering the full length of the arms and the legs, and facility socks covering the feet, shall be worn before entry to change rooms for grades B and C. Facility suits and socks shall not present a risk of contamination to the gowning area or processes.

VI.14. Every operator entering grade B or A areas shall gown into clean, sterilised protective garments (including eye coverings and masks) of an appropriate size at each entry. The maximum period for which the sterilised gown may be worn before replacement during a shift shall be defined as part of the garment qualification.

VI.15. Gloves shall be regularly disinfected during operations. Garments and gloves shall be changed immediately if they become damaged and present any risk of product contamination.

VI.16. Reusable clean area clothing shall be cleaned in a laundry facility adequately segregated from production operations, using a qualified process ensuring that the clothing is not damaged or contaminated by fibres or particles during the repeated laundry process. Laundry facilities used shall not introduce a risk of contamination or cross-contamination. After washing and before packing, garments shall be visually inspected for damage and visual cleanliness. The garment management processes shall be established as part of the garment qualification programme and shall include a maximum number of laundry and sterilisation cycles.

VI.17. Activities in clean areas that are not critical to the production processes shall be kept to a minimum, especially when aseptic operations are in progress. With a view to avoid excessive shedding of particles and organisms, movement of personnel shall be slow, controlled and methodical. Operators performing aseptic operations shall adhere to aseptic technique at all times to prevent changes in air currents that may introduce air of lower quality into the critical zone. In addition, movement adjacent to the critical zone shall be restricted and the obstruction of the path of the unidirectional (first air) airflow shall be avoided.

SECTION VII

PRODUCTION AND SPECIFIC TECHNOLOGIES

VII.1. **Terminally sterilised products** ([14])

VII.1.1. Preparation of components and materials shall be performed in at least a grade D cleanroom in order to limit the risk of microbial, endotoxin/pyrogen and particle contamination, so that the product is suitable for sterilisation. However, where the product is at a high or unusual risk of microbial contamination (e.g. the product actively supports microbial growth, the product must be held for long periods before filling or the product is not processed mostly in closed vessels), then preparation shall be carried out in at least a grade C environment. Preparation of ointments, creams, suspensions and emulsions shall also be carried out in at least a grade C environment before terminal sterilisation.

By way of derogation from the C grade environment as foreseen above, in exceptional cases, e.g. where the manufacturing process involves the generation of powder/dust that cannot be prevented by reasonable means, preparation of products to be terminally sterilised may be performed in a grade D environment. For the implementation of grade D in this exceptional case, the manufacturer shall be required to perform a risk assessment and apply suitable measures to ensure that there is no negative impact on the quality of the product. This shall be documented as part of the contamination control strategy.

VII.1.2. Primary packaging containers and components shall be cleaned using validated processes to ensure that particle, endotoxin/pyrogen and bioburden contamination is appropriately controlled.

([14]) For the purposes of this Annex, 'terminal sterilisation' means the application of a lethal sterilising agent or conditions to a product in its final container to achieve a predetermined sterility assurance level of $10^{\&\#x2013;6}$ or below (e.g. the theoretical probability of there being a single viable microorganism present on or in a sterilised unit is equal to or less than 1×10^{-6}).

VII.1.3. Filling of products for terminal sterilisation shall be carried out in at least a grade C environment. However, if the product is at an unusual risk of contamination from the environment (for example, the filling operation is slow, the containers are wide necked or are necessarily exposed for more than a few seconds before closing), the product shall be filled in grade A with at least a grade C background, unless additional measures to ensure the absence of a negative impact to the quality of the product are implemented, in which case the filling operation shall take place – as a minimum – in a grade D environment.

VII.1.4. To reduce the level of bioburden and particles prior to filling into the final product container, processing of the bulk solution shall include, where possible, a filtration step with a microorganism retaining filter and a maximum time between preparation and filling shall be set.

VII.1.5. Examples of operations to be carried out in the various grades are given in Table 3.

Table 3

Examples of operations and grades for terminally sterilised preparation and processing operations

Grade A	Filling of products when unusual/high risk of microbial contamination, unless a lower grade can be justified in accordance with Section VII.1.3.
Grade C	Preparation of solutions when unusual/high risk of microbial contamination, unless grade D can be justified in accordance with the second subparagraph of Section VII.1.1. Filling of products (other than when grade A is required), unless grade D can be justified in accordance with Section VII.1.3.
Grade D	Preparation of solutions and components for subsequent filling.

VII.2. **Aseptic preparation and processing**

VII.2.1. The aseptic process shall be documented as part of the contamination control strategy. Specifically, the risks associated with the aseptic process, and any associated requirements, shall be identified, assessed and appropriate controls shall be identified including the acceptance criteria for these controls, requirements for monitoring and the review of their effectiveness. Methods and procedures to control those risks shall be clearly described and implemented. Accepted residual risks shall be formally documented.

VII.2.2. Precautions to minimise microbial, endotoxin/pyrogenic and particle contamination in the site shall be described in the contamination control strategy and shall be implemented during the preparation of the aseptic environment, during all processing stages (including the stages before and after bulk product sterilisation), and until the product is sealed in its final container. The presence of materials liable to generate particles and fibres shall be minimised in cleanrooms.

VII.2.3. Where possible, the use of equipment such as RABS, isolators or other systems shall be used in order to reduce the need for critical interventions ([15]) into grade A and to minimise the risk of contamination. Robotics and automation of processes may also be considered to eliminate direct human critical interventions (e.g. dry heat tunnel, automated lyophilizer loading, sterilisation in place).

VII.2.4. Examples of operations to be carried out in the various environmental grades are given in Table 4.

([15]) For the purposes of this Annex 'critical intervention' means an intervention into the critical zone.

Table 4

Examples of operations and grades for aseptic preparation and processing operations

Grade A	— Aseptic assembly of filling equipment. — Connections made under aseptic conditions (where sterilised product contact surfaces are exposed) that are post the final sterilising grade filter. These connections shall be sterilised by steam-in-place whenever possible. — Aseptic compounding and mixing. — Replenishment of sterile bulk product, containers and closures. — Removal and cooling of unprotected (e.g. with no packaging) items from sterilisers. — Staging and conveying of sterile primary packaging components in the aseptic filling line while not wrapped. — Aseptic filling, sealing of containers such as ampoules, vial closure, transfer of open or partially stoppered vials. — Loading of a lyophilizer.
Grade B	— Background support for grade A (when not in an isolator). — Conveying or staging, while protected from the surrounding environment, of equipment, components and ancillary items for introduction into grade A.
Grade C	— Preparation of solutions to be filtered including sampling and dispensing.
Grade D	— Cleaning of equipment. — Handling of components, equipment and accessories after cleaning. — Assembly under HEPA filtered airflow of cleaned components, equipment and accessories prior to sterilisation. — Assembly of closed and sterilised single use systems using intrinsic sterile connection devices ([1])

([1]) For the purposes of this Annex, 'intrinsic sterile connection device' means a device that reduces the risk of contamination during the connection process; it can be mechanical or fusion sealing.

VII.2.5. For products where the final formulation cannot be filtered, the following measures shall be considered as appropriate:

— all product and component contact equipment shall be sterilised prior to use;

— all raw materials or intermediates shall be sterilised and aseptically added;

— bulk solutions or intermediates shall be sterilised.

VII.2.6. The unwrapping, assembly and preparation of sterilised equipment, components and ancillary items with direct or indirect product contact shall be treated as an aseptic process and performed in grade A with a grade B background. The filling line set-up and filling of the product shall be treated as an aseptic process and performed in grade A with a grade B background. Where an isolator is used, the background shall be in accordance with Section III.3.3 of this Annex.

VII.2.7. Preparation and filling of products such as ointments, creams, suspensions and emulsions shall be performed in grade A with a grade B background when the product and components are exposed to the environment and the product is not subsequently filtered (via a sterilising grade filter) or terminally sterilised. Where an isolator or RABS is used, the background shall be in accordance with Section III.3.3 of this Annex.

VII.2.8. Aseptic connections shall be performed in grade A with a grade B background unless subsequently sterilised in place or conducted with intrinsic sterile connection devices that minimise any potential contamination from the immediate environment. Intrinsic sterile connection devices shall be designed to mitigate the risk of contamination. Where an isolator is used, the background shall be in accordance with Section III.3.3 of this Annex.

Aseptic connections shall be appropriately assessed and their effectiveness verified.

VII.2.9. Aseptic manipulations (including non-intrinsic sterile connection devices) shall be minimised through the use of engineering design solutions such as preassembled and sterilised equipment. Whenever feasible, product contact piping and equipment shall be pre-assembled and sterilised in place.

VII.2.10. A list of allowed and qualified interventions, both inherent ([16]) and corrective, that may occur during production shall be set. The type of inherent and corrective interventions, and how to perform them, shall be first evaluated in accordance with quality risk management principles and the outcome of the aseptic process simulation and be kept up to date.

Interventions shall be carefully designed to ensure that the risk of contamination of the environment, process and product is effectively minimised, including consideration of any impact on air-flows and critical surfaces ([17]) and products. Engineering solutions shall be used whenever possible to minimise incursion by operators during the intervention. Aseptic technique shall be observed at all times, including the use of sterile tools for manipulations.

Non-authorised/non-qualified interventions shall only be performed in exceptional circumstances, with due consideration of the risks associated with the intervention and with the authorisation of the quality unit. Moreover, the details of the intervention conducted shall be recorded, be thoroughly assessed by the quality department and be duly considered during batch release.

VII.2.11. Interventions and stoppages shall be recorded in the batch record. Each line stoppage or intervention shall be sufficiently documented in batch records with the associated time, duration of the event, and operators involved.

VII.2.12. The duration of each aspect of aseptic preparation and processing shall be minimised as far as possible and validated maximum times shall be set including:

— the holding time between equipment, component, and container cleaning, drying and sterilisation;

— the holding time for the sterilised equipment, components, and containers before use and during filling/assembly;

— the holding time for a decontaminated environment, such as the RABS or isolator before use;

— the time between the start of the preparation of a product and its sterilisation or filtration through a microorganism-retaining filter (if applicable), through to the end of the aseptic filling process. A maximum permissible time for each product shall be set taking into account its composition and the method of storage;

— the holding time for the sterilised product prior to filling;

— the aseptic processing time; and

— the filling time.

([16]) For the purposes of this Annex, 'inherent interventions' means interventions that are an integral part of the aseptic process and required for either set-up, routine operation or monitoring (e.g. aseptic assembly, container replenishment, environmental sampling) and which are foreseen in relevant standard operating procedures/work instructions.

([17]) For the purposes of this Annex, 'critical surface' means a surface that may come directly in contact with, or otherwise directly affect the sterility/absence of contamination of, a product or its containers or closures.

VII.2.13. Aseptic operations (including aseptic process simulation) shall be monitored on a regular basis by personnel with specific expertise in aseptic processing to verify the correct performance of operations, including operator's behaviour in the cleanroom, and to address inappropriate practices if detected.

VII.3. **Finishing activities**

VII.3.1. Open primary packaging containers shall be maintained under grade A conditions with the appropriate background for the technology as described in Section III.3.3. For vials that are partially stoppered or prefilled syringes, the additional considerations as set forth in Section VII.7.6 apply also.

VII.3.2. Final containers shall be closed by appropriately validated methods.

VII.3.3. Where final containers are closed by fusion, e.g. Blow-Fill-Seal, Form-Fill-Seal, small and large volume parenteral bags, glass or plastic ampoules, the critical parameters and variables that affect seal integrity shall be set and be effectively controlled and monitored during operations.

Glass ampoules, Blow-Fill-Seal units and small volume containers (≤ 100 ml) closed by fusion shall be subject to 100 % integrity testing using validated methods. For large volume containers (> 100 ml) closed by fusion, reduced sampling may be acceptable where scientifically justified and based on data demonstrating the consistency of the existing process and a high level of process control. Visual inspection is not an acceptable integrity test method.

VII.3.4. Samples of products using systems other than fusion shall be taken and checked for integrity using validated methods. The frequency of testing shall be based on the knowledge and experience of the container and closure systems being used. The sampling plan shall be scientifically justified and be based on information such as the supplier's management, the packaging component specifications and the process knowledge.

VII.3.5. Containers sealed under vacuum shall be tested for maintenance of vacuum after an appropriate pre-determined period prior to certification/release and during shelf life.

VII.3.6. The container closure integrity validation shall take into consideration any transportation or shipping requirements that may negatively impact the integrity of the container (e.g. by decompression or extreme temperatures).

VII.3.7. Where the equipment used to crimp vial caps can generate large quantities of non-viable particle, measures shall be taken to prevent particle contamination, such as locating the equipment at a physically separate station equipped with adequate air extraction.

VII.3.8. Vial capping of aseptically filled products may be undertaken as an aseptic process using sterilised caps or as a clean process outside the aseptic processing area. Where the latter approach is adopted, vials shall be protected by grade A conditions up to the point of leaving the aseptic processing area, and thereafter stoppered vials shall be protected with a grade A air supply ([18]) until the cap has been crimped. The supporting background environment of grade A air supply shall meet at least grade D requirements.

Where capping is a manual process, it shall be performed under grade A conditions either in an appropriately designed isolator or in grade A with a grade B background.

([18]) For the purposes of this Annex, 'grade A air supply' means air that has passed through a filter qualified as capable of producing grade A total particle quality air, but where there is no requirement to perform continuous total particle monitoring or meet grade A viable monitoring limits.

VII.3.9. Where capping of an aseptically filled product is conducted as a clean process with grade A air supply protection, vials with missing or displaced stoppers shall be rejected prior to capping. Appropriately qualified, automated methods for stopper height detection shall be in place.

VII.3.10. Where human intervention is required at the capping station, appropriate technological and organisational measures shall be used to prevent direct contact with the vials and to minimise contamination. RABS and isolators may be beneficial in assuring the required conditions.

VII.3.11. All filled containers of parenteral products shall be inspected individually for extraneous contamination or other defects. A defect classification including the criticality thereof shall be established during qualification and based on risk and historical knowledge. Factors to consider include, but are not limited to, the potential impact of the defect to the treated animal and the route of administration. A defect library capturing all known types of defects shall be established and be used for the training of production and quality assurance personnel.

Critical defects shall be identified upfront and not during subsequent sampling and inspection of acceptable containers. Any critical defect identified subsequently shall trigger an investigation as it indicates a possible failure of the original inspection process.

Batches with unusual levels of defects, when compared with routine defect numbers for the process (based on routine and trend data) shall be investigated.

VII.3.12. When inspections are performed manually, suitable and controlled conditions of illumination and background shall be ensured. Inspection rates shall be appropriately controlled and qualified. Operators performing the inspection shall undergo visual inspection qualification (whilst wearing corrective lenses, if these are normally worn) at least annually. The qualification shall be performed using appropriate samples from the manufacturer's defect library sets and taking into consideration worst case scenarios (e.g. inspection time, line speed where the product is transferred to the operator by a conveyor system, container size or fatigue) and shall also include eyesight checks. Work conditions shall be adequate to reduce elements of distraction and, in order to minimise operator fatigue, frequent breaks of an appropriate duration shall be taken.

VII.3.13. Where automated methods of inspection are used, the process shall be validated to detect known defects (which may impact product quality or safety). The performance of the automated methods shall be equal to, or better than, manual inspection methods. The performance of the equipment shall be challenged using representative defects prior to start up and at regular intervals throughout the batch.

VII.3.14. Results of the inspection shall be recorded and defect types and numbers trended. Reject levels for the various defect types shall also be trended based on statistical principles. When adverse trends are observed, the impact on batches on the market shall be assessed.

VII.4. **Sterilisation**

VII.4.1. *General requirements*

VII.4.1.1. Where possible, finished products shall be terminally sterilised, using a validated and controlled sterilisation process, as this provides a greater assurance of sterility than a validated and controlled sterile filtration process and/or aseptic processing. Where it is not possible for a product to undergo terminal sterilisation, consideration shall be given to using post-aseptic processing terminal heat treatment ([19]), combined with aseptic process to give improved sterility assurance.

([19]) For the purposes of this Annex, 'post-aseptic processing terminal heat treatment' means a terminal moist heat process employed after aseptic processing which has been demonstrated to provide a sterility assurance level ≤ 10^{-6} but where the requirements of steam sterilisation (for example, F_0 ≥ 8 min) are not fulfilled. This may also be beneficial in the destruction of viruses that may not be removed through filtration.

VII.4.1.2. The selection, design and location of the equipment and cycle/programme used for the sterilisation shall be based on scientific principles and data which demonstrate repeatability and reliability of the sterilisation process. All parameters shall be defined and critical parameters shall be controlled, monitored and recorded.

VII.4.1.3. All sterilisation processes shall be validated. Validation studies shall take into account the product composition, the storage conditions and the maximum time between the start of the preparation of a product or material to be sterilised and its sterilisation. Before any sterilisation process is implemented, its suitability for the product and the equipment, and its efficacy in consistently achieving the desired sterilising conditions in all parts of each type of load to be processed shall be validated by physical measurements and, where appropriate, by biological indicators ([20]). For an effective sterilisation, the process shall be designed to ensure that the whole of the product, as well as the surfaces of the equipment and components are subject to the required treatment.

VII.4.1.4. Particular attention shall be paid when the adopted product sterilisation method is not described in the current edition of the Pharmacopoeia, or when it is used for a product that is not a simple aqueous solution. Where possible, heat sterilisation shall be the method of choice.

VII.4.1.5. Validated loading patterns shall be established for all sterilisation processes and load patterns shall be subject to periodic revalidation. Maximum and minimum loads shall also be addressed as part of the overall load validation strategy.

VII.4.1.6. The validity of the sterilising process shall be reviewed at scheduled intervals based on risk. Heat sterilisation cycles shall be revalidated at least annually for load patterns that are considered worst case. Other load patterns shall be validated at an appropriate frequency that shall be justified as part of the contamination control strategy.

VII.4.1.7. Routine operating parameters shall be established and adhered to for all sterilisation processes, e.g. physical parameters and loading patterns.

VII.4.1.8. Mechanisms shall be put in place to detect a sterilisation cycle that does not conform to the validated parameters. Any failed sterilisation or any sterilisation that deviated from the validated process (e.g. have longer or shorter phases such as heating cycles) shall be investigated.

VII.4.1.9. Suitable biological indicators placed at appropriate locations shall be considered as an additional method to support the validation of the sterilisation process. Biological indicators shall be stored and used according to the manufacturer's instructions. Where biological indicators are used to support the validation and/or to monitor a sterilisation process (e.g. with ethylene oxide), positive controls shall be tested for each sterilisation cycle. Moreover, if biological indicators are used, strict precautions shall be taken to avoid transferring microbial contamination to the manufacturing or other testing processes. Biological indicator results in isolation cannot be used to override other critical parameters and process design elements.

VII.4.1.10. The reliability of biological indicators is important. Therefore, suppliers shall be qualified and transportation and storage conditions shall be controlled to ensure that the quality thereof is not compromised. Prior to the use of a new batch/lot of biological indicators, the population, purity and identity of the indicator organism of the batch/lot shall be verified. For other critical parameters, e.g. D-value ([21]), Z-value ([22]), the batch certificate provided by the qualified supplier may normally be used.

([20]) For the purposes of this Annex, 'biological indicators' means a population of microorganisms inoculated onto a suitable medium (e.g. solution, container or closure) and placed within a steriliser or load or room locations to determine the sterilisation or disinfection cycle efficacy of a physical or chemical process. The challenge microorganism shall be selected and validated based upon its resistance to the given process. Incoming lot D-value, microbiological count and purity define the quality of the biological indicator.

([21]) For the purposes of this Annex, 'D value' means the value of a parameter of sterilisation (duration or absorbed dose) required to reduce the number of viable organisms to 10 percent of the original number.

([22]) For the purposes of this Annex, 'Z value' means the temperature difference that leads to a 10-fold change in the D-value of the biological indicators.

VII.4.1.11. Products, equipment and components that have not been subject to the sterilisation process shall be clearly distinguished from those that have through appropriate means. Equipment such as baskets or trays used to carry products, other items of equipment and/or components shall be clearly labelled (or electronically tracked) with the product name and batch number and an indication of whether or not it has been sterilised. Indicators such as autoclave tape or irradiation indicators may be used, where appropriate, to indicate whether or not a batch (or sub-batch material, component, equipment) has passed through a sterilisation process. It is noted that these indicators show only that the sterilisation process has occurred but are not indicative of product sterility or achievement of the required sterility assurance level.

VII.4.1.12. Sterilisation records shall be available for each sterilisation run. Each cycle shall have a unique identifier. These records shall be reviewed and considered as part of the batch certification/release procedure.

VII.4.1.13. Where required, materials, equipment and components shall be sterilised by validated methods appropriate to the specific material. Suitable protection after sterilisation shall be provided to prevent recontamination.

If sterilised items are not used immediately after sterilisation, these shall be stored using appropriately sealed packaging and a maximum hold time shall be established. Where justified, components that have been packaged with multiple sterile packaging layers need not be stored in a cleanroom if the integrity and configuration of the sterile pack allows the items to be readily disinfected during transfer by operators into grade A (e.g. by the use of multiple sterile coverings that can be removed at each transfer from lower to higher grade). Where protection is achieved by containment in sealed packaging, that packaging process shall take place prior to sterilisation.

VII.4.1.14. The transfer into grade A of sterilised materials, equipment, components and ancillary items in sealed packaging shall be done using appropriate validated methods (for example, airlocks or pass-through hatches) with accompanying disinfection of the exterior of the sealed packaging. The use of rapid transfer port technology ([23]) may also be considered. The methods used shall be demonstrated to effectively control the potential risk of contamination of the grade A and grade B areas and, likewise, the disinfection procedure shall be demonstrated to be effective in reducing any contamination on the packaging to acceptable levels for entry of the item into the grade B and grade A areas.

VII.4.1.15. Where materials, equipment, components and ancillary items are sterilised in sealed packaging or containers, the packaging shall be qualified for minimizing the risk of particulate, microbial, endotoxin/pyrogen or chemical contamination, and for compatibility with the selected sterilisation method. The packaging sealing process shall be validated. The validation shall consider the integrity of the sterile protective barrier system, the maximum hold time before sterilisation and the maximum shelf life assigned to the sterilised items. The integrity of the sterile protective barrier system for each of the sterilised items shall be checked prior to use.

VII.4.1.16. For materials, equipment, components and ancillary items that are not a direct or indirect product contact part and are necessary for aseptic processing but cannot be sterilised, an effective and validated disinfection and transfer process shall be put in place. These items, once disinfected, shall be protected to prevent recontamination. These items, as well as other items that are potential routes of contamination, shall be included in the environmental monitoring programme.

VII.4.2. *Sterilisation by heat*

VII.4.2.1. Each heat sterilisation cycle shall be recorded either electronically or by hardcopy, using equipment with suitable accuracy and precision. The system used shall have safeguards and/or redundancy in its control and monitoring instrumentation to detect a cycle that is not conforming to the validated cycle parameter requirements and to abort or fail such cycle (e.g. by the use of duplex/double probes connected to independent control and monitoring systems).

([23]) For the purposes of this Annex, 'rapid transfer system/port' means a system used for the transfer of items into RABS or isolators that minimises the risk to the critical zone. An example would be a rapid transfer container with an alpha/beta port.

VII.4.2.2. The position of the temperature probes used for controlling and/or recording shall be determined during the validation having regard to the system's design and with a view to correctly record and represent routine cycle conditions. Validation studies shall demonstrate the suitability of the system's control and recording probe locations, and shall include the verification of the function and location of these probes by the use of an independent monitoring probe located at the same position during validation.

VII.4.2.3. The entire load shall reach the required temperature before the measurement of the sterilising time-period starts. For sterilisation cycles controlled by using a reference probe within the load, specific consideration shall be given to ensuring that the load probe temperature is controlled within a defined temperature range prior to the start of the cycle.

VII.4.2.4. After completion of the high temperature phase of a heat sterilisation cycle, precautions shall be taken against contamination of a sterilised load during cooling. Any cooling liquid or gas that comes into contact with the product or sterilised material shall be sterilised. Additional requirements applicable where parametric release has been authorised are laid down in Annex IX.

VII.4.3. *Moist heat sterilisation*

VII.4.3.1. Moist heat sterilisation can be achieved using steam (direct or indirect contact) or with other systems such as superheated water systems (cascade or immersion cycles) that can be used for containers that may be damaged by other cycle designs (e.g. Blow-Fill-Seal containers, plastic bags).

VII.4.3.2. The items to be sterilised, other than products in sealed containers, shall be dry and packaged in a protective barrier system that allows removal of air and penetration of steam and prevents recontamination after sterilisation. All loaded items shall be dry upon removal from the steriliser. Load dryness shall be confirmed by visual inspection as a part of the sterilisation process acceptance.

VII.4.3.3. For porous cycles (hard goods), time, temperature and pressure shall be used to monitor the process and be recorded. Each sterilised item shall be inspected for damage, packaging material integrity and moisture upon removal from the autoclave. Any item found not to be fit for purpose shall be removed from the manufacturing area and an investigation shall be performed.

VII.4.3.4. For autoclaves capable of performing prevacuum sterilisation cycles, the temperature shall be recorded at the chamber drain throughout the sterilisation period. Load probes may also be used where appropriate, but the controlling system shall remain related to the load validation. For steam in place systems, the temperature shall be recorded at appropriate condensate drain locations throughout the sterilisation period. Validation of porous cycles shall include a calculation of equilibration time ([24]), exposure time, correlation of pressure and temperature and the minimum/maximum temperature range during the exposure. Validation of fluid cycles shall include temperature, time and/or F_0 value ([25]). Critical processing parameters shall be subject to defined limits (including appropriate tolerances) and be confirmed as part of the sterilisation validation and of the routine cycle acceptance criteria.

VII.4.3.5. Leak tests on the steriliser shall be carried out periodically (normally weekly) when a vacuum phase is part of the cycle, and when the system is returned – post-sterilisation – to a pressure lower than the environment surrounding the steriliser.

([24]) For the purposes of this Annex, 'equilibration time' means the time that elapses between the attainment of the sterilisation temperature at the refence measurement point and the attainment of the sterilisation temperature at all points within the load.

([25]) For the purposes of this Annex, 'F_0 value' means the lethality expressed in terms of the equivalent time in minutes at the reference temperature delivered by the process to the sterilisation load, with reference to micro-organisms possessing the relevant theoretical z-value.

VII.4.3.6. When the sterilisation process includes air purging (e.g. porous autoclave loads, lyophilizer chambers), there shall be adequate assurance of air removal prior to and during sterilisation. For autoclaves, this shall include an air removal test cycle (normally performed on a daily basis) or the use of an air detector system. Loads to be sterilised shall be designed to support effective air removal and be free draining to prevent the build-up of condensate.

VII.4.3.7. Distortion and damage of non-rigid containers that are terminally sterilised, such as containers produced by Blow-Fill-Seal or Form-Fill-Seal technologies, shall be prevented by appropriate cycle design and control (for instance setting correct pressure, heating and cooling rates and loading patterns).

VII.4.3.8. Where steam in place systems are used for sterilisation (e.g. for fixed pipework, vessels and lyophilizer chambers), the system shall be appropriately designed and validated to ensure that all parts of the system are subject to the required treatment. The system shall be monitored for temperature, pressure and time at appropriate locations during routine use to ensure all areas are effectively and reproducibly sterilised. These locations shall be demonstrated as being representative of, and correlated with, the slowest to heat locations during initial and routine validation. Once a system has been sterilised by steam in place, it shall remain integral and, where required by the relevant operations, maintained under positive pressure or otherwise equipped with a sterilising vent filter prior to use.

VII.4.3.9. In fluids load cycles where superheated water is used as the heat transfer medium, the heated water shall consistently reach all of the required contact points. Initial qualification studies shall include temperature mapping of the entire load. There shall be routine checks on the equipment to ensure that nozzles (where the water is introduced) are not blocked and drains remain free from debris.

VII.4.3.10. Validation of the sterilisation of fluids loads in a superheated water autoclave shall include temperature mapping of the entire load and heat penetration and reproducibility studies. All parts of the load shall heat up uniformly and achieve the desired temperature for the specified time. Routine temperature monitoring probes shall be correlated to the worst case positions identified during the qualification process.

VII.4.4. *Dry heat sterilisation*

VII.4.4.1. Dry heat sterilisation utilizes high temperatures of air or gas to sterilise a product or an article. It is of particular use in the thermal removal of difficult-to-eliminate thermally robust contaminants such as endotoxin/pyrogen. The combination of time and temperature to which the product, components or equipment are exposed shall produce an adequate and reproducible level of lethality and/or endotoxin/pyrogen inactivation/removal when operated routinely within the established limits. The process may be operated in an oven or in a continuous tunnel process, e.g. for sterilisation and depyrogenation of glass containers.

VII.4.4.2. Dry heat sterilisation/depyrogenation tunnels shall be configured to ensure that airflow protects the integrity and performance of the grade A sterilising zone by maintaining appropriate pressure differentials and airflow through the tunnel. Air pressure difference profiles shall be assessed. The impact of any airflow change shall be assessed to ensure that the heating profile is maintained. All air supplied to the tunnel shall pass through at least a HEPA filter and periodic tests (at least biannually) shall be performed to demonstrate air filter integrity. In addition, any tunnel parts that come into contact with sterilised components shall be appropriately sterilised or disinfected.

Critical process parameters that shall be addressed during validation and/or routine processing include, but are not limited to:

— belt speed or dwell time within the sterilising zone;

— temperature – minimum and maximum temperatures;

— heat penetration of the material/article;

— heat distribution/uniformity;

— airflows determined by air pressure difference profiles correlated with the heat distribution and penetration studies.

VII.4.4.3. When a thermal process is used as part of the depyrogenation process for any component or product contact equipment/material, validation studies shall be performed to demonstrate that the process provides a suitable F_h value ([26]) and results in a minimum 3 $\log_{10}$ reduction in endotoxin concentration. When this is attained, there is no additional requirement to demonstrate sterilisation.

VII.4.4.4. During validation, containers spiked with endotoxin shall be used and a full reconciliation performed. Containers shall be representative of the materials normally processed (in respect to composition of the packaging materials, porosity, dimensions, nominal volume). Endotoxin quantification and recovery efficiency shall also be demonstrated.

VII.4.4.5. Dry heat ovens are typically employed to sterilise or depyrogenate primary packaging components, starting materials or active substances but may be used for other processes. They shall be maintained at a positive pressure relative to lower grade clean areas throughout the sterilisation and post sterilisation hold process unless the integrity of the packaging is maintained. All air entering the oven shall pass through a HEPA filter. Critical process parameters that shall be considered in qualification and/or routine processing include, but are not limited to:

— temperature;

— exposure period/time;

— chamber pressure (for maintenance of over pressure);

— air speed;

— air quality within the oven;

— heat penetration of material/article (slow to heat spots);

— heat distribution/uniformity;

— load pattern and configuration of articles to be sterilised/depyrogenated including minimum and maximum loads.

VII.4.5. *Sterilisation by radiation*

VII.4.5.1. Sterilisation by radiation is used mainly for the sterilisation of heat sensitive materials and products. Ultraviolet irradiation is not an acceptable method of sterilisation. Specific requirements related to the use of ionising radiation sterilisation are laid down in Annex VII.

VII.4.5.2. Validation procedures shall ensure that the effects of variation in density of the product and packages are considered.

VII.4.6. *Sterilisation with ethylene oxide*

VII.4.6.1. This method shall only be used when no other method is practicable. During process validation, it shall be shown that there is no damaging effect on the product and that the conditions and time allowed for degassing are suitable to attain a reduction of any residual ethylene oxide gas and reaction products to defined acceptable limits for the given product or material.

([26]) For the purposes of this Annex, 'F_h value' means the lethality expressed in terms of the equivalent time in minutes at the reference temperature delivered by the process to the sterilisation load, with reference to micro-organisms possessing the relevant theoretical z-value.

VII.4.6.2. Direct contact between the gas and microbial cells is essential. Therefore, precautions shall be taken to avoid the presence of organisms likely to be enclosed in material such as crystals or dried protein. The nature, porosity and quantity of packaging materials can also significantly affect the process.

VII.4.6.3. Before exposure to the gas, materials shall be brought into equilibrium with the humidity and temperature required by the process. Where steam is used to condition the load for sterilisation, it shall be of an appropriate quality. The time required for this operation shall be balanced against the need to minimise the time before sterilisation.

VII.4.6.4. Each sterilisation cycle shall be monitored with suitable biological indicators, using the appropriate number of test units distributed throughout the load at defined locations that have been shown to be worst case locations during validation.

VII.4.6.5. Critical process parameters to be considered as part of the sterilisation process validation and routine monitoring include, but are not limited to:

— ethylene oxide gas concentration;

— pressure;

— amount of ethylene oxide gas used;

— relative humidity;

— temperature;

— exposure time.

VII.4.6.6. After sterilisation, the load shall be aerated to allow ethylene oxide gas and/or its reaction products to desorb from the packaged product to predetermined levels. Aeration can occur within a steriliser chamber and/or in a separate aeration chamber or aeration room. The aeration phase shall be validated as part of the overall ethylene oxide sterilisation process validation.

VII.4.7. *Filter sterilisation of products that cannot be sterilised in their final container*

VII.4.7.1 Solutions or liquids that cannot be sterilised in their final container shall be sterilised by filtration through a sterile sterilising grade filter (with a nominal pore size of a maximum of 0,22 μm that has been appropriately validated to obtain a sterile filtrate) and subsequently aseptically filled into a previously sterilised container. The selection of the filter used shall ensure that it is compatible with the product and in compliance with the marketing authorisation.

VII.4.7.2. Suitable bioburden reduction prefilters and/or sterilising grade filters may be used at multiple points during the manufacturing process to ensure a low and controlled bioburden of the liquid prior to the final sterilising filter. Due to the potential additional risks of a sterile filtration process, as compared with other sterilisation processes, an additional filtration through a sterile sterilising grade filter, as close to the point of fill as possible, shall be considered as part of an overall contamination control strategy.

VII.4.7.3. The selection of components for the filtration system and their interconnection and arrangement within the filtration system, including pre-filters, shall be based on the critical quality attributes of the product, justified and documented. The filtration system shall minimise the generation of fibres and particles, not cause or contribute to unacceptable levels of impurities, or possess characteristics that otherwise alter the quality or the efficacy of the product. Similarly, the filter characteristics shall be compatible with the fluid and not be adversely affected by the product to be filtered. Adsorption of product components and extraction/leaching of filter components shall be evaluated.

VII.4.7.4. The filtration system shall be designed to:

— allow operation within validated process parameters;

— maintain the sterility of the filtrate;

— minimise the number of aseptic connections required between the final sterilising grade filter and the final filling of the product;

— allow cleaning procedures to be conducted as necessary;

— allow sterilisation procedures, including sterilisation in place, to be conducted as necessary;

— permit in-place integrity testing of the 0,22 µm final sterilising grade filter, preferably as a closed system, both prior to and following filtration as necessary. In-place integrity testing methods shall be preferably used to avoid any adverse impact on the quality of the product.

VII.4.7.5. Sterile filtration of liquids shall be validated in accordance with relevant Pharmacopeia requirements. Validation may be grouped by different strengths or variations of a product but shall be done under worst-case conditions. The rationale for grouping shall be justified and documented.

VII.4.7.6. Wherever possible during filter validation, the product to be filtered shall be used for bacterial retention testing ([27]) of the sterilising grade filter. Where the product to be filtered is not suitable for use in bacterial retention testing, a suitable surrogate product shall be justified for use in the test. The challenge organism used in the bacterial retention test shall also be justified.

VII.4.7.7. Filtration parameters that shall be considered and established during validation include, but are not limited to:

(a) The wetting fluid used for filter integrity testing:

— it shall be based on the filter manufacturer's recommendation or the fluid to be filtered. The appropriate integrity test value specification shall be established;

— if the system is flushed or integrity tested *in situ* with a fluid other than the product, appropriate actions shall be taken to avoid any deleterious effect on product quality.

(b) Filtration process conditions including:

— fluid pre-filtration holding time and effect on bioburden;

— filter conditioning, with fluid if necessary;

— maximum filtration time/total time that the filter is in contact with the fluid;

— maximum operating pressure;

— flow rate;

— maximum filtration volume;

— temperature;

— the time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter.

([27]) For the purposes of this Annex, 'bacterial retention testing' means a test performed to validate that a filter can remove bacteria from a gas or liquid. The test is usually performed using a standard organism, such as *Brevundimonas diminuta* at a minimum concentration of 10^7 Colony Forming Units/cm^2.

VII.4.7.8. Routine process controls shall be implemented to ensure adherence to validated filtration parameters. Results of critical process parameters shall be included in the batch record, including – but not limited to – the minimum time taken to filter a known volume of bulk solution and pressure difference across the filter. Any significant difference from critical parameters during manufacturing shall be documented and investigated.

VII.4.7.9. The integrity of the sterilised filter assembly shall be verified by integrity testing before use (pre-use post sterilisation integrity test or PUPSIT), to check for damage and loss of integrity caused by the filter preparation prior to use. However, it is recognised that PUPSIT may not always be possible after sterilisation due to process constraints (e.g. the filtration of very small volumes of solution). In these cases, an alternative approach may be taken providing that a thorough risk assessment has been performed and compliance is achieved by the implementation of appropriate controls to mitigate any risk of a non-integral filtration system.

Points to consider in such a risk assessment shall include but are not limited to:

— in-depth knowledge and control of the filter sterilisation process to ensure that the potential for damage to the filter is minimised;

— in-depth knowledge and control of the supply chain including contract sterilisation facilities, defined transport conditions and packaging of the sterilised filter (to prevent damage to the filter during transportation and storage);

— in-depth process knowledge such as the specific product type, including particle burden and whether there exists any risk of impact on filter integrity values (such as the potential to alter integrity-testing values and therefore prevent the detection of a non-integral filter during a post-use filter integrity test), and the implementation of pre-filtration or processing steps prior to the final sterilising grade filter that would remove particle burden prior to the sterile filtration.

In addition, a sterilising grade filter that is used to sterilise a fluid shall be subject to a non-destructive integrity test post-use prior to removal of the filter from its housing. The integrity test process shall be validated and test results shall correlate to the microbial retention capability of the filter established during validation. Examples of tests that are used include bubble point, diffusive flow, water intrusion or pressure hold test.

VII.4.7.10. The integrity of critical sterile gas and air vent filters (that are directly linked to the sterility of the product) shall be verified by testing after use, with the filter remaining in the filter assembly or housing.

VII.4.7.11. The integrity of non-critical air or gas vent filters shall be confirmed and recorded at appropriate intervals. Where gas filters are in place for extended periods, integrity testing shall be carried out at installation and prior to replacement. The maximum duration of use shall be specified and monitored based on risk (e.g. considering the maximum number of uses and heat treatment/sterilisation cycles permitted as applicable).

VII.4.7.12. For gas filtration, unintended moistening or wetting of the filter or filter equipment shall be avoided.

VII.4.7.13. If the sterilising filtration process has been validated as a system consisting of multiple filters to achieve the sterility for a given fluid, the filtration system is considered to be a single sterilising unit and all filters within the system shall satisfactorily pass integrity testing after use.

VII.4.7.14. In a redundant filtration system (where a second redundant sterilising grade filter is present as a backup but the sterilising process is validated as only requiring one filter), post-use integrity test of the primary sterilising grade filter shall be performed and, if demonstrated to be integral, a post-use integrity test of the redundant (backup) filter is not necessary. However, in the event of a failure of the post-use integrity test on the primary filter, post-use integrity test on the secondary (redundant) filter shall be performed, in conjunction with an investigation and risk assessment to determine the reason for the primary filter test failure.

VII.4.7.15. Bioburden samples shall be taken from the bulk product and immediately prior to the final sterile filtration. In case where a redundant filtration set-up is used, the samples shall be taken prior to the first filter. Procedures for taking samples shall be designed so as not to introduce contamination.

VII.4.7.16. Liquid sterilising grade filters shall be discarded after the processing of a single batch and the same filter shall not be used continuously for more than one working day, unless such use has been validated.

VII.4.7.17. Where campaign manufacture of a product has been appropriately justified in the contamination control strategy and validated, the manufacturer shall:

(a) assess and document the risks associated with the duration of filter use for the sterile filtration process for a given fluid;

(b) conduct and document effective validation and qualification studies to demonstrate that the duration of filter use for a given sterile filtration process and for a given fluid does not compromise the performance of the final sterilising grade filter or the filtrate quality;

(c) document the maximum validated duration of use for the filter and implement controls to ensure that filters are not used beyond the validated maximum duration. Records of these controls shall be maintained;

(d) implement controls to ensure that filters contaminated with fluid or cleaning agent residues or otherwise considered defective, are removed from use.

VII.5. **Form-Fill-Seal** ([28])

VII.5.1. Form-Fill-Seal machines used for terminally sterilised products shall comply with the environmental requirements set out in Section VII.1.3 of this Annex, while Form-Fill-Seal machines used in aseptic manufacture shall comply with the environmental requirements set out in table 4 of this Annex.

VII.5.2. Contamination of the packaging films used during the Form-Fill-Seal process shall be minimised by the implementation of appropriate controls regarding components, supply and handling. Due to the criticality of packaging films, procedures shall be implemented to ensure that the films supplied meet defined specifications and are of the appropriate quality, including material thickness and strength, microbial and particulate contamination, integrity of printed information and packaging design, as relevant. The sampling frequency, the bioburden and, where applicable, endotoxin/pyrogen levels of packaging films and associated components shall be addressed as part of the contamination control strategy.

VII.5.3. The operation of the equipment, including set-up, filling, sealing and cutting processes shall be assessed so that critical process parameters can be identified, validated, controlled and monitored appropriately.

VII.5.4. Any product contact gases (e.g. those used to inflate the container or used as a product overlay) shall be appropriately filtered, as close to the point of use as possible. The quality of gases used and the effectiveness of the gas filtration systems shall also be verified periodically in accordance with Section V.4 of this Annex.

VII.5.5. The controls to be identified during the qualification of Form-Fill-Seal processes, which shall be part of the contamination control strategy, include but are not limited to:

— determination of the boundaries of the critical zone;

— environmental control and monitoring, both of the machine and of the background in which it is placed;

([28]) For the purposes of this Annex, 'Form-Fill-Seal' means an automated filling process, typically used for terminally sterilised products, which constructs the primary container out of a continuous flat roll of packaging film while simultaneously filling the formed container with product and sealing the filled containers in a continuous process. Form-Fill-Seal processes may utilize a single web system (where a single flat roll of film is wrapped around itself to form a cavity), or a dual web system (where two flat rolls of film are brought together to form a cavity), often with the aid of vacuum moulds or pressurised gases. The formed cavity is filled, sealed and cut into sections. Films typically consist of a polymeric material, polymeric coated foil or other suitable material.

— personnel gowning requirements;

— integrity testing of the product filling lines and filtration systems (as relevant);

— duration of the batch or filling campaign;

— control of the packaging films, including any requirements for film decontamination or sterilisation;

— cleaning-in-place and sterilisation-in-place of the equipment as necessary;

— machine operation, settings and alarm management (as relevant).

VII.5.6. Critical process parameters for Form-Fill-Seal shall be established during the equipment qualification and shall include, but are not limited to:

— settings for uniform package dimensions and cutting in accordance with validated parameters;

— setting, maintenance and monitoring of validated forming temperatures (including preheating and cooling), forming times and pressures as relevant;

— setting, maintenance and monitoring of validated sealing temperatures, sealing temperature uniformity across the seal, sealing times and pressures as relevant;

— environmental and product temperature;

— batch-specific testing of package seal strength and uniformity;

— settings for correct filling volumes, speeds and uniformity;

— settings for any additional printing (batch coding), embossing or debossing to ensure that unit integrity is not compromised;

— methods and parameters for integrity testing of filled containers.

VII.5.7. Appropriate procedures for the verification, monitoring and recording of Form-Fill-Seal critical process parameters and equipment operation shall be implemented during production.

VII.5.8. Operational procedures shall describe how forming and sealing issues are detected and rectified. Rejected units or sealing issues shall be recorded and investigated.

VII.5.9. Appropriate maintenance procedures shall be established based on risks, and shall include maintenance and inspection plans for tooling critical to the effectiveness of unit sealing. Any issues identified that indicate a potential product quality concern shall be documented and investigated.

VII.6. **Blow-Fill-Seal** ([29])

VII.6.1. Blow-Fill-Seal equipment used for the manufacture of products that are terminally sterilised shall be installed in at least a grade D environment. The conditions at the point of fill shall comply with the environmental requirements set out in Section VII.1.3 of this Annex.

([29]) For the purposes of this Annex, 'Blow-Fill-Seal' means a technology in which containers are formed from a thermoplastic granulate, filled with product, and then sealed in a continuous, integrated, automatic operation. The two most common types of Blow-Fill-Seal machines are the Shuttle type (with Parison cut) and the Rotary type (Closed Parison).

VII.6.2. Where Blow-Fill-Seal equipment is used for aseptic processing, the following requirements shall apply:

(a) For shuttle type equipment used for aseptic filling, the parison ([30]) is open to the environment and therefore the areas where parison extrusion, blow-moulding and sealing take place shall meet grade A conditions at the critical zones. In addition, the filling environment shall be designed and maintained to meet grade A conditions for viable and total particle limits both at rest and when in operation.

(b) For rotary-type equipment used for aseptic filling, the parison is generally closed to the environment once formed and therefore the filling environment within the parison shall be designed and maintained to meet grade A conditions for viable and total particle limits both at rest and when in operation.

(c) The equipment shall be installed in at least a grade C environment, provided that grade A/B clothing is used. The microbiological monitoring (including setting of limits and frequencies applied) of operators wearing grade A/B clothing in a grade C area shall be performed in accordance with risk management principles.

VII.6.3. Due to the generation of particles from polymer extrusion and cutting during operation and the restrictive size of critical filling zones of Blow-Fill-Seal equipment, in operation monitoring of total particle for the equipment is not required. However, data shall be available to demonstrate that the design of the equipment ensures that critical zones of the filling process environment meet grade A conditions in operation.

VII.6.4. Viable environmental monitoring of Blow-Fill-Seal processes shall be risk-based and in accordance with Section VIII of this Annex. In operation viable monitoring shall be performed for the full duration of critical processing, including during equipment assembly, with the exception of rotary-type equipment where monitoring of the critical filling zone is not possible.

VII.6.5. The environmental control and monitoring programme shall take into consideration the moving parts and complex airflow paths generated by the Blow-Fill-Seal process and the effect of the high heat outputs of the process (e.g. through the use of airflow visualisation studies and/or other equivalent studies). Environmental monitoring programmes shall also consider factors such as air-filter configuration, air-filter integrity, cooling systems integrity, equipment design and qualification.

VII.6.6. Air or other gases in contact with critical surfaces of the container during extrusion, formation or sealing of the moulded container shall undergo appropriate filtration. The quality of the gas used and the effectiveness of the gas filtration systems shall be verified periodically in accordance with Section V.4 of this Annex.

VII.6.7. Particulate and microbial contamination of the polymer granulate shall be prevented by appropriate design, control and maintenance of the polymer granulate storage, sampling and distribution systems.

VII.6.8. The capability of the extrusion system to provide appropriate sterility assurance for the moulded container shall be validated. The sampling frequency, the bioburden and, where applicable, endotoxin/pyrogen levels of the raw polymer shall be defined and controlled.

VII.6.9. Interventions requiring cessation of filling and/or extrusion, moulding and sealing and, where required, re-sterilisation of the filling machine shall be clearly defined and described in the filling procedure, and included in the aseptic process simulation as relevant.

([30]) For the purposes of this Annex, 'parison' means the tube of polymer extruded by the Blow-Fill-Seal machine from which containers are formed.

VII.6.10. The controls identified during qualification of Blow-Fill-Seal equipment shall be in alignment with the site's contamination control strategy. Aspects to be considered include but are not limited to:

— determination of the boundaries of the critical zone;

— environmental control and monitoring, both of the machine and of the background in which it is placed;

— personnel gowning requirements;

— integrity testing of the product filling lines and filtration systems (as relevant);

— duration of the batch or filling campaign;

— control of polymer granulate, including distribution systems and critical extrusion temperatures;

— cleaning-in-place and sterilisation-in-place of equipment as necessary;

— machine operation, settings and alarm management (as relevant).

VII.6.11. Critical process parameters for Blow-Fill-Seal equipment shall be determined during equipment qualification and shall include, but are not limited to:

— clean-in-place and sterilisation-in-place of product pipelines and filling needles (mandrels);

— setting, maintenance and monitoring of extrusion parameters, including the temperature, speed and extruder throat settings for parison thickness;

— setting, maintenance and monitoring of mould temperatures, including the rate of cooling where necessary for product stability;

— preparation and sterilisation of ancillary components added to the moulded unit, e.g. bottle caps;

— environmental control, cleaning, sterilisation and monitoring of the critical extrusion, transfer and filling areas as relevant;

— batch-specific testing of the package wall-thickness at critical points of the container;

— settings for correct filling volumes, speeds and uniformity;

— settings for any additional printing (batch coding), embossing or debossing to ensure that unit integrity and quality is not compromised;

— methods and parameters for integrity testing of 100 % of all filled containers;

— settings for cutters or punches used to remove waste plastic surrounding filled units (flash removal).

VII.6.12. Appropriate procedures for the verification, monitoring and recording of Blow-Fill-Seal critical process parameters and equipment operation shall be implemented during production.

VII.6.13. Operational procedures shall describe how blowing, forming and sealing issues are detected and rectified. Rejected units or sealing issues shall be recorded and investigated.

VII.6.14. Where the Blow-Fill-Seal process includes the addition of components to moulded containers (e.g. addition of caps to large volume parenteral bottles), these components shall be appropriately decontaminated and added to the process using a clean, controlled process. The following shall apply:

(a) For aseptic processes, the addition of components shall be performed under grade A conditions, to ensure the sterility of critical surfaces, using pre-sterilised components.

(b) For terminally sterilised products, the validation of terminal sterilisation processes shall ensure the sterility of all critical product pathways between the component and moulded container, including areas that are not wetted during sterilisation.

(c) Testing procedures shall be established and validated to ensure the effective sealing of components and moulded containers.

VII.6.15. Appropriate maintenance procedures shall be established based on risk, including maintenance and inspection plans for items critical to unit sealing, integrity and sterility.

VII.6.16. The moulds used to form containers are considered critical equipment. Therefore, any changes or modification to moulds requires an assessment of finished product container integrity, and where appropriate having regard to the outcome of the assessment, shall be supported by validation. Any issues identified that indicate a potential product quality concern shall be documented and investigated.

VII.7. **Lyophilisation** ([31])

VII.7.1. Lyophilisation is a critical process step and all activities that can affect the sterility of the product or material shall be regarded as extensions of the aseptic processing. In particular, the lyophilisation equipment and its processes shall be designed to ensure that product or material sterility is maintained during lyophilisation by preventing microbial and particle contamination between the filling of products for lyophilisation and the completion of lyophilisation process. The control measures shall form part of the contamination control strategy.

VII.7.2. The sterilisation of the lyophilizer and any associated equipment (e.g. trays, vial support rings) shall be validated and the holding time between the sterilisation cycle and use shall be appropriately challenged during the aseptic process simulation. The lyophilizer shall be sterilised regularly, based on system design. In addition, re-sterilisation shall be performed after maintenance or cleaning. Sterilised lyophilizers and any associated equipment shall be protected from contamination after sterilisation.

VII.7.3. Lyophilizers and any associated product transfer and loading/unloading areas shall be designed to minimise operator intervention as far as possible. The frequency of the lyophilizer sterilisation shall be determined based on the design and risks related to system contamination during use. Lyophilizers that are manually loaded or unloaded with no barrier technology separation shall be sterilised before each load. For lyophilizers loaded and unloaded by automated systems or protected by closed barrier systems, the frequency of sterilisation shall be justified and documented as part of the contamination control strategy.

VII.7.4. The integrity of the lyophilizer shall be maintained following sterilisation and during lyophilisation. The filter used to maintain the lyophilizer's integrity shall be sterilised before each use of the system and the integrity testing results shall be part of the batch certification/release. In addition, the frequency of vacuum/leak integrity testing of the chamber shall be documented and the maximum permitted leakage of air into the lyophilizer shall be specified and checked at the start of every cycle.

([31]) For the purposes of this Annex, 'lyophilisation' means a physical-chemical drying process designed to remove solvents, by way of sublimation, from both aqueous and non-aqueous systems, primarily to achieve product or material stability. Lyophilisation is synonymous to the term freeze-drying.

VII.7.5. Lyophilisation trays shall be checked regularly to ensure that they are not misshapen or damaged.

VII.7.6. Points to consider for the design of loading (and unloading, where the lyophilised material is still unsealed and exposed), include but are not limited to:

— the loading pattern within the lyophilizer shall be specified and documented;

— the transfer of partially closed containers to a lyophilizer shall take place under grade A conditions at all times and handled in a manner designed to minimise direct operator intervention. Technologies such as conveyor systems or portable transfer systems (e.g. clean air transfer carts, portable unidirectional airflow workstations) shall be used to ensure that the cleanliness of the system used to transfer the partially closed containers is maintained. Alternatively, where supported by validation, trays closed in grade A and not reopened whilst in the grade B area may be used to protect partially stoppered vials (e.g. appropriately closed boxes);

— airflow patterns shall not be adversely affected by transport devices and venting of the loading zone;

— unsealed containers (such as partially stoppered vials) shall be maintained under grade A conditions and shall normally be separated from operators by means of a physical barrier technology or any other appropriate measures;

— where the seating of the stoppers is not completed prior to the opening of the lyophilizer chamber, the product removed from the lyophilizer shall remain under grade A conditions during subsequent handling;

— tools used during loading and unloading of the lyophilizer (e.g. trays, bags, placing devices, tweezers) shall be sterile.

VII.8. **Closed systems**

VII.8.1. The use of closed systems can reduce the risk of microbial, particle and chemical contamination from the adjacent environment. Closed systems shall be designed to reduce the need for manual manipulations and the associated risks.

VII.8.2. It is critical to ensure the sterility of all product contact surfaces of closed systems used for aseptic processing. Therefore, the design and selection of any closed system used for aseptic processing shall ensure maintenance of sterility. Connection of sterile equipment (e.g. tubing/pipework) used after the final sterilising grade filter shall be connected aseptically (e.g. by intrinsic sterile connection devices).

VII.8.3. Appropriate measures shall be put in place to ensure the integrity of components used in aseptic connections. The means by which this is achieved shall be determined and addressed in the contamination control strategy. In particular, appropriate system integrity tests shall be considered when there is a risk of compromising product sterility. Supplier assessment shall include the collation of data in relation to potential failure modes that may lead to a loss of system sterility.

VII.8.4. The background environment in which closed systems are located shall be determined having regard to the system's design and the processes undertaken. For aseptic processing and where there is a risk that the system's integrity may be compromised, the system shall be located in grade A. If the system can be shown to remain integral at every usage (e.g. via pressure testing and/or monitoring) then a lower classified area may be used. Any transfer between classified areas shall be thoroughly assessed in accordance with Section III.2 of this Annex. When the closed system is opened (e.g. for maintenance of a bulk manufacturing line), this shall be performed in a classified area appropriate to the materials (e.g. grade C for terminal sterilisation processes, or grade A for aseptic processing) or be subject to further cleaning and disinfection (and sterilisation in case of aseptic processes).

VII.9. **Single use systems** ([32])

VII.9.1. Single use systems may be used in the manufacture of sterile products as an alternative to reusable equipment. Single use systems can be individual components or be made up of multiple components such as bags, filters, tubing, connectors, valves, storage bottles and sensors. Single use systems shall be designed to reduce the need for manipulations and complexity of manual interventions.

VII.9.2. There are some specific risks associated with single use systems that shall be assessed as part of the contamination control strategy, including but not limited to:

— the interaction between the product and product contact surface (such as adsorption, or leachables ([33]) and extractables ([34]));

— the fragile nature of the system compared with fixed reusable systems;

— the increase in the number and complexity of manual operations (including inspection and handling of the system) and connections made;

— the complexity of the assembly;

— the performance of the pre- and post-use integrity testing for sterilising grade filters;

— the risk of holes and leakage;

— the potential for compromising the system at the point of opening the outer packaging;

— the risk of particle contamination.

VII.9.3. Sterilisation processes for single use systems shall be validated and shown to have no adverse impact on the system's performance.

VII.9.4. Assessment of suppliers of disposable systems including sterilisation is critical to the selection and use of these systems. Therefore, for sterile single use systems, verification of sterility assurance shall be performed as part of the supplier qualification and evidence of sterilisation of each unit shall be checked on receipt.

VII.9.5. The adsorption and reactivity of the product with product contact surfaces shall be evaluated under process conditions.

VII.9.6. The extractable and leachable profiles of the single use systems and any impact on the quality of the product – especially where the system is made from polymer-based materials – shall be evaluated. An assessment shall be carried out for each component to evaluate the extractable profile data. For components considered to be at high risk from leachables, including those that may absorb processed materials or those with extended material contact times, an assessment of leachable profile studies, including safety concerns, shall be taken into consideration. When applying simulated processing conditions, these shall accurately reflect the actual processing conditions and be based on a scientific rationale.

([32]) For the purposes of this Annex, 'single use systems' means systems in which product contact components are used only once to replace reusable equipment such as stainless-steel transfer lines or bulk containers.

([33]) For the purposes of this Annex, 'leachables' means chemical entities that, under normal conditions of use or storage, migrate from the product contact surface of the process equipment or containers into the product or material being processed.

([34]) For the purposes of this Annex, 'extractables' means chemical entities that migrate from the surface of the process equipment, when exposed to an appropriate solvent at extreme conditions, into the product or material being processed.

VII.9.7. Single use systems shall be designed to maintain integrity throughout processing under the intended operational conditions. Attention to the structural integrity of the single use components is necessary where these may be exposed to extreme conditions (e.g. freezing and thawing processes) during routine processing or transportation, including verification that intrinsic sterile connection devices (both heat sealed and mechanically sealed) remain integral under these conditions.

VII.9.8. Acceptance criteria shall be established and implemented for single use systems corresponding to the risks or criticality of the products and its processes. On receipt, each piece of single use systems shall be checked to ensure that they have been manufactured, supplied and delivered in accordance with the approved specification. A visual inspection of the outer packaging (e.g. appearance of exterior carton, product pouches), label printing, and review of attached documents (e.g. certificate of conformance and proof of sterilisation) shall be carried out and documented prior to use.

VII.9.9. Critical manual handling operations of single use systems such as assembly and connections shall be subject to appropriate controls and verified during aseptic process simulation.

SECTION VIII

ENVIRONMENTAL AND PROCESS MONITORING

VIII.1. **General requirements**

VIII.1.1. Each site shall have an environmental and process monitoring programme to monitor the controls designed to minimise the risk of microbial and particle contamination. The programme, which shall form part of the overall contamination control strategy, shall typically consist of the following elements:

— environmental monitoring – total particle;

— environmental and personnel monitoring – viable particle;

— temperature, relative humidity and other specific characteristics;

— aseptic process simulation (only for aseptically manufactured products).

VIII.1.2. The reliability of each of the elements of the monitoring system when taken in isolation is limited. Therefore, the outcome from the each of the elements above-described cannot be considered – on its own – as an indicator of asepsis. However, the results from all the elements of the programme help confirm the reliability of the design, validation and operation of the monitored system.

VIII.1.3. The information from the programme shall be used for routine batch certification/release and for periodic assessment during process review or investigation. While this applies to both terminal sterilisation and aseptic processes, it is acknowledged that the criticality of the impact may differ depending upon the product and process type.

VIII.2. **Environmental and process monitoring**

VIII.2.1. The purpose of the environmental monitoring programme is twofold:

— to provide assurance that cleanrooms and clean air equipment continue to provide an environment of appropriate air cleanliness, in accordance with design and regulatory requirements;

— to effectively detect excursions from environmental limits, which -in turn- shall trigger an investigation and an assessment of the risks to product quality.

Risk assessments shall be performed in order to establish a comprehensive environmental monitoring programme, including sampling locations, frequency of monitoring, monitoring methods and incubation conditions (e.g. time, temperature(s), aerobic and/or anaerobic conditions). In particular, the risk assessment shall include the determination of critical monitoring locations, those locations where the presence of microorganisms during processing may have an impact on product quality (e.g. grade A, aseptic processing areas and the grade B areas that directly interface with the grade A area).

The risk assessments shall be performed on the basis of the specific characteristics of the process inputs and the final product, the facility, the equipment, the criticality of specific processes and steps, the operations involved, the routine monitoring data, the monitoring data obtained during qualification and the knowledge of typical microbial flora isolated from the environment. Detailed knowledge of those aspects is therefore required for the establishment of the environmental monitoring program. Other relevant information such as air visualisation studies shall also be considered.

The risk assessments shall be reviewed regularly to confirm the effectiveness of the site's environmental monitoring programme.

VIII.2.2. Routine monitoring of cleanrooms, clean air equipment and personnel shall be performed in operation throughout all critical stages of processing, including equipment set-up.

VIII.2.3. Other characteristics, such as temperature and relative humidity, shall be controlled within ranges that align with product/processing/personnel requirements and support the maintenance of the defined cleanliness standards (e.g. grade A or B).

VIII.2.4. The monitoring of grade A shall demonstrate the maintenance of aseptic processing conditions during critical operations. Monitoring shall be performed at locations posing the highest risk of contamination to the sterile equipment surfaces, the containers, the closures and the product. The selection of monitoring locations and the orientation and positioning of sampling devices shall be appropriate to obtain reliable data from the critical zones.

VIII.2.5. Sampling methods shall not pose a risk of contamination to the manufacturing operations.

VIII.2.6. Appropriate alert levels and action limits shall be set for the results of viable and total particle monitoring. The maximum total particle action limits are described in Table 5 and the maximum viable particle action limits are described in Table 6. However, more stringent action limits may be required based on data trending, the nature of the process or as determined in the contamination control strategy. Both viable and total particle alert levels shall be established based on results of cleanroom qualification tests and periodically reviewed based on ongoing trend data.

VIII.2.7. Alert levels for grade A (total particle only) grade B, grade C and grade D shall be set such that adverse trends (e.g. a number of events or individual events that indicate a deterioration of environmental control) are detected and addressed.

VIII.2.8. Monitoring procedures shall define the approach to trending. Trends shall include, but are not limited to:

— increasing numbers of excursions from action limits or alert levels;

— consecutive excursions from alert levels;

— regular but isolated excursion from action limits that may have a common cause (e.g. single excursions that always follow planned preventative maintenance);

— changes in microbial flora type and numbers and predominance of specific organisms. Particular attention shall be paid to organisms recovered that may indicate a loss of control, deterioration in cleanliness or organisms that may be difficult to control such as spore-forming microorganisms and moulds.

VIII.2.9. The monitoring of grade C and D cleanrooms in operation shall be performed on the basis on data collected during qualification and routine data to allow effective trend analysis. The requirements of alert levels and action limits will depend on the nature of the operations carried out. Action limits may be more stringent than those listed in Table 5 and Table 6.

VIII.2.10. If action limits are exceeded, a root cause investigation, an assessment of the potential impact to the product (including batches produced between the monitoring and the reporting) and implementation of corrective and preventive actions (as appropriate) shall be required.

If alert levels are exceeded, an assessment and follow-up is mandatory, including consideration of an investigation and/or corrective actions to avoid any further deterioration of the environment.

The above shall be reflected in operating procedures.

VIII.3. **Environmental monitoring – total particle**

VIII.3.1. A total particle monitoring programme shall be established to obtain data for assessing the potential contamination risks and to ensure the maintenance of the environment for sterile/aseptic operations in a qualified state.

VIII.3.2. The limits for environmental monitoring of airborne particle concentration for each graded area are given in Table 5.

Table 5

Maximum permitted total particle concentration for monitoring

Grade	Maximum limits for total particle ≥ 0,5 μm/m³		Maximum limits for total particle ≥ 5 μm/m³	
	at rest	in operation	at rest	in operation
A	3 520	3 520	29	29
B	3 520	352 000	29	2 930
C	352 000	3 520 000	2 930	29 300
D	3 520 000	not pre-defined ([1])	29 300	not pre-defined ([1])

([1]) For grade D, in operation limits are not predetermined. The manufacturer shall establish in operation limits based on a risk assessment and on routine data, where applicable.

Note 1: The particle limits given in the table for the 'at rest' state shall be achieved after a short 'clean up' period defined during qualification (guidance value of less than 20 minutes) in an unmanned state, after the completion of operations.

Note 2: The occasional indication of macro particle counts, especially ≥ 5 μm, within grade A may be considered to be false counts due to electronic noise, stray light, coincidence loss etc. However, a consecutive or regular counting of low levels may be indicative of a possible contamination event and shall therefore be investigated. Such events may be indicative of an early failure of the room air supply filtration system, an equipment failure, or may also be a signal of poor practices during machine set-up and routine operation.

VIII.3.3. For grade A, particle monitoring shall be undertaken for the full duration of the critical processing, including equipment assembly.

VIII.3.4. The grade A area shall be monitored continuously (for particles ≥ 0,5 and ≥ 5 μm) and with a suitable sample flow rate (at least 28 litres (1 ft^3) per minute) so that all interventions, transient events and any system deterioration is captured. The system shall frequently correlate each individual sample result with alert levels and action limits at such a frequency that any potential excursion can be identified and responded to in a timely manner. Alarms shall be triggered if alert levels are exceeded. Procedures shall define the actions to be taken in response to alarms including the consideration of additional microbial monitoring.

VIII.3.5. It is recommended that a similar system be used for the grade B area although the sample frequency may be decreased. The grade B area shall be monitored at such a frequency and with a suitable sample size to ensure that the programme captures any increase in levels of contamination and a system deterioration. If alert levels are exceeded, alarms shall be triggered.

VIII.3.6. The selection of the monitoring system shall take into account any risk presented by the materials used in the manufacturing operation (e.g. those involving live organisms, powdery products or radiopharmaceuticals) that may give rise to biological, chemical or radiation hazards.

VIII.3.7. In case where contaminants are present due to the processes involved and can potentially damage the particle counter or present a hazard (e.g. live organisms, powdery products and radiation hazards), the frequency and strategy employed shall be adequate to ensure the environmental classification, both prior to and post exposure to the risk. An increase in the monitoring of viable particle shall be considered to ensure a comprehensive monitoring of the process where appropriate. Additionally, monitoring shall be performed during simulated operations at appropriate intervals. The defined approach is part of the contamination control strategy.

VIII.3.8. The size of the monitoring samples taken using automated systems will usually depend on the sampling rate of the system used. It is not necessary for the sample volume to be the same as that used for formal classification of the cleanrooms and of the clean air equipment. The monitoring sample volumes shall be justified.

VIII.4. **Environmental and personnel monitoring – viable particle**

VIII.4.1. Frequent microbial monitoring using a combination of methods such as settle plates, volumetric air sampling, glove, gown and surface sampling (e.g. swabs and contact plates) shall be required where aseptic operations are performed. Specifically:

— Viable particle monitoring shall be performed within the cleanrooms when normal manufacturing operations are not occurring (e.g. post disinfection, prior to start of manufacturing, on completion of the batch and after a shutdown period) and in associated rooms that have not been used, in order to detect potential incidents of contamination that may affect the controls within the cleanrooms. In case of an incident, additional sample locations may be used as a verification of the effectiveness of a corrective action (e.g. cleaning and disinfection).

— Continuous viable air monitoring in grade A (e.g. air sampling or settle plates) shall be performed for the full duration of critical processing, including equipment assembly (aseptic set-up) and critical processing. A similar approach shall be considered for grade B cleanrooms based on the risk of impact on the aseptic processing. The monitoring shall be performed in such a way that all interventions, transient events and any system deterioration are captured and any risk caused by interventions of the monitoring operations is avoided.

The method of sampling used shall be justified as part of the contamination control strategy and be demonstrated not to have a detrimental impact on grade A and B airflow patterns. Cleanroom and equipment surfaces shall be monitored at the end of an operation.

VIII.4.2. Monitoring of personnel shall be conducted on the basis of a risk assessment, which shall evaluate the locations, type and frequency of monitoring based on the activities performed and the proximity to critical zones. Microbial monitoring of personnel in the grade A and grade B areas is essential. Where operations are manual in nature (e.g. aseptic compounding or filling), an enhanced emphasis shall be placed on microbial monitoring of gowns and the implemented monitoring measures shall be justified within the contamination control strategy.

VIII.4.3. Monitoring shall include the sampling of personnel at periodic intervals during the process. Sampling of personnel shall be performed in such a way that it does not compromise the process. Particular consideration shall be paid to the monitoring of personnel following involvement in critical interventions (as a minimum gloves, but other parts of gown may also need to be monitored as applicable to the process) and on each exit from the grade B cleanroom (gloves and gown).

VIII.4.4. Where monitoring of gloves is performed after critical interventions, the outer gloves shall be replaced prior to continuation of activity. Where monitoring of gowns is required after critical interventions, the gown shall be replaced before further activity in the cleanroom.

VIII.4.5. Regular oversight by the quality unit is required if monitoring is routinely performed by manufacturing personnel.

VIII.4.6. The adoption of suitable alternative monitoring systems such as rapid methods may be considered by manufacturers in order to expedite the detection of microbiological contamination issues and to reduce the risks to the product. These rapid and automated microbial monitoring methods may be adopted after validation has demonstrated their equivalency or superiority to the established methods.

VIII.4.7. Procedures shall be in place for the assessment and interpretation of appropriate actions (where required) in light of the results obtained from the sampling. Supporting data for the recovery efficiency of the sampling methods chosen shall be available. Action limits for viable particle contamination are shown in Table 6.

Table 6

Maximum action limits for viable particle contamination

Grade	Air sample CFU/m^3	Settle plates (diam. 90 mm) CFU/4 hours ([1])	Contact plates (diam. 55mm), CFU/plate ([2])	Glove print, Including 5 fingers on both hands CFU/glove
A	No growth ([3])			
B	10	5	5	5
C	100	50	25	—
D	200	100	50	—

([1]) — Settle plates shall be exposed in grade A and B areas for the duration of operations (including equipment set-up) and changed as required after a maximum of 4 hours (exposure time shall be based on validation including recovery studies and it shall not have any negative effect on the suitability of the media used).
— For grade C and D areas, exposure time (with a maximum of 4 hours) and frequency shall be based on quality risk management principles.
— Individual settle plates may be exposed for less than 4 hours.

([2]) Contact plate limits apply to equipment, room and gown surfaces within the grade A and grade B areas. Routine gown monitoring is not normally required for grade C and D areas, depending on their function.

([3]) For grade A, any growth shall trigger an investigation.

Note 1: The types of monitoring methods listed in the table above are examples and other methods may be used provided they are capable of providing information across the entire critical process where the product may be contaminated (e.g. aseptic line set-up, aseptic processing, filling and lyophilizer loading).

Note 2: Limits are applied using CFU throughout the document. If different or new technologies are used that present results in a manner different from CFU, the manufacturer shall scientifically justify the limits applied and where possible correlate them to CFU.

VIII.4.8. Microorganisms detected in the grade A and grade B areas shall be identified to the species level and the potential impact of such microorganisms on product quality (for each batch implicated) and overall state of control shall be evaluated. The identification of microorganisms detected in grade C and D areas shall be considered, as appropriate, as part of the contamination control strategy (for example where action limits or alert levels are exceeded) or following the isolation of organisms that may indicate a loss of control or deterioration in cleanliness, or the isolation of organisms that may be difficult to control such as spore-forming microorganisms and moulds and at a sufficient frequency to maintain a current understanding of the typical flora of these areas.

VIII.5. **Aseptic process simulation (also known as media fill)** ([35])

VIII.5.1. The periodic verification of the effectiveness of the controls in place for aseptic processing shall include an aseptic process simulation using a sterile nutrient media and/or a surrogate in place of the product. The selection of the nutrient media and/or the surrogate shall be made based on the ability of the media and/or the surrogate to imitate physical product characteristics posing a risk to the product sterility during the aseptic process. Where processing stages may indirectly impact the viability of any introduced microbial contamination, (e.g. aseptically produced semi-solids, powders, solid materials, microspheres, liposomes and other formulations where product is cooled, heated or lyophilised), alternative procedures that represent the operations as closely as possible shall be developed. Where surrogate materials, such as buffers, are used in parts of the aseptic process simulation, the surrogate material shall not inhibit the growth of any potential contamination.

The aseptic process simulation is not the primary means to validate the aseptic process or aspects of the aseptic process. The effectiveness of the aseptic process shall be determined through process design and process controls, training, and evaluation of monitoring data.

VIII.5.2. The aseptic process simulation shall imitate as closely as possible the routine aseptic manufacturing process and include all the critical manufacturing steps, specifically:

(a) the aseptic process simulation shall assess all aseptic operations performed subsequent to the sterilisation and decontamination cycles of materials utilised in the process to the point where the container is sealed;

(b) for non-filterable formulations, any additional aseptic steps shall be assessed;

(c) where aseptic manufacturing is performed under an inert atmosphere, the inert gas shall be substituted with air in the process simulation unless anaerobic simulation is intended;

(d) processes requiring the addition of sterile powders shall use an acceptable surrogate material in the same containers as those used in the process under evaluation;

(e) separate simulations of individual unit operations (e.g. processes involving drying, blending, milling and subdivision of a sterile powder) shall be avoided. Any use of individual simulations shall be supported by a documented justification and ensure that the sum total of the individual simulations continues to fully cover the whole process;

(f) the process simulation procedure for lyophilised products shall represent the entire aseptic processing chain including filling, transport, loading, a representative duration of the chamber dwell, unloading and sealing under specified, documented and justified conditions representing worst case operating parameters;

([35]) For the purposes of this Annex, 'aseptic process simulation' means the simulation of the entire aseptic manufacturing process to verify whether the process is adequate to ensure sterility/prevent contamination during production. It includes all operations associated with routine manufacturing, such as equipment assembly, formulation, filling, lyophilisation and sealing process as necessary.

(g) the lyophilisation process simulation shall mimic all aspects of the process, except those that may affect the viability or recovery of contaminants. For instance, boiling-over or actual freezing of the solution shall be avoided. Factors to consider in determining aseptic process simulation design include, where applicable:

— the use of air to break vacuum instead of nitrogen or other process gases;

— replicating the maximum interval between sterilisation of the lyophilizer and its use;

— replicating the maximum period of time between filtration and lyophilisation;

— quantitative aspects of worst-case situations, e.g. loading the largest number of trays, replicating the longest duration of loading where the chamber is open to the environment.

VIII.5.3. The aseptic process simulation shall take into account the aseptic manipulations and interventions known to occur during normal production as well as worst-case situations, as well as the following:

(a) inherent and corrective interventions representative of the routine process shall be performed in a manner and frequency similar to that during the routine aseptic process;

(b) the inclusion and frequency of interventions in the aseptic process simulation shall be based on the assessed risks posed to the product sterility.

VIII.5.4. The aseptic process simulation shall not be used to justify practices that pose unnecessary contamination risks.

VIII.5.5. The following elements are relevant for the development of the aseptic process simulation plan:

(a) identification of worst-case conditions covering the relevant variables, such as container size and line speed, and their impact on the process. The outcome of the assessment shall justify the variables selected;

(b) identification of the representative sizes of container/closure combinations to be used for validation. A bracketing or matrix approach may be considered for validation of the same container/closure configuration for different products where the process equivalence is scientifically justified;

(c) identification of the maximum permitted holding times for the product and for the equipment exposed during the aseptic process;

(d) identification of the volume filled per container, which shall be sufficient to ensure that the media contacts all the equipment and component surfaces that may directly contaminate the product. The volume used shall also provide sufficient headspace to support potential microbial growth and ensure that turbidity can be detected during inspection;

(e) substitution of any inert gas used in the routine aseptic manufacturing process by air, unless anaerobic simulation is intended. In this case, the inclusion of occasional anaerobic simulations as part of the overall validation strategy shall be considered as appropriate;

(f) the selected nutrient media shall be capable of growing a designated group of reference microorganisms as described by the relevant pharmacopeia and suitably representative local isolates ([36]);

(g) the method of detection of microbial contamination shall be scientifically justified to ensure that contamination is reliably detected;

([36]) For the purposes of this Annex, 'local isolates' means suitably representative microorganisms of the site that are frequently recovered through environmental monitoring within the classified zone/areas especially grade A and B areas, personnel monitoring or positive sterility test results.

(h) the process simulation shall be of sufficient duration to challenge the process, the operators that perform interventions, shift changes and the suitability of the processing environment;

(i) where the manufacturer operates different or extended shifts, the aseptic process simulation shall be designed to capture factors specific to those shifts that may pose a risk to product sterility, for example the maximum duration for which an operator may be present in the cleanroom;

(j) simulating normal aseptic manufacturing interruptions where the process is idle (e.g. shift changeovers, recharging dispensing vessels, introduction of additional equipment);

(k) ensuring that the environmental monitoring is conducted as required for routine production and throughout the entire duration of the process simulation;

(l) where campaign manufacturing occurs, such as in the use of barrier technologies or manufacture of sterile active substances, consideration shall be given to designing and performing the process simulation so that it simulates the risks associated with both the beginning and the end of the campaign and demonstrating that the campaign duration does not pose any risk;

(m) the performance of 'end of production or campaign aseptic process simulation' may be used as additional assurance; however, such approach cannot replace routine aseptic process simulation.

VIII.5.6. For sterile active substances, the batch size shall be large enough to represent the routine operation, simulate operation at the worst case, and cover all surfaces that may come into contact with the sterile product. In addition, all the simulated materials (surrogates or growth medium) shall be subject to microbial evaluation. The simulation materials shall be sufficient to ensure the robustness of the evaluation of the process being simulated and shall not compromise the recovery of microorganisms.

VIII.5.7. Aseptic process simulation shall be performed as part of the initial validation, with at least three consecutive satisfactory simulation tests that cover all working shifts that the aseptic process may occur in. In addition, an aseptic process simulation is also mandatory after any significant modification to operational practices, facilities, services or equipment that may have an impact on the sterility assurance of the product (e.g. modification to the HVAC system, the equipment, changes to process, the number of shifts or number of personnel, or after a major facility shut down). Moreover, an aseptic process simulation (periodic revalidation) shall usually be repeated twice a year (approximately every six months) for each aseptic process, each filling line and each shift. Each operator shall participate in at least one successful aseptic process simulation annually. Consideration shall be given to performing an aseptic process simulation after the last batch prior to shut down, before long periods of inactivity or before the decommissioning (i.e. definitively removing from the manufacturing process) or the relocation of a line.

VIII.5.8. Where manual operation occurs (e.g. aseptic compounding or filling), each type of container, container closure and equipment train shall be initially validated with each operator participating in at least 3 consecutive successful aseptic process simulation and revalidated with one aseptic process simulation approximately every 6 months for each operator. The aseptic process simulation batch size shall mimic the one used in the routine aseptic manufacturing process.

VIII.5.9. The number of units processed (filled) for aseptic process simulation shall be sufficient to effectively simulate all the activities that are representative of the aseptic manufacturing process. Justification for the number of units to be filled shall be addressed as part of the contamination control strategy. Typically, a minimum of 5 000 to 10 000 units shall be filled. For small batches (e.g. those under 5 000 units), the number of containers for aseptic process simulation shall at least equal the size of the production batch.

VIII.5.10. Filled aseptic process simulation units shall be agitated, swirled or inverted before incubation to ensure contact of the media with all interior surfaces in the container. All integral units from the aseptic process simulation shall be incubated and evaluated, including units with defects without a critical impact on the integrity of the container (e.g. those with cosmetic defects) or those which have gone through non-destructive in-process control checks.

If units are discarded during the process simulation and not incubated, those shall be comparable to the units discarded during a routine fill, and only if the standard operating procedures applicable to production specify that units must be removed under the same circumstances (i.e. type of intervention, line location, specific number of units removed). Under no circumstances may more units be removed during a media fill intervention than during a production run. Examples may include those that shall be discarded during routine production after the set-up process or following a specific type of intervention.

VIII.5.11. Where the manufacturing process includes materials that are in contact with the product surface but are then discarded (e.g. product flushes), the discarded material shall be simulated with nutrient media and be incubated as part of the aseptic process simulation, unless it can be clearly demonstrated that this waste process does not have an impact on the sterility of the product.

VIII.5.12. Filled aseptic process simulation units shall be incubated in a clear container to ensure visual detection of microbial growth. Where the product container is not clear (e.g. amber glass, opaque plastic), clear containers of identical configuration may be substituted to aid in the detection of contamination. When a clear container of identical configuration cannot be substituted, a suitable method for the detection of microbial growth shall be developed and validated. Microorganisms isolated from contaminated units shall be identified to the species level where possible, to assist in the determination of the likely source of the contaminant.

VIII.5.13. Filled aseptic process simulation units shall be incubated without unnecessary delay to achieve the best possible recovery of potential contamination. The selection of the incubation conditions and duration shall be scientifically justified and validated to provide an appropriate level of sensitivity for the detection of microbial contamination.

VIII.5.14. Upon completion of incubation, filled aseptic process simulation units shall be inspected by personnel who have been appropriately trained and qualified for the detection of microbiological contamination. Such inspection shall be conducted under conditions that facilitate the identification of any microbial contamination. In addition, samples of the filled units shall undergo a positive control by inoculation with a suitable range of reference organisms and suitably representative local isolates.

VIII.5.15. The target is zero growth. Any contaminated unit shall be considered as a failed aseptic process simulation and the following actions shall be taken:

(a) investigation to determine the most probable root cause(s);

(b) determination and implementation of appropriate corrective measures;

(c) a sufficient number of successful, consecutive aseptic process simulations (normally a minimum of 3) shall be conducted in order to demonstrate that the process has been returned to a state of control;

(d) a prompt review of all appropriate records relating to aseptic production since the last successful aseptic process simulation shall be made. The outcome of the review shall include a risk assessment of the potential breaches in batches manufactured since the last successful aseptic process simulation. In addition, all other batches not released to the market shall be included in the scope of the investigation. Any decision regarding their release status shall take into account the investigation outcome;

(e) all products that have been manufactured on a line subsequent to a process simulation failure shall be quarantined until a successful resolution of the process simulation failure has occurred;

(f) where the root cause investigation indicates that the failure was related to operator activity, actions to limit the involved operator's activities, until retrained and requalified, shall be taken;

(g) production shall resume only after completion of successful revalidation.

VIII.5.16. All aseptic process simulation runs shall be fully documented and include a reconciliation of the units processed (e.g. units filled, incubated and not incubated). Justification for the filled and the non-incubated units shall be included in the documentation. All interventions performed during the aseptic process simulation shall be recorded, including the start and the end time of each intervention and the involved person(s). All microbial monitoring data as well as other testing data shall be recorded in the aseptic process simulation batch record.

VIII.5.17. An aseptic process simulation run shall only be aborted under circumstances in which written procedures require commercial lots to be equally handled. An investigation shall be performed and documented in such cases.

VIII.5.18. The validation of the aseptic process shall be repeated when the specific aseptic process has not been in operation for an extended period of time or when there is a change to the process, the equipment, the procedures or the environment that has the potential to affect the aseptic process, or when new product containers or container closure combinations are added.

SECTION IX

QUALITY CONTROL

IX.1. There shall be personnel available with appropriate training and experience in microbiology, sterility assurance and knowledge of the processes to support the design of the manufacturing activities, environmental monitoring regime and any investigation assessing the impact of microbiologically linked events to the safety of the sterile product.

IX.2. Specifications for raw materials, components and products shall include requirements for microbial, particulate and endotoxin/pyrogen limits when considered necessary having regard to the monitoring data and the overall contamination control strategy.

IX.3. The bioburden assay shall be performed on each batch for both aseptically filled product and terminally sterilised products and the results shall be taken into consideration as part of the final batch review. Limits for bioburden immediately before the final sterilising grade filter or the terminal sterilisation process shall be set having regard to the efficiency of the method to be used. Samples shall be taken to be representative of the worst-case scenario (e.g. at the end of hold time). Where overkill sterilisation ([37]) parameters are set for terminally sterilised products, bioburden shall be monitored at suitable scheduled intervals.

IX.4. For products authorised for parametric release, a supporting pre-sterilisation bioburden monitoring programme for the filled product prior to initiating the sterilisation cycle shall be developed and the bioburden assay shall be performed for each batch. The sampling locations of filled units before sterilisation shall be based on a worst-case scenario and be representative of the batch. Any organisms found during the bioburden testing shall be identified and their impact on the effectiveness of the sterilising process determined. Where appropriate, the level of endotoxin/pyrogen shall also be monitored.

IX.5. The sterility test applied to the finished product shall be validated for the product concerned. This test is only the last in a series of critical control measures by which sterility is assured and it may not be used to ensure sterility of a product that does not meet the relevant design, procedural or validation parameters.

([37]) For the purposes of this Annex, 'overkill sterilisation' means a process that is sufficient to provide at least a 12 $\log_{10}$ reduction of microorganisms having a minimum D-value of 1 minute.

IX.6. The sterility test shall be performed under aseptic conditions. In addition, samples taken for sterility testing shall be representative of the whole batch but shall in particular include samples taken from parts of the batch considered to be most at risk of contamination, for example:

— for products which have been filled aseptically, samples shall include containers filled at the beginning and end of the batch. The taking of additional samples shall be considered based on risk (e.g. after critical interventions);

— for products that have been heat sterilised in their final containers, samples taken shall be representative of the worst case locations (e.g. the potentially coolest or slowest to heat part of each load);

— for products that have been lyophilised, samples shall be taken from different lyophilisation loads.

Note: Where the manufacturing process results in sub-batches (e.g. for terminally sterilised products), samples from each sub-batch shall be taken and a sterility test performed for each sub-batch. Where appropriate, consideration shall be given to performing separate testing for other finished product tests.

IX.7. When it is not possible to have the sterility test result prior to release because the shelf life of the product is too short, additional process controls and monitoring and/or alternative test methods implemented to mitigate the identified risks shall be scientifically justified and documented.

IX.8. Any process (e.g. vaporised hydrogen peroxide, ultra violet) used to decontaminate the external surfaces of the sterility samples prior to testing shall not negatively impact the sensitivity of the test method or the reliability of the sample.

IX.9. Media used for product testing shall be quality control tested according to the Pharmacopeia before use. Media used for environmental monitoring and aseptic process simulation shall be tested for growth promotion before use, using a scientifically justified and designated group of reference microorganisms and including suitably representative local isolates. Media quality control testing shall usually be performed by the end user. Reliance on outsourced testing or supplier testing of media shall be justified and transportation and shipping conditions be duly considered.

IX.10. Environmental monitoring data and trend data generated for classified areas shall be reviewed as part of the product batch certification/release. A written procedure shall be available describing the actions to be taken when data from environmental monitoring are found out of trend or exceeding the established limits. For products with a short shelf life, where the environmental data for the time of manufacture is not available, a review of the most recent available data is required. In addition, the use of rapid/alternative methods may be considered.

IX.11. Where rapid and automated microbial methods are used in manufacturing, those methods shall be validated for the product(s) or processes concerned.

ANNEX II

BIOLOGICAL AND IMMUNOLOGICAL PRODUCTS

I. SCOPE

I.1. The additional requirements set out in this Annex shall apply to the manufacture, control and testing of biological and immunological veterinary medicinal products, with the exception of inactivated immunological veterinary medicinal products which are manufactured from pathogens and antigens obtained from an animal or animals in an epidemiological unit and used for the treatment of that animal or those animals in the same epidemiological unit or for the treatment of an animal or animals in a unit having a confirmed epidemiological link.

Throughout the Annex, reference to 'biological veterinary medicinal products' or 'biologicals' is to be understood as encompassing also immunologicals.

I.2. Antibiotics are generally not considered biologicals. Nevertheless, manufacturers are advised to follow the requirements set out in this Annex with regard to manufacturing procedures described in this document that are used in the manufacture of such veterinary medicinal products.

I.3. Table 1 illustrates the manufacturing activities which are generally within the scope of this Annex.

Table 1

Type and source of material	Example product	Manufacturing steps covered by this Annex shown in grey GMP requirements shall increase from the earlier steps (e.g. collection) to the final manufacturing steps (formulation, filling). For earlier stages of manufacturing, GMP principles shall at least be adhered to.			
Human source	Urine derived enzymes, hormones	Collection of material ([1])	Mixing, and/ or initial processing	Isolation and purification	Formulation, filling
Animal or plant sources (not genetically modified/ edited)	Heparins, insulin, enzymes, proteins, allergen extract, immunosera	Collection of plant or animal material ([2])	Cutting, mixing, and/ or initial processing	Isolation and purification	Formulation, filling
Virus or bacteria /fermentation/cell culture, etc.	Viral or bacterial vaccines; enzymes, proteins	Establishment & maintenance of MCB, WCB, MSL, WSL ([3])	Cell culture and/or fermentation	Inactivation when applicable, isolation and purification	Formulation, filling
Biotechnology-fermentation/cell culture	Recombinant products, MAb, allergens, vaccines	Establishment & maintenance of MCB and WCB, MSL, WSL ([4])	Cell culture and/or fermentation	Isolation, purification, modification	Formulation, filling
Animal sources, (genetically modified/edited)	Recombinant proteins	Master and working (genetically modified/edited) bank	Collection, cutting, mixing, and/ or initial processing	Isolation, purification, modification	Formulation, filling

Type and source of material	Example product	Manufacturing steps covered by this Annex shown in grey GMP requirements shall increase from the earlier steps (e.g. collection) to the final manufacturing steps (formulation, filling). For earlier stages of manufacturing, GMP principles shall at least be adhered to.			
Plant sources: (genetically modified/edited)	Recombinant proteins, vaccines, allergen	Master and working (genetically modified/edited) bank	Growing, harvesting ([5])	Initial extraction, isolation, purification, modification	Formulation, filling

([1]) GMP principles shall be adhered to.
([2]) See Section IV for the extent to which GMP principles apply.
([3]) See Section VI for the extent to which GMP applies.
([4]) See Section VI for the extent to which GMP applies. Maintenance of working cell bank is expected to take place in a GMP environment.
([5]) The standards of good agricultural and collection practice for starting materials of herbal origin (GACP) is applicable.

I.4. In cases where there is a continuous process from the sourcing/isolation of the active substance from a biological source to the manufacturing of the finished product (e.g. veterinary medicinal products that consists of cells, viral-based vaccines, phages), the requirements of this Regulation shall apply to the entire manufacturing process.

II. PERSONNEL

II.1. Personnel (including those concerned with cleaning and maintenance) employed in areas where biological products are manufactured and tested shall receive initial and periodic retraining specific to the products manufactured and their respective tasks, including measures to protect the product, personnel and the environment, as well as – where appropriate – training on microbiology.

II.2. Personnel shall be protected against a possible infection with the biological agents used in the manufacture. In the case of biological agents known to cause disease in humans, adequate measures shall be taken to prevent infection of personnel working with the agent or with experimental animals. Where appropriate, relevant vaccination and health monitoring shall be offered having regard to the specific characteristics of the manufactured product (e.g. BCG vaccine ([1]), rabies, brucella, leptospira, tuberculin products) and the tasks of the staff.

II.3. When a heath condition that may have a negative impact on the quality of the product is declared by the relevant personnel or otherwise becomes apparent, access to the production or control area shall be barred.

II.4. Where required to minimise the opportunity for cross-contamination, restrictions on the movement of all personnel (including quality control, maintenance and cleaning staff) shall be applied on the basis of quality risk management principles ([2]). In general, personnel shall not pass from areas where exposure to live micro-organisms, genetically modified/genome edited organisms, toxins or animals occurs to areas where other products, or different organisms are handled. If such passage is unavoidable, appropriate contamination control measures commensurate to the risks shall be implemented.

([1]) Bacillus Calmette–Guérin (BCG) vaccine.
([2]) Personnel entering a contained area where organisms have not been handled in open circuit operations in the previous twelve hours are not regarded as being at risk of contamination, unless the organism involved is a biological agent where the corresponding disease does not exist in the relevant country or geographical area, or where the corresponding disease is subject to prophylactic measures or an eradication programme undertaken in the relevant country or geographical area.

II.5. Adequate measures shall be implemented to prevent biological agents being taken outside the manufacturing plant by personnel acting as a carrier. Dependent on the type of biological agent, such measures may include a complete change of clothes and compulsory showering before leaving the production area.

III. PREMISES AND EQUIPMENT

III.1. **Premises**

III.1.1. Premises shall be designed in such a way as to control the risks to the product and the risks to the environment. This may be achieved by the use of contained, clean, or controlled areas. In particular:

(a) Live biological agents that are highly pathogenic shall be handled in contained areas (including quality control operations, research and diagnostic services, etc). The level of containment shall be adapted to the pathogenicity of the agent.

(b) Without prejudice to the containment measures that may be required for certain biological organisms as provided for under (a), production of biological agents may generally take place in controlled areas provided it is carried out in totally enclosed and sterilised equipment and all relevant connections are made in accordance with the requirements set out in Annex I.

(c) Inactivated biological agents shall be handled in clean areas. Clean areas shall also be used when handling non-infected cells isolated from multicellular organisms and, where appropriate, filtration-sterilised media.

(d) Open circuit operations involving products or components not subsequently sterilised shall be carried in accordance with the requirements set out in Annex I, where relevant.

(e) With the exception of blending and subsequent filling operations (or when closed systems are used), only one biological agent shall be handled at a given time within an area.

(f) Production operations such as cell maintenance, media preparation, virus culture, etc. which are likely to cause contamination shall be performed in separate areas, unless appropriate organisational and technical measures may be put in place to prevent contamination.

(g) Production areas where biological agents particularly resistant to disinfection (e.g. spore-forming bacteria) are handled shall be separated and dedicated to that particular purpose until the biological agents have been inactivated, unless appropriate organisational and technical measures may be put in place to prevent contamination.

III.1.2. As part of the contamination control strategy, the degree of environmental control of particulate and microbial contamination of the production premises shall be adapted to the active substance, intermediate or finished product and the production step, bearing in mind the potential level of contamination of the starting materials and the risks to the product. Where relevant in accordance with quality risk management principles, the environmental monitoring programme shall be supplemented by the inclusion of methods to detect the presence of specific microorganisms (i.e. host organism, yeast, moulds, anaerobes, etc.).

III.1.3. Manufacturing and storage facilities, processes and environmental classifications shall be designed to prevent the extraneous contamination of products. Where processes are not closed and there is therefore exposure of the product to the immediate room environment (e.g. during additions of supplements, media, buffers, gases) adequate control measures shall be put in place, including engineering and environmental controls. Relevant aspects addressed in Annex I shall be applied, including aspects related to the required environmental grades and associated controls.

III.1.4. Air handling units shall be designed, constructed and maintained to minimise the risk of cross-contamination between different manufacturing areas, to provide relevant containment where applicable, and may need to be specific for an area. Consideration, based on quality risk management principles, shall be given to the use of single pass air systems.

III.1.5. Positive pressure areas shall be used to process sterile products but negative pressure in specific areas at the point of exposure of pathogens is acceptable for containment reasons. Where negative pressure areas or safety cabinets are used for aseptic processing of materials with particular risks (e.g. pathogens) they shall be surrounded by a positive pressure clean zone of appropriate grade. These pressure cascades shall be clearly defined and continuously monitored with appropriate alarm settings.

III.1.6. Air vent filters shall be hydrophobic and validated for their scheduled life span with integrity testing at appropriate intervals based on appropriate quality risk management principles.

III.1.7. Where necessary to address the contamination risks, equipment passes and changing rooms shall have an interlock mechanism or other appropriate system to prevent the opening of more than one door at a time. Changing rooms shall be supplied with air filtered to the same standard as that for the work area and equipped with air extraction facilities to produce an adequate air circulation independent of that of the work area. Equipment passes shall normally be ventilated in the same way, but unventilated passes, or those equipped with supply air only, may be acceptable.

III.1.8. Drainage systems shall be designed so that effluents can be effectively neutralised or decontaminated to minimise the risk of cross-contamination. Local regulation shall be followed to minimise the risk of contamination of the external environment according to the risk associated with the biohazardous nature of waste materials.

Containment

III.1.9. Containment premises shall be designed so as to ensure that they can be easily disinfected and shall have the following characteristics:

(a) Absence of direct venting to the outside.

(b) Ventilation with air at negative pressure: Air shall be extracted through HEPA filters and not be re circulated except to the same area, and provided further HEPA filtration is used (normally this condition would be met by routing the recirculated air through the normal supply HEPAs for that area). Recycling of air between areas is acceptable only if it passes through two exhaust HEPAs, the first of which is continuously monitored for integrity, and there are adequate measures for safe venting of exhaust air should this filter fail.

Where negative pressure areas are used for containment purposes of aseptic processing of materials with particular risks, they shall be combined with a positive pressure clean zone of appropriate grade (pressure bubble or sink airlock). These pressure cascades shall be clearly defined and continuously monitored with appropriate alarm settings.

(c) By way of derogation from (b), air from manufacturing areas used for the handling of exotic organisms ([3]) shall be vented through two sets of HEPA filters in series, and air from production areas shall not be re-circulated.

(d) A system shall be put in place for the collection and disinfection of liquid effluents including the contaminated condensate from sterilisers, biogenerators, etc. In addition, solid wastes, including animal carcasses, shall be disinfected, sterilised or incinerated as appropriate. Contaminated filters shall be removed using a safe method.

(e) Changing rooms shall be designed and used as air locks and equipped with washing and showering facilities if appropriate. Air pressure differentials shall be such that there is no flow of air between the work area and the external environment or a risk of contamination of the outer clothing worn outside the area.

([3]) For the purpose of this Annex, 'exotic organism' means a biological agent where the corresponding disease does not exist in a relevant country or geographical area, or where the disease is the subject of prophylactic measures or an eradication programme undertaken in the relevant country or geographical area.

(f) An airlock system is in place for the passage of equipment, which is constructed so that there is no flow of contaminated air between the work area and the external environment or a risk of contamination of the equipment within the lock. The airlock shall be of a suitable size to enable the effective surface decontamination of materials being passed through it. Consideration shall be given to having a timing device on the door interlock to allow sufficient time for the decontamination process to be effective.

(g) Where appropriate, a barrier double-door autoclave shall be used for the secure removal of waste materials and introduction of sterile items.

III.1.10. The measures and procedures implemented for containment to address operator and environmental safety shall not conflict with those required to ensure product quality.

Multiproduct facility

III.1.11. Manufacture of biologicals in a multi-product facility is acceptable where appropriate measures are implemented to prevent cross-contamination, such as:

— measures to prevent cross-contamination to non-related areas or equipment (e.g. use of single use components and engineering measures such as closed systems);

— validated cleaning and decontamination procedures before the subsequent manufacture of other products, covering also heating, ventilation and air conditioning (HVAC) system;

— environmental monitoring in adjacent areas – during manufacture and after completion of cleaning and decontamination – specific for the micro-organism being manufactured. Risks arising from the use of certain monitoring equipment (e.g. airborne particle monitoring) in areas handling live and/or spore-forming organisms shall be duly considered;

— controls on the movement/removal of products, equipment, ancillary equipment (e.g. for calibration and validation) and disposable items to prevent contamination of other areas, other products or different product stages (e.g. prevent contamination of inactivated or toxoided products with non-inactivated products);

— campaign-based manufacturing.

Where production involves the manufacture of multiple small batches from different starting materials, factors such as the health status of donors and the risk of total loss of product shall be taken into account when considering the acceptance of concurrent working.

III.1.12. For finishing operations (formulation, filling and packaging), the assessment whether dedicated facilities are required shall also take into consideration the specific characteristics of the concerned biological product and the characteristics of other products, including any non-biological products, handled in the same facility.

Other control measures for finishing operations may include the need for specific addition sequences, mixing speeds, time and temperature controls, limits on exposure to light, as well as containment and cleaning procedures in the event of spillages.

III.2. **Equipment**

III.2.1. Equipment used during handling of live organisms and cells, including equipment used for sampling, shall be suitable to prevent contamination during processing, facilitate decontamination and sterilisation (where applicable), and to avoid any mix-up between different organisms or products.

Particular attention shall be paid to control measures to avoid cross-contamination from parts of equipment that are not fixed, such as pipes, valves and filters (e.g. appropriate identification as to their function).

III.2.2. Equipment used for the storage of biological agents or products shall be suitable and used in such a manner as to prevent any possible mix-up. All stored items shall be clearly and unambiguously labelled and in leak-proof containers.

III.2.3. Where relevant, equipment shall be fitted with recording and/or alarm systems (e.g. equipment requiring temperature control). To avoid breakdowns, a system of preventive maintenance, together with trend analysis of recorded data, shall be implemented.

III.2.4. Close equipment used for primary containment shall be designed and periodically tested to ensure the prevention of escape of biological agents into the immediate working environment. Inlets and outlets for gases shall be protected so as to achieve adequate containment, e.g. by the use of sterilising hydrophobic filters. The introduction or removal of material shall take place using a sterilisable closed system, or possibly in an appropriate laminar air flow.

III.2.5. Where necessary, equipment shall be properly sterilised by a validated method. Equipment used for purification, separation or concentration shall be sterilised or disinfected at least between each use for different products. The effect of the sterilisation methods on the effectiveness and validity of the equipment shall be studied in order to determine the life span of the equipment.

III.2.6. The use of 'clean in place' ([4]) and 'steam in place' ([5]) ('sterilisation in place') systems shall be used where appropriate. Valves on fermentation vessels shall be completely steam sterilisable.

III.2.7. The loading of freeze dryers requires an appropriate clean/contained area. Unloading freeze dryers contaminates the immediate environment. Therefore, for single-ended freeze dryers, the clean room shall be decontaminated before a further manufacturing batch is introduced into the area, unless that batch involves the same organism(s). Double door freeze dryers shall be sterilised after each cycle unless opened in a clean area. Sterilisation of freeze dryers shall be done in accordance with Annex I. In case of campaign working, they shall at least be sterilised after each campaign.

IV. ANIMALS

The use of animals or animal materials in the manufacture of veterinary medicinal products is subject to specific additional requirements:

(a) Biological substances and products shall comply with the latest version of the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products.

(b) Specifications for materials of animal origin shall consider aspects such as age, weight and health status of the animals, as appropriate, and in accordance with the terms of the marketing authorisation.

(c) Where applicable, pharmacopeia requirements shall be complied with, including the need for specific tests at defined stages.

(d) A health programme shall be established to monitor adventitious agents that are of concern (zoonotic diseases, diseases of source animals). Specialist advice shall be obtained for the establishment of such programme. In particular, reports from trustworthy sources on national disease prevalence shall be considered when performing the assessment of risk and mitigation factors. Such sources include the World Organisation for Animal Health (WOAH) ([6]), as well as information on health monitoring and control programme(s) at national and local level.

([4]) For the purposes of this Annex, 'clean in place' means a method, usually automated, used to clean the internal surfaces of equipment, piping, vessels, and associated fittings without disassembling them.

([5]) For the purposes of this Annex, 'steam in place' means a method, usually automated, of sterilising the internal surfaces of equipment, piping, vessels, and associated fittings by using steam, without disassembling the equipment.

([6]) https://www.woah.org/en/home.

(e) Instances of ill-health occurring in the source/donor animals shall be investigated with respect to their suitability and the suitability of in-contact animals for continued use (in manufacture, as sources of starting and raw materials, in quality control and safety testing). Decisions shall be documented.

A look-back procedure shall be in place to inform the decision-making process on the continued suitability of the biological active substance or medicinal product in which the animal sourced starting or raw materials have been used or incorporated. This decision-making process may include the re-testing of retained samples from previous collections from the same donor animal (where applicable) to establish the last negative donation.

The withdrawal period of therapeutic agents used to treat source/donor animals shall be documented and used to determine the removal of those animals from the programme for defined periods.

(f) Particular care shall be paid to the prevention and monitoring of infections in the source/donor animals, including addressing aspects regarding the sourcing, the facilities, the husbandry, the biosecurity procedures, the testing regimes or the control of bedding and feed materials. This is of special relevance to specified pathogen free ([7]) animals where PhEur monograph requirements shall be met. Housing and health monitoring shall be defined for other categories of animals (e.g. healthy flocks or herds).

(g) For products manufactured from animals that have been genetically modified or whose genome has been edited, traceability shall be maintained in the creation of such animals from the source animals.

(h) Housing for animals used in production and control of biological active substances and medicinal products shall be separated from production and control areas. Such houses shall be provided with the appropriate containment and/or clean area measures and shall be separate from other animal accommodation. It is particularly important to ensure that animal houses where animals used for quality control involving the use of pathogenic biological agents are accommodated are adequately contained.

(i) At the production site, animals, biological agents and tests carried out on them shall be duly identified to prevent any risk of confusion and to control all the identified hazards.

(j) Suitable measures shall be implemented to ensure the quality and the traceability of materials of animal origin sourced from abattoirs. In particular, the contract/supply agreement with the abattoir shall address the required measures to ensure traceability of sourced materials, as well as the implementation of adequate hygiene and other necessary control measures at the abattoir.

(k) Adequate controls (based on quality risk management principles) shall be applied over the supply chain and during the transport of animals or animal materials used in the manufacture of veterinary medicinal products, including detailed documentation to ensure traceability. Traceability shall be ensured, including the movement of material between sites of initial collection, partial and final purification(s), storage sites, hubs, consolidators and brokers. Details of such arrangements shall be recorded and any breaches recorded, investigated and actions taken.

([7]) For the purposes of this Annex, 'specified pathogen free' means animals free from specified pathogens. Such flocks or herds share a common environment and have their own caretakers who have no contact with non-specified pathogen free groups.

V. STARTING AND RAW MATERIALS

V.1. The source, origin and suitability of biological starting and raw materials (e.g. cryoprotectants, feeder cells, reagents, culture media, buffers, serum, enzymes, cytokines, growth factors) shall be clearly defined in written specifications. Specifications shall include quality requirements necessary to ensure the suitability of the materials for the intended use and to minimise variability (covering relevant aspects of the production and control). Microbiological controls are particularly important. The specifications set shall be in compliance with the terms of the marketing authorisation. Starting and raw materials shall be appropriately identified through the various stages of production.

V.2. Where the results from the test(s) required to release the starting materials take a long time (e.g. sterility test), it may be permissible to process the starting materials before the results of the test(s) are available, provided that the risk of using a potentially failed material and its potential impact on other batches is understood and assessed under quality risk management principles. In such cases, the release of a finished product shall be conditional on the satisfactory results of these tests.

V.3. The risk of contamination of the starting and raw materials during their passage along the supply chain shall be assessed, with particular emphasis on TSE. Materials that come into direct contact with the manufacturing equipment or with the product (such as media used in media fill experiments and lubricants that may contact the product) shall also be taken into account.

V.4. A control strategy to protect the product and the preparation of solutions, buffers and other additions based on the principles set out in Annex I shall be implemented. The controls required for the quality of starting and raw materials and on the aseptic manufacturing process are particularly important for products in respect of which final sterilisation is not possible.

V.5. Where sterilisation of starting and raw materials is required, it shall be carried out – where possible – by heat. Where necessary, other appropriate methods may also be used for inactivation of biological materials (e.g. irradiation and filtration).

V.6. The use of antibiotics at early manufacturing stages to reduce bioburden (e.g. bioburden associated with the procurement of living tissues and cells) shall generally be avoided. The use thereof shall be duly justified. In such cases, the presence of antibiotics shall be removed from the manufacturing process at the stage specified in the marketing authorisation.

V.7. Adequate measures shall be implemented throughout the supply chain to ensure the traceability of substances of animal and human origin that are used in the manufacture of veterinary medicinal products.

Donor (human or animal) health information having an impact on the quality of the veterinary medicinal product which becomes available after procurement shall be taken into account in recall procedures.

VI. SEED LOT AND CELL BANK SYSTEM

VI.1. In order to prevent the unwanted drift of properties that may result from repeated subcultures or multiple generations, the production of biological substances and products obtained by microbial culture, cell culture or propagation in embryos and animals shall be based on a system of master and working seed lots ([8]) and/or cell banks ([9]).

([8]) For the purposes of this Annex, 'master seed lot' means a culture of a micro-organism distributed from a single bulk into containers and processed together in a single operation in such a manner as to ensure uniformity and stability and to prevent contamination.
For the purposes of this Annex, 'working seed lot' means a culture of a micro-organism derived from the master seed lot and intended for use in production.

([9]) For the purposes of this Annex, 'master cell bank' means a culture of cells distributed into containers in a single operation, processed together and stored in such a manner as to ensure uniformity and stability and to prevent contamination.
For the purposes of this Annex, 'working cell bank' means a culture of cells derived from the master cell bank and intended for use in the preparation of production cell cultures. Genetically modified/genome edited working bank is used with the same meaning but for plants or animals that have been genetically modified or whose genome has been edited.

VI.2. The number of generations (doublings, passages) between the seed lot or cell bank, the active biological substance and the finished product shall be consistent with the specifications in the marketing authorisation.

VI.3. As part of the product lifecycle management, the establishment of seed lots and cell banks, including master and working generations, shall be performed under circumstances which are demonstrably appropriate, including a controlled environment which is adequate to protect the seed lot and the cell bank and the personnel handling it. In addition, during the establishment of the seed lot and cell bank, no other living or infectious material (e.g. virus, cell lines or cell strains) shall be handled simultaneously in the same area or by the same persons.

VI.4. For stages prior to the master seed or cell bank generation, where only the principles of GMP may be applied, documentation shall be available to support traceability, including regarding components used during the development with a potential impact on product safety (e.g. reagents of biological origin), from initial sourcing and genetic development if applicable. For vaccines, compliance with the requirements in Pharm. Eur. monograph on Vaccines for veterinary use 01/2023:0062 is required.

VI.5. Following the establishment of master and working cell banks and master and working seed lots, quarantine and release procedures shall be followed, including adequate characterisation and testing for contaminants. Their on-going suitability for use shall be further demonstrated by the consistency of the characteristics and quality of the successive batches of product. Evidence of the stability and recovery of the seeds and banks shall be documented and records shall be kept in a manner permitting trend evaluation.

VI.6. Seed lots and cell banks shall be stored and used in such a way as to minimise the risks of contamination (e.g. stored in the vapour phase of liquid nitrogen in sealed containers) or alteration. Control measures for the storage of different seeds and/or cells in the same area or equipment shall prevent mix-up and take into account the infectious nature of the materials to prevent cross contamination.

VI.7. Storage containers shall be sealed, clearly labelled and kept at an appropriate temperature. A stock inventory shall be kept. The storage temperature shall be recorded continuously and, where used, the liquid nitrogen level monitored. Deviation from set limits and corrective and preventive action taken shall be recorded.

VI.8. It is desirable to split stocks and to store the split stocks at different locations so as to minimise the risks of total loss. The controls at such locations shall provide the assurances outlined in the preceding paragraphs.

VI.9. The storage and handling conditions for stocks shall be managed according to the same procedures and parameters. Once containers are removed from the seed lot/cell bank management system, the containers shall not be returned to stock.

VII. PRODUCTION

VII.1. Quality risk management principles shall be implemented across all the stages of the manufacture of biological veterinary medicinal products to minimise process variability and to enhance reproducibility. The effectiveness of the implemented measures shall be reassessed during product quality reviews.

VII.2. Critical operational (process) parameters and other input parameters that affect product quality shall be identified, validated, documented and be shown to be maintained within required parameters.

VII.3. Changes introduced in the manufacturing process shall comply with the requirements laid down in Article 26(3). In addition, the cumulative effects of changes introduced in the manufacturing process on the quality, safety and efficacy of the finished product shall be evaluated on periodic basis.

VII.4. Where starting materials from different donors are used, adequate controls shall be implemented to minimise the risk of cross-contamination or mix-ups.

VII.5. For biological materials that cannot be sterilised (e.g. by filtration), processing shall be conducted aseptically to minimise the introduction of contaminants. The requirements on aseptic manufacturing set forth in Annex I shall be implemented.

VII.6. The terms of the marketing authorisation or – as appropriate – Pharmacopoeia monographs, shall determine whether, and up to what stage, substances and materials used in the manufacturing of biological veterinary medicinal products can have a defined level of bioburden or need to be sterile. Appropriate controls shall be implemented to ensure that the specified limits are respected.

VII.7. Appropriate measures shall be implemented throughout all the production stages and controls to prevent or minimise the occurrence of unwanted bioburden and associated metabolites and endotoxins.

VII.8. A control strategy for the entry of articles and materials into production areas shall be implemented based on quality risk management principles. The following shall be implemented where applicable:

(a) For aseptic processes, heat stable articles and materials entering a clean/contained area ([10]) shall preferably do so through a double-ended autoclave or oven. Heat labile articles and materials shall enter through an airlock with interlocked doors where they shall be subject to effective surface sanitisation procedures. The sterilisation of articles and materials elsewhere is acceptable provided that multiple wrappings are used, as appropriate to the number of stages of entry to the clean area, and enter through an airlock with the appropriate surface sanitisation precautions.

(b) Equipment, glassware, the external surfaces of product containers and other such materials shall be disinfected before being transferred from a contained area using a validated method. Only the absolute minimum of materials shall enter or leave the area.

(c) Liquid or solid wastes such as the debris after harvesting eggs, disposable culture bottles, unwanted cultures or biological agents, shall preferably be sterilised or disinfected before being transferred from a contained area. However, alternatives such as the use of sealed containers or piping may be appropriate in some cases.

(d) Where relevant/critical raw materials (such as culture media and buffers) have to be measured or weighed during the production process (e.g. due to variability concerns), small stocks of these raw materials may be kept in the production area for a specified duration based on defined criteria (e.g. for the duration of manufacture of the batch or of the campaign).

VII.9. The growth promoting properties of culture media shall be demonstrated to be suitable for its intended use. If possible, media shall be sterilised in situ.

VII.10. The addition of materials or cultures to fermenters and other vessels and sampling shall be carried out under carefully controlled conditions to prevent contamination and, in case of live micro-organism, egress. It shall be verified that vessels are correctly connected when the addition or the sampling takes place. Gases, media, acid or alkalis, defoaming agents and other materials introduced into sterile biogenerators shall be sterile where appropriate.

VII.11. Continuous monitoring of some production processes, such as e.g. fermentation, may be necessary (e.g. continuous monitoring of parameters such as temperature, pH, pO_2, CO_2 and the rate of feed or carbon source with respect to growth of cells) and such data shall form part of the batch record. Special consideration shall be given to the quality controls required when continuous culture is used.

([10]) For the purposes of this Annex, 'clean/contained area' means an area constructed and operated in such a manner that it achieves the aims of both a clean area and a contained area at the same time.

VII.12. The formation of droplets and the production of foam shall be avoided or minimised as far as possible during manufacturing. Centrifugation and blending of products can lead to aerosol formation. Therefore, such activities shall be adequately contained with a view to minimise the risk of cross-contamination or, where relevant, risks to operators or the environment.

VII.13. Accidental spillages, especially of live organisms, shall be dealt with quickly and safely. Validated decontamination measures shall be available for each organism or groups of related organisms. Where different strains of single bacteria species or very similar viruses are involved, the decontamination process may be validated with one representative strain, unless there is reason to believe that they may vary significantly in their resistance to the agent(s) involved.

VII.14. Production and control materials, including paperwork, that are obviously contaminated, such as by spills or aerosols, or if a potential hazardous organism is involved, shall be adequately decontaminated, or the information be transferred out by other means.

VII.15. Precautions shall be taken to avoid contamination or confusion during incubation. Separate incubators shall be used for infected and non-infected containers and also generally for different organisms or cells. Incubators containing more than one organism or cell type are only acceptable if adequate steps are taken to seal, decontaminate the surface and segregate the containers. Culture vessels and any other container shall be carefully and clearly labelled. Specific cleaning/decontamination procedures for incubators shall be laid down.

VII.16. In cases where a virus inactivation or a removal process is performed during manufacture, measures shall be taken to avoid the risk of recontamination of treated products by non-treated products. Vessels containing inactivated products shall not be opened or sampled in areas containing live biological agents. For sterile products and for aseptic manufacturing, handling shall be done in accordance with Annex I.

VII.17. The inactivation process for live organisms shall be validated. For products that are inactivated by the addition of a reagent (e.g. micro-organisms in the course of vaccine manufacture) the process shall ensure the complete inactivation of the live organism and prevent any subsequent contamination from any equipment surface.

VII.18. Where chromatography equipment is used in campaign manufacture and in multi-product environments, a suitable control strategy (based on risk management principles) for matrices, the housings and associated equipment shall be implemented. The re-use of the same matrix at different stages of processing is discouraged. When it occurs, such re-usage shall be supported by appropriate validation data. Acceptance criteria, operating conditions, regeneration methods, life span, and sanitisation or sterilisation methods of chromatography columns shall be defined.

VII.19. Applicable requirements when irradiated equipment and materials are used are laid down in Annex VII.

VII.20. Filling shall be carried out as soon as possible following production. Containers of bulk product prior to filling shall be sealed, appropriately labelled and stored under specified conditions of temperature.

VII.21. When there is a delay between the filling of final containers and their labelling and packaging, procedures shall be laid down for the storage of unlabelled containers in order to prevent confusion and to ensure satisfactory storage conditions. Special attention shall be paid to the storage of heat labile or photosensitive products. Storage temperatures shall be specified.

VII.22. A system to ensure the integrity and closure of containers after filling shall be implemented where the final products or intermediates pose specific risks and procedures shall be established to deal with any leaks or spillages. There shall be also procedures in place regarding filling and packaging operations so as to maintain the product within relevant specified limits, e.g. time and/or temperature.

VII.23. The handling of vials (including the capping thereof) containing live biological agents shall be performed so as to prevent the contamination of other products or egress of the live agents into the work environment or the external environment. The viability of such organisms and their biological classification shall be taken into consideration as part of the management of such risks.

VII.24. The suitability of primary packaging materials having regard to the characteristics of the product and the storage conditions (*e.g.* products that should be stored at ultra-low temperature) shall be ensured. The compatibility of labels with ultra-low storage temperatures, where such temperatures are used, shall be verified.

VIII. QUALITY CONTROL

VIII.1. As controls for biological products usually involve biological analytical techniques, which typically have a greater variability than physico-chemical determinations, particular attention shall be paid to in-process controls. In-process control testing shall be performed at appropriate stages of production to control those conditions that are important for the quality of the finished product. Particular attention shall be paid to quality controls when continuous culture is used.

VIII.2. Continuous monitoring of data during a production process may be required, for example monitoring of physical parameters during fermentation.

VIII.3. It may be necessary to retain samples of intermediate products in sufficient amount and under appropriate storage conditions to allow repetition or confirmation of a batch control.

VIII.4. Where intermediates can be stored for extended periods of time (days, weeks or longer), consideration shall be given to the inclusion of finished product batches made from materials held for their maximum in-process periods in the on-going stability programme.

VIII.5. The ongoing stability monitoring may require animal testing. In such cases, where no alternative testing methods are available and with a view to reduce the use of animals for testing purposes, the frequency of testing may be adapted under a risk-based approach. Bracketing and matrix approaches may also be applied if scientifically justified in the stability protocol.

VIII.6. For cellular products, sterility tests shall be conducted on antibiotic-free cultures of cells or cell banks to provide evidence for absence of bacterial and fungal contamination and to be able to detect fastidious organisms where appropriate.

VIII.7. For biological medicinal products with a short shelf life (i.e. a period of 14 days or less) requiring batch certification before completion of all end product quality control tests (e.g. sterility tests) a suitable control strategy shall be put in place taking into account the specific characteristics of the product and manufacturing process and taking into account the controls and attributes of starting and raw materials. A detailed description of the release procedure, including the responsibilities of the different personnel involved in assessment of production and analytical data is required. A continuous assessment of the effectiveness of the quality assurance system shall be in place including records kept in a manner that permits trend evaluation.

Where end product tests are not available due to their short shelf life, alternative methods of obtaining equivalent data to permit initial batch certification may be considered (e.g. rapid microbiological methods). The procedure for batch certification and release may be carried out in two or more stages:

— assessment (by a designated person) of batch processing records, the results from environmental monitoring (where available), all deviations from standard procedures and the available analytical results;

— assessment of the final analytical tests and other information available for final certification by the Qualified Person. A procedure shall be in place to describe the measures to be taken where out of specification test results are obtained. Such events shall be fully investigated and the relevant corrective and preventive actions taken to prevent recurrence documented.

IX. SPECIFIC REQURIMENTS FOR SELECTED PRODUCT TYPES

IX.1. **Allergen products**

The following additional requirements are applicable for allergen products:

(a) Source materials shall be described in sufficient detail to ensure consistency in their supply, e.g. common and scientific name, origin, nature, contaminant limits, method of collection. Materials derived from animals shall be from healthy sources. Appropriate biosecurity controls shall be in place for colonies (e.g. mites, animals) used for the extraction of allergens. Allergen products shall be stored under defined conditions to minimise deterioration.

(b) The production process steps including pre-treatment, extraction, filtration, dialysis, concentration or freeze-drying steps shall be described in detail and validated.

(c) The modification processes to manufacture modified allergen extracts (e.g. allergoids ([11]), conjugates) shall be described. Intermediates in the manufacturing process shall also be identified and controlled.

(d) Allergen extract mixtures shall be prepared from individual extracts from single source materials. Each individual extract shall be considered as one active substance.

For recombinant allergens, the additional requirements in Section IV.4 also apply.

IX.2. **Animal immunosera products**

The following additional requirements are applicable for animal immunosera products:

(a) Particular care shall be paid to the control of antigens of biological origin to assure their quality, consistency and absence of contamination from adventitious agents. The preparation of materials used to immunise the source animals (e.g. antigens, hapten ([12]) carriers, adjuvants, stabilising agents) as well as the storage conditions for such material immediately prior to immunisation shall be in accordance with documented procedures.

(b) The immunisation, test bleed and harvest bleed schedules shall be in accordance with the terms of the marketing authorisation.

(c) The manufacturing conditions for the preparation of antibody sub-fragments (e.g. Fab or F(ab')2) and any further modifications shall be in accordance with validated parameters. Where such enzymes are made up of several components, their consistency shall be assured.

IX.3. **Vaccines**

The following additional requirements are applicable for vaccines:

(a) Where eggs are used, the health status of all source flocks used in the production of eggs (whether specified pathogen free or healthy flocks) shall be assured.

(b) The integrity of containers used to store intermediate products and the hold times shall be validated.

(c) The sequence of addition of active ingredients, adjuvants and excipients during the formulation of an intermediate or final product shall be in compliance with specifications.

([11]) Allergens that are chemically modified to reduce IgE reactivity.
([12]) A low molecular weight molecule that is not in itself antigenic unless conjugated to a 'carrier' molecule.

(d) Where the manufacture or testing involves the handling of organisms with a higher biological safety level (e.g. panzootic vaccine strains), appropriate containment arrangements shall be in place in accordance with relevant national requirements. Relevant approvals shall be available for verification.

IX.4. **Recombinant products**

The following additional requirements are applicable for recombinant products:

(a) Process conditions during cell growth, protein expression and purification shall be maintained within validated parameters to ensure consistent production with a defined range of impurities. Depending on the type of cell used in production, additional measures may be required to ensure viral safety. When the manufacturing process involves multiple harvests, the period of continuous cultivation shall be within specified limits.

(b) The purification processes to remove unwanted host cell proteins, nucleic acids, carbohydrates, viruses and other impurities shall be within defined validated limits.

IX.5. **Monoclonal antibody products**

The following additional requirements are applicable for monoclonal antibody products:

(a) Monoclonal antibodies may be manufactured from hybridomas or by recombinant DNA technology. Control measures appropriate to the different source cells (including feeder cells if used) and materials used to establish the hybridoma/cell line shall be in place to assure the safety and quality of the product. It shall be verified that these are within approved limits. Viral safety is particularly important. Data originating from products generated by the same manufacturing technology platform may be acceptable to demonstrate suitability.

(b) Production and product parameters at the end of a production cycle (e.g. temperature, Ph, density, oxygen, cell viability, etc.) and for early termination of production cycles shall be defined and monitored.

(c) The manufacturing conditions for the preparation of antibody sub-fragments (e.g. Fab, F(ab')2, scFv) and any further modifications (e.g. radio labelling, conjugation, chemical linking) shall be in accordance with validated parameters.

IX.6. **Veterinary medicinal products derived from genetically modified/genome edited animals**

The following additional requirements are applicable for veterinary medicinal products derived from genetically modified/genome edited animals:

(a) Animals used for production shall be clearly and uniquely identified and backup arrangements shall be put in place in the event of loss of the primary marker.

(b) The genealogy of the founder animals through to production animals shall be documented. Since the genetically modified/genome edited line will be derived from a single genetic founder animal, materials from different genetically modified/genome edited lines shall not be mixed.

(c) The conditions under which the product is harvested shall be in accordance with the terms of the marketing authorisation. The harvest schedule and conditions under which animals may be removed from production shall be performed according to approved procedures and acceptance limits.

(d) Particular attention shall be made to demonstration of batch-to-batch consistency.

IX.7. **Veterinary medicinal products derived from genetically modified/genome edited plants**

The following additional requirements are applicable for veterinary medicinal products derived from genetically modified/genome edited plants.

(a) Additional specific measures may be required to prevent contamination of the master and working genetically modified/genome edited banks by extraneous plant materials and relevant adventitious agents. The stability of the gene within the defined generation numbers shall be monitored.

(b) Plants shall be clearly and uniquely identified, the presence of key plant features, including health status, across the crop shall be verified at defined intervals through the cultivation period to assure consistency of yield between crops.

(c) Security arrangements for the protection of crops shall be defined, wherever possible, to minimise the exposure to contamination by microbiological agents and cross-contamination with non-related plants. Measures shall be put in place to prevent materials such as pesticides and fertilisers from contaminating the product. A monitoring programme shall be established and all results documented. Any incident shall be investigated and its impact on the continuation of the crop in the production programme shall be determined.

(d) Conditions under which plants may be removed from production shall be defined. Acceptance limits shall be set for materials (e.g. host proteins) that may interfere with the purification process. It shall be verified that the results are within the approved limits.

(e) Environmental conditions (temperature, rain) that may affect the quality attributes and yield of the recombinant protein from the time of planting, through cultivation to harvest and interim storage of harvested materials shall be documented. The principles in documents such as 'Guideline on Good Agricultural and Collection Practice for Starting Materials of Herbal Origin' ([13]) shall be taken into account when drawing up such conditions.

(f) Particular attention shall be made to the demonstration of batch-to-batch consistency.

([13]) EMEA/HMPC/246816/2005.

ANNEX III

SPECIFIC REQUIREMENTS FOR CERTAIN VETERINARY MEDICINAL PRODUCTS

This Annex provides for additional requirements and specific adaptations to the requirements set out in this Regulation which shall apply to certain types of veterinary medicinal products.

Unless stated otherwise, the requirements contained in this Annex shall apply in addition to the requirements provided for in the Regulation. In case of conflict, the specific requirements set out in this Annex shall prevail.

I. HERBAL VETERINARY MEDICINAL PRODUCTS

I.1. Taking into account the variability of herbal materials, the control of herbal materials (herbal substances and herbal preparations) used in the manufacture of veterinary medicinal products is particularly important.

I.2. Herbal materials used in the manufacture of veterinary medicinal products shall be of suitable quality. The selection of seeds, cultivation and harvesting conditions are important aspects of the quality of the herbal substance that can influence the consistency of the finished product.

I.3. Table 1 illustrates the application of good practices in connection with the manufacture of veterinary medicinal products.

Table 1

Activity	Good agricultural and collection practice	GMP for active substances used in the manufacture of veterinary medicinal products or GMP for veterinary medicinal products, as applicable	GMP for veterinary medicinal products
Cultivation, collection and harvesting of plants, algae, fungi and lichens, and collection of exudates	Applicable		
Cutting, and drying of plants, algae, fungi, lichens and exudates ([1])	Applicable	Applicable	
Expression from plants and distillation ([2])		Applicable	
Comminution, processing of exudates, extraction from plants, fractionation, purification, concentration or fermentation of herbal substances		Applicable	

Activity	Good agricultural and collection practice	GMP for active substances used in the manufacture of veterinary medicinal products or GMP for veterinary medicinal products, as applicable	GMP for veterinary medicinal products
Further processing into a dosage form, including packaging as finished veterinary medicinal product			Applicable

([1]) Manufacturers shall carry out these steps in accordance with the marketing authorisation. For initial steps that take place in the field, as justified in the marketing authorisation, the standards of good agricultural and collection practice for starting materials of herbal origin (GACP) shall apply. Good manufacturing practice shall apply to further cutting and drying steps.

([2]) Regarding the expression from plants and distillation, if it is necessary for these activities to be an integral part of harvesting to maintain the quality of the product within the approved specifications, it is acceptable that they are performed in the field, provided that the cultivation is in compliance with GACP. This approach may only be accepted in exceptional cases and provided that it is agreed in the relevant marketing authorisation. For activities carried out in the field, appropriate documentation, control and validation according to good manufacturing principles shall be assured.

I.4. The herbal materials used in the manufacture of veterinary medicinal products shall comply with the following:

(a) Specifications shall be set in compliance with the marketing authorisation and shall include:

— the binomial scientific name of plant (genus, species, subspecies/variety and author (e.g. Linnaeus); other relevant information such as the cultivar name and the chemotype shall also be provided, as appropriate;

— details of the source of the plant (country or region of origin, and where applicable, cultivation, time of harvesting, collection procedures, possible pesticides used, possible radioactive contamination, etc.);

— which part(s) of the plant is/are used;

— when a dried plant is used, the drying system shall be specified;

— a description of the herbal substance and its macro and microscopic examination;

— suitable identification tests including, where appropriate, identification tests for constituents with known therapeutic activity or markers. Specific distinctive tests are required where an herbal substance is liable to be adulterated/ substituted. A reference authentic specimen shall be available for identification purposes;

— the water content for herbal substances, which is to be determined in accordance with the European Pharmacopoeia;

— assay of constituents of known therapeutic activity or, where appropriate, of markers;

— methods to determine a possible pesticide contamination and the accepted limits, in accordance with European Pharmacopoeia methods or, in the absence thereof, with an appropriate validated method, unless otherwise justified;

— tests to determine fungal and/or microbial contamination, including aflatoxins, other mycotoxins, pest-infestations and limits accepted, as appropriate;

— tests for toxic metals and for likely contaminants and adulterants, as appropriate;

— tests for foreign materials, as appropriate;

— any other additional test according to the European Pharmacopoeia general monograph on herbal substances or to the specific monograph of the herbal substance, as appropriate.

Any treatment used to reduce fungal/microbial contamination or other infestation shall be specified.

Specifications shall include details of the process, tests and limits for residues, as appropriate.

(b) Suppliers of herbal materials shall comply with good agricultural and collection practice. The suppliers shall be audited by the manufacturer of the herbal veterinary medicinal product in accordance with quality risk management principles. Such audits may be outsourced.

I.5. The following precautions shall be taken regarding storage areas for herbal materials used in the production of veterinary medicinal products:

(a) effective measures shall be implemented to prevent the spread of insects, other animals or micro-organisms brought in with the herbal substance, to prevent fermentation or mould growth and to prevent cross-contamination. Separate enclosed areas shall be used to quarantine incoming herbal substances and for the approved herbal substances;

(b) storage areas shall be well aerated, and the containers shall be located in such a way so as to allow free circulation of air;

(c) where necessary, specific conditions of humidity, temperature or light protection shall be defined and monitored.

I.6. The identity and quality of herbal materials and of herbal medicinal products shall be determined in accordance with the relevant current European guidance on quality and specifications for herbal medicinal products and traditional herbal medicinal products or, where relevant, with the requirements of specific relevant monographs of the European Pharmacopoeia.

I.7. The processing instructions shall describe the different operations to be carried out upon the herbal substance such as cleaning, drying, crushing and sifting, including drying time and temperatures, and methods used to control the cut size or the particle size. Written instructions shall be developed and records shall be kept to ensure that each container of herbal substance is carefully examined to detect any adulteration/substitution or presence of foreign matter, such as metal or glass pieces, animal parts or excrement, stones, sand, or rot and signs of decay.

The processing instructions shall also describe security sieving or other methods of removing foreign materials and appropriate procedures for the cleaning/selection of the plant material before the storage of the approved herbal substance or before the start of manufacturing.

For the production of an herbal preparation, instructions shall include details of solvent, time and temperature of extraction, details of any concentration stages and methods used.

I.8. If dust is generated during processing (including sampling), the use of dust extraction, dedicated premises or other means shall be considered to prevent cross-contamination and facilitate cleaning.

I.9. The equipment and filtering materials used in the manufacturing process shall be compatible with the extraction solvent, in order to prevent any release or undesirable absorption of the substance that could affect the product.

I.10. Due to the fact that medicinal plant/herbal substances are heterogeneous in nature, the following measures shall be implemented regarding sampling:

(a) each batch shall be identified by its own documentation;

(b) a reference sample of the plant material is necessary, especially in those cases where the herbal substance is not described in the European Pharmacopoeia or in another Pharmacopoeia of a Member State. Samples of unmilled plant material are required if powders are used.

I.11. Quality control personnel shall have particular expertise and experience in herbal substances, herbal preparations and/or herbal medicinal products in order to be able to carry out identification tests and recognise adulteration, the presence of fungal growth, infestations, non-uniformity within a delivery of crude material, etc.

II. VETERINARY MEDICINAL PRODUCTS INTENDED FOR INCORPORATION INTO MEDICATED FEEDINGSTUFFS

II.1. Because the manufacture of medicated premixes requires the use of large quantities of vegetable matter which is likely to attract insects and rodents, it is particularly important to ensure that premises are designed, equipped and operated in a way that minimises the risk of intrusion thereof in the site. Enhanced pest control systems shall be put in place to monitor and minimise pest ingress and to take action where appropriate.

II.2. Because of the large volume of dust generated during the production of bulk material for premixes, specific attention shall be paid to the need to avoid cross contamination and facilitate cleaning, for example through the installation of sealed transport systems and dust extraction, whenever possible. The installation of such systems does not, however, eliminate the need for regular cleaning of production areas.

II.3. Parts of the process likely to have a significant adverse influence on the stability of the active ingredient(s) (e.g. use of steam in pellet manufacture) shall be carried out in an uniform manner from batch to batch.

II.4. Whenever possible, the manufacture of premixes shall be made in dedicated areas which, if possible, do not form part of the main manufacturing plant. Alternatively, such dedicated areas shall be surrounded by a buffer zone in order to minimise the risk of contamination of other manufacturing areas.

III. ECTOPARASITIC VETERINARY MEDICINAL PRODUCTS

Ectoparasitic veterinary medicinal products for external application to animals may be produced and filled on a campaign basis in pesticide specific areas. However, other categories of veterinary medicinal products shall not be produced in such areas.

IV. LIQUIDS, CREAMS AND OINTMENTS

As liquids, creams and ointments may be particularly susceptible to microbial and other contamination during manufacture, the following measures shall be considered:

(a) the use of closed systems for processing and transfer is recommended. In cases where the products or open clean containers are exposed to the environment, there shall be effective ventilation with filtered air;

(b) tanks, containers, pipework and pumps shall be designed and installed to facilitate cleaning. In particular, equipment shall include a minimum of dead-legs or sites where residues can accumulate and promote microbial proliferation;

(c) the use of glass apparatus shall be avoided wherever possible. High quality stainless steel is often the material of choice for parts coming into contact with the product;

(d) the chemical and microbiological quality of water used in production shall be specified and monitored. Care shall be taken in the maintenance of water systems in order to avoid the risk of microbial proliferation. After any chemical sanitisation of the water systems, a validated flushing procedure shall be applied to ensure that the sanitising agent has been effectively removed;

(e) materials likely to shed fibres or other contaminants, like cardboard or wooden pallets, shall not enter the areas where products or clean containers are exposed;

(f) the homogeneity of mixtures or suspensions, shall be kept during filling. Special care shall be taken at the beginning of a filling process, after stoppages and at the end of the process to ensure that homogeneity is maintained;

(g) when the finished product is not immediately packaged, the maximum period of storage and the storage conditions shall be specified and adhered to.

V. MEDICINAL GASES

V.1. **Scope**

This Section provides for additional requirements that are applicable to the manufacture of veterinary medicinal products that contain medicinal gases. For the purposes of this Section, the term 'gas' covers any substance that is completely gaseous at 1,013 bar and + 20 °C or has a vapour pressure exceeding 3 bar at + 50 °C.

In the exceptional case of continuous manufacturing, where no intermediate storage of the gas between the manufacture of the active substance and the manufacture of the medicinal product is possible, the whole process (from starting materials of active substance to medicinal finished product) falls under the scope of this Regulation.

V.2. **Personnel**

Personnel shall be specifically trained on the specific hazards from these products; training programs shall include tanker lorries drivers and subcontracted personnel that can influence the quality of medicinal gases (such as personnel in charge of maintenance of cylinders ([1]) or valves).

V.3. **Premises**

V.3.1. Cylinders and mobile cryogenic vessels ([2]) shall be checked, prepared, filled and stored in separate areas from non-medicinal gases, and there shall be no exchange of cylinders/mobile cryogenic vessels between these areas. However, it is acceptable to check, prepare, fill and store other gases in the same areas, provided that such operations are performed according to good manufacturing practice.

V.3.2. Premises shall be designed to provide separate marked areas for different gases and clear identification and segregation of cylinders/mobile cryogenic vessels at various stages of processing (e.g. 'waiting checking' 'awaiting filling', 'quarantine', 'certified', 'rejected', 'prepared deliveries'). The method used to achieve these various levels of segregation will depend on the nature, extent and complexity of the overall operation. Marked-out floor areas, partitions, barriers, signs, labels or other appropriate means may be used.

V.3.3. Cylinders/home cryogenic vessels ([3]) (whether empty after sorting or maintenance or filled) shall be stored under cover and protected from adverse weather conditions. Filled cylinders/mobile cryogenic vessels shall be stored in a manner that ensures that they will be delivered in a clean state, compatible with the environment in which they will be used.

([1]) For the purposes of this Section, 'cylinder' means a container, usually cylindrical, suited for compressed, liquefied or dissolved gas, fitted with a device to regulate the spontaneous outflow of gas at atmospheric pressure and room temperature.

([2]) For the purposes of this Section, 'mobile cryogenic vessel' means a mobile thermally insulated container designed to maintain the contents in a liquid state. This term does not include the tankers.

([3]) For the purposes of this Section, 'home cryogenic vessel' means a mobile cryogenic vessel designed to hold liquid oxygen and dispense gaseous oxygen at patients' home.

V.3.4. Specific storage conditions required by the marketing authorisation (e.g. for gas mixtures where phase separation occurs on freezing) shall be respected.

V.4. **Equipment**

V.4.1. Equipment shall be designed to ensure that the correct gas is filled into the correct container. ([4]) There shall normally be no cross connections between pipelines carrying different gases. If cross connections are needed (e.g. filling equipment of mixtures), as part of the qualification process, it shall be ensured that there is no risk of cross contamination between the different gases. In addition, manifolds ([5]) shall be equipped with specific connections. The use of connections meeting different standards at the same filling site shall be carefully controlled, as well as the use of adaptors that may be needed to bypass the specific fill connection systems.

V.4.2. Tanks ([6]) and tankers ([7]) shall be dedicated to a single and defined quality of gas. However, medicinal gases may be stored or transported in the same tanks/containers for intermediate storage/tankers as the same non-medicinal gas, provided that the quality of the latter is at least equal to the quality of the medicinal gas, that standards of good manufacturing practice are maintained and that the approach is justified in accordance with quality risk management principles.

V.4.3. A common system supplying gas to medicinal and non-medicinal gas manifolds is only acceptable if there is a validated method to prevent backflow from the non-medicinal gas line to the medicinal gas line.

V.4.4. Filling manifolds shall be dedicated to a single medicinal gas or to a given mixture of medicinal gases. In exceptional cases, filling gases used for non-medicinal purposes on manifolds used for medicinal gases may be acceptable if duly justified and performed under control. In these cases, the quality of the non-medicinal gas shall be at least equal to the required quality of the medicinal gas and standards of good manufacturing practice shall be maintained. Further, in such cases, the filling shall be carried out on campaign basis.

V.4.5. Repair and maintenance operations (including cleaning and purging ([8])) of equipment, shall not adversely affect the quality of the medicinal gases. In particular, procedures shall describe the measures to be taken after repair and maintenance operations involving breaches of the system's integrity. Specifically, it shall be demonstrated that the equipment is free from any contamination that may adversely affect the quality of the finished product before releasing it for use. Records shall be maintained.

V.4.6. A procedure shall describe the measures to be taken when a tanker is back into medicinal gas service (after transporting non-medicinal gas under the conditions referred in Section V.4.2, or after a maintenance operation), which shall include appropriate analytical testing.

V.5. **Documentation**

V.5.1. Data included in the records for each batch of medicinal gases shall ensure that each filled container is traceable to significant aspects of the relevant filling operations. As appropriate, the following shall be entered:

— name of the product;

— batch number;

([4]) For the purposes of this Section, 'container' means a cryogenic vessel (tank, tanker or other type of mobile cryogenic vessel) a cylinder, a cylinder bundle or any other package that is in direct contact with the gas.

([5]) For the purposes of this Section, 'manifold' means equipment or apparatus designed to enable one or more gas containers to be emptied or filled at the same time.

([6]) For the purposes of this Section, 'tank' means a static thermally insulated container designed for the storage of a liquefied or a cryogenic gas. A tank can also be called 'fixed cryogenic vessel'.

([7]) For the purposes of this Section, 'tanker' means a thermally insulated container fixed on a vehicle for the transport of a liquefied or a cryogenic gas.

([8]) For the purposes of this Section, 'purge' means the removal of residual gas from a container/system by first pressurising and then venting the gas used for purging to 1.013 bar.

— date and time of the filling operation;

— identification of the person(s) carrying out each significant step (e.g. line clearance, receipt, preparation before filling, filling, etc.);

— batch(es) reference(s) for the gas(es) used for the filling operation, including status;

— equipment used (e.g. filling manifold);

— quantity of cylinders/mobile cryogenic vessels before filling, including individual identification references and water capacity(ies);

— pre-filling operations performed;

— key parameters that are needed to ensure correct filling at standard conditions;

— results of the appropriate checks to ensure that the cylinders/mobile cryogenic vessels have been filled;

— a sample of the batch label;

— specification of the finished product and results of the quality control tests (including reference to the calibration status of the test equipment);

— quantity of rejected cylinders/mobile cryogenic vessels, with individual identification references and reasons for rejections;

— details of any problems or unusual events, and signed authorisation for any deviation from filling instructions;

— certification statement by the qualified person, date and signature.

V.5.2. Records shall be maintained for each batch of gas intended to be delivered into tanks in healthcare facilities. These records shall, as appropriate, include the following:

— name of the product;

— batch number;

— identification reference for the tank;

— date and time of the filling operation;

— identification of the person(s) carrying out the filling of the tank (tanker);

— reference to the supplying tanker (tank), reference to the source gas as applicable;

— relevant details concerning the filling operation;

— specification of the finished product and results of the quality control tests (including reference to the calibration status of the test equipment);

— details of any problems or unusual events, and signed authorisation for any deviation from filling instructions;

— certification statement by the qualified person, date and signature.

V.6. **Production**

V.6.1. Transfers and deliveries of cryogenic and liquefied gas ([9]) shall be done in accordance with the following requirements:

(a) The transfer of cryogenic or liquefied gases from primary storage, including the controls before the transfer, shall be in accordance with validated procedures designed to avoid the possibility of contamination. Transfer lines shall be equipped with non-return valves ([10]) or other suitable alternatives. Flexible connections, coupling hoses and connectors shall be flushed with the relevant gas before use.

(b) The transfer hoses used to fill tanks and tankers shall be equipped with product-specific connections. The use of adaptors allowing the connection of tanks and tankers not dedicated to the same gases shall be adequately controlled.

(c) Deliveries of gas may be added to tanks containing the same defined quality of gas provided that a sample is tested to ensure that the quality of the delivered gas is acceptable. That sample may be taken from the gas to be delivered or from the receiving tank after delivery.

(d) The filling of tanks retained by customers at customer's premises is to be done according to Section V.7.3.

V.6.2. Filling and labelling of cylinders and mobile cryogenic vessels shall be done in accordance with the following requirements:

(a) Before filling cylinders and mobile cryogenic vessels, a batch (batches) of gas(es) shall be determined, controlled according to specifications and approved for filling.

(b) In the case of continuous processes, adequate in-process controls shall be implemented to ensure that the gas complies with the specifications.

(c) Cylinders, mobile cryogenic vessels and valves shall conform to appropriate technical specifications and relevant requirements of the marketing authorisation. They shall be dedicated to a single medicinal gas or to a given mixture of medicinal gases. Cylinders shall be colour-coded according to relevant standards. They shall preferably be fitted with minimum pressure retention valves ([11]) with non-return mechanism in order to provide adequate protection against contamination.

(d) Cylinders, mobile cryogenic vessels and valves shall be checked before first use in production and shall be properly maintained. Where CE marked medical devices are used, the maintenance shall be in accordance with the manufacturer's instructions.

(e) Checks and maintenance operations shall not affect the quality and the safety of the medicinal product. The water used for the hydrostatic pressure testing carried out on cylinders shall be at least of drinking quality.

(f) As part of the checks and maintenance operations, cylinders shall be subject to an internal visual inspection before fitting the valve, to make sure that they are not contaminated with water or other contaminants. Specifically, this is required when they are new and initially put into medicinal gas service, following any hydrostatic statutory pressure test or equivalent test where the valve is removed, or whenever the valve is replaced.

([9]) For the purposes of this Section, 'liquefied gas' means a gas which, when packaged for transport, is partially liquid (or solid) at a temperature above – 50 °C.

([10]) For the purposes of this Section, 'non-return valve' means a valve that permits flow in one direction only.

([11]) For the purposes of this Section, 'minimum pressure retention valve' means a cylinder valve, which maintains a positive pressure above atmospheric pressure in a gas cylinder after use, in order to prevent internal contamination of the cylinder.

(g) After fitting, the valve shall be kept closed to prevent any contamination from entering the cylinder. If there is any doubt about the internal condition of the cylinder, the valve shall be removed and the cylinder internally inspected to ensure that it has not been contaminated.

(h) Maintenance and repair operations of cylinders, mobile cryogenic vessels and valves are the responsibility of the manufacturer of the medicinal product. If subcontracted, they shall only be carried out by approved subcontractors, and contracts – including technical specifications – shall be established. Subcontractors shall be audited to ensure that appropriate standards are maintained.

(i) A system to ensure the traceability of cylinders, mobile cryogenic vessels and valves shall be put in place.

(j) Checks to be performed before filling include:

— For cylinders, a check according to a defined procedure shall be carried out to ensure there is a positive residual pressure in each cylinder.

If the cylinder is fitted with a minimum pressure retention valve and there is no signal indicating that there is a positive residual pressure, the correct functioning of the valve shall be checked. If the valve is shown not to function properly, the cylinder shall be sent to maintenance.

If the cylinder is not fitted with a minimum pressure retention valve and there is no positive residual pressure, the cylinder shall be put aside for additional measures, to make sure that it is not contaminated with water or other contaminants; additional measures such as of internal visual inspection followed by cleaning using a validated method may be considered.

— A check to ensure that all previous batch labels have been removed.

— A check to verify that any damaged product labels have been removed and replaced.

— A visual external inspection of each cylinder, mobile cryogenic vessel and valve for dents, arc burns, debris, other damage and contamination with oil or grease; cleaning shall be done if necessary.

— A check of each cylinder or mobile cryogenic vessel outlet connection to determine that it is the proper type for the particular gas involved.

— A check of the date of the next test to be performed on the valve (in the case of valves that need to be periodically tested).

— A check of the cylinders or mobile cryogenic vessels to ensure that any tests required by national or international regulations (e.g. hydrostatic pressure test or equivalent for cylinders) have been conducted and are still valid.

— A check to determine that each cylinder is colour-coded as specified in the marketing authorisation (colour-coding of the relevant national/international standards).

(k) Cylinders that have been returned for refilling shall be prepared with care in order to minimise the risks of contamination, in line with the procedures defined in the marketing authorisation. These procedures, which shall include evacuation ([12]) and/or purging operations, shall be validated ([13]).

(l) Mobile cryogenic vessels that have been returned for refilling shall be prepared with care in order to minimise the risks of contamination, in line with the procedures defined in the marketing authorisation. In particular, mobile vessels with no residual pressure shall be prepared using a validated method.

([12]) For the purposes of this Section, 'evacuation' means the removal of a residual gas from a container/system to a pressure less than 1,013 bar, using a vacuum system.

([13]) For compressed gases, a maximum theoretical impurity of 500 ppm v/v should be obtained for a filling pressure of 200 bar at 15 °C (and equivalent for other filling pressures).

(m) There shall be appropriate checks to ensure that each cylinder/mobile cryogenic vessel has been properly filled.

(n) Each filled cylinder shall be tested for leaks using an appropriate method, prior to fitting the tamper evident seal. The test method shall not introduce any contaminant into the valve outlet and, where applicable, shall be performed after any quality sample is taken.

(o) After filling, cylinders valves shall be fitted with covers to protect the outlets from contamination. Cylinders and mobile cryogenic vessels shall be fitted with tamper-evident seals.

(p) Each cylinder or mobile cryogenic vessel shall be labelled. The batch number and the expiry date may be on a separate label.

(q) In the case of medicinal gases produced by mixing two or more different gases (in-line before filling or directly into the cylinders), the mixing process shall be validated to ensure that the gases are properly mixed in every cylinder and that the mixture is homogeneous.

V.7. **Quality control**

V.7.1. For cylinders, the sampling plan and the analysis to be performed shall meet, the following requirements, unless stated otherwise in the marketing authorisation:

(a) In the case of a single medicinal gas filled into cylinders via a multi-cylinder manifold, the gas from at least one cylinder from each manifold filling cycle shall be tested for identity and assay each time the cylinders are changed on the manifold.

(b) In the case of a single medicinal gas filled into cylinders one at a time, the gas from at least one cylinder of each uninterrupted filling cycle shall be tested for identity and assay. An example of an uninterrupted filling cycle is one shift's production using the same personnel, equipment and batch of gas to be filled.

(c) In the case of a medicinal gas produced by mixing two or more gases in a cylinder from the same manifold, the gas from every cylinder shall be tested for assay and identity of each component gas. For excipients, if any, testing on identity may be performed on one cylinder per manifold filling cycle (or per uninterrupted filling cycle in case of cylinders filled one at a time). It is acceptable to test fewer cylinders in case of validated automated filling system.

(d) Premixed gases shall follow the same principles as single gases when continuous in-line testing of the mixture to be filled is performed. Premixed gases shall follow the same principle as medicinal gases produced by mixing gases in the cylinders when there is no continuous in-line testing of the mixture to be filled.

Testing for water content shall be performed unless otherwise justified.

V.7.2. Final testing on mobile cryogenic vessels shall include a test for assay and identity on each vessel, unless otherwise stated in the marketing authorisation. Testing by batches is only acceptable if it has been demonstrated that the critical attributes of the gas remaining in each vessel before refilling have been maintained.

V.7.3. Cryogenic vessels retained by customers (tanks in healthcare facilities or home cryogenic vessels) which are refilled in place from dedicated tankers do not need to be sampled after filling provided that a certificate of analysis on the contents of the tanker accompanies the delivery. However, it shall be demonstrated that the specification of the gas in the vessels is maintained over the successive refillings.

V.7.4. Reference and retention samples are not required, unless otherwise specified. On-going stability studies are not required in case initial stability studies have been replaced by bibliographic data ([14]).

([14]) Note for Guidance CPMP/QWP/1719/00.

VI. PRESSURISED METERED DOSE AEROSOL PREPARATIONS FOR INHALATION

VI.1. **General**

VI.1.1. The manufacture of pressurised metered dose aerosol veterinary medicinal products for inhalation with metering valves shall be done under conditions which minimise microbial and particulate contamination.

VI.1.2. Assurance of the quality of the valve components and, in the case of suspensions, of uniformity is particularly important.

VI.2. **Premises and equipment**

VI.2.1. Whenever possible, manufacture and filling shall be carried out in a closed system.

VI.2.2. Where products or clean components are exposed, the area shall be fed with filtered air, comply with the requirements of at least a Grade D environment and be entered through airlocks.

VI.3. **Production and quality control**

VI.3.1. The specifications, sampling and testing for the metering valves shall adequately address the complexity thereof.

VI.3.2. The valve manufacturer shall be audited as regards compliance with quality requirements.

VI.3.3. All fluids (e.g. liquid or gaseous propellants) shall be filtered to remove particles greater than 0,2 micron. An additional filtration immediately before filling shall be considered, where possible.

VI.3.4. Containers and valves shall be cleaned using a validated procedure appropriate to the use of the product to ensure the absence of any contaminants such as processing aids (e.g. lubricants) or undue microbiological contaminants. After cleaning, valves shall be kept in clean, closed containers and precautions shall be taken not to introduce contamination during subsequent handling, e.g. taking samples. Containers shall be fed to the filling line in a clean condition or cleaned on-line immediately before filling.

VI.3.5. Precautions shall be taken to ensure uniformity of suspensions at the point of fill throughout the filling process.

VI.3.6. When a two-shot filling process is used, it is necessary to ensure that both shots are of the correct weight in order to achieve the correct composition. For this purpose, 100 % weight checking at each stage is recommended.

VI.3.7. Controls after filling shall ensure the absence of undue leakage. Any leakage test shall be performed in a way that avoids microbial contamination or residual moisture.

ANNEX IV

COMPUTERISED SYSTEMS

I. SCOPE

The requirements set out in this Annex shall apply to computerised systems that are used in connection with the manufacture of veterinary medicinal products, in so far as such use falls under the scope of good manufacturing practices. The use of computer systems in manufacturing sites for purposes not connected with the pharmaceutical quality system (e.g. staff matters, commercial issues, etc.) are not concerned by the requirements in this Annex.

II. GENERAL REQUIREMENTS

II.1. IT infrastructure [1] used in the manufacture of veterinary medicinal products shall be qualified. Any related software application shall also be validated. The extent of the validation shall be based on risk management principles having regard to the need to ensure product quality and data integrity.

II.2. The outsourcing of tasks/operations related to the installation, configuration, validation, maintenance, modification of a computerised system or any other related service or for data processing shall be made by means of a written contract that shall provide for a clear delineation of the responsibilities of each party.

II.3. The suitability of the contractor (including by means of audits where appropriate) shall be assessed applying risk management principles.

II.4. Documentation supplied with commercial off-the-shelf products shall be reviewed by the manufacturer to check that user requirements are fulfilled.

II.5. Suppliers of software specifically developed/adapted for use within the manufacturing process shall be qualified. Where necessary and upon the request of inspectors, the manufacturer of veterinary medicinal products shall be able to produce information from the quality system of the suppliers or developers of such specific software. The contractual agreements between the software suppliers and the manufacturer of veterinary medicinal products shall contain adequate provisions to this effect.

III. DEVELOPMENT PHASE

III.1. The manufacturer shall take all reasonable steps to ensure that the system is suitable to ensure the quality of the product, the consistency of the manufacturing process and compliance with the goals of the pharmaceutical quality system.

III.2. User requirements specifications shall describe the required functions of the computerised system and shall be based on risk assessment principles. User requirement specifications shall be traceable throughout the life-cycle of the computerised system.

III.3. The standards, protocols, acceptance criteria, procedures and records shall be justified on the basis of a risk assessment.

III.4. The validation documentation and reports shall cover the relevant steps of the entire life cycle. The validation documentation shall include change control records (if applicable) and reports on any deviations observed during the validation process.

III.5. A process shall be in place for the validation of bespoke or customised computerised systems which ensures the formal assessment and reporting of the quality and performance parameters for all the life-cycle stages of the system.

[1] For the purposes of this Annex, 'IT infrastructure' means the hardware and software that is necessary for the system to function (e.g. networking software and operation systems).

III.6. The suitability of the testing procedures and test scenarios shall be demonstrated. System (process) parameter limits, data limits and error handling shall be duly considered. When automated testing tools are used, an assessment of their adequacy, including of the environment where the test is conducted, shall be required.

III.7. When data are transferred to another data format or system, it shall be verified that the migration process has not altered the data (in value or meaning).

IV. OPERATIONAL PHASE

IV.1. An up-to-date listing of all the relevant systems and their functionality (inventory) shall be kept. In the case of critical systems, the system description shall detail the physical and logical arrangements, data flows and interfaces with other systems or processes, any hardware and software pre-requisites and security measures.

IV.2. Computerised systems exchanging data electronically with other systems shall include appropriate built-in checks for the correct and secure entry and processing of data.

IV.3. For critical data entered manually, an additional check on the accuracy of the data shall be performed. This check may be done by a second operator or by validated electronic means. The criticality and the potential consequences of erroneous or incorrectly entered data shall be addressed under risk management principles.

IV.4. Data shall be secured by both physical and electronic means against damage. The readability and accuracy of stored data shall be ensured, as well as the accessibility thereof throughout the retention period.

IV.5. Regular back-ups of all relevant data shall be done. Integrity and accuracy of backup data and the ability to restore the data shall be checked during validation and be periodically monitored.

IV.6. It shall be ensured that electronically stored data can be printed. For records supporting the batch release it shall be possible to generate printouts indicating if any of the data has been changed since the original entry.

IV.7. Based on a risk assessment, it may be appropriate to build into the system the creation of a record of all changes that are relevant to demonstrate compliance with good manufacturing practice and deletions (a system generated "audit trail"). In case of change or deletion of relevant data, the reason shall be documented. Audit trails shall be available and convertible to a generally intelligible form and regularly reviewed.

IV.8. Changes to a computerised system, including system configurations, shall only be made in a controlled manner in accordance with a defined procedure.

IV.9. Computerised systems shall be periodically evaluated to confirm that they remain in a valid state and in compliance with the requirements set out in this Annex. Such evaluations shall include, where appropriate, the current range of functionality, deviation records, incidents, problems, upgrade history, performance, reliability, security and validation status reports.

IV.10. Physical or logical controls shall be in place to restrict the access to computerised systems and the data storage area to authorised persons only. Suitable methods of preventing unauthorised entry to the system, commensurate to the criticality of the computerised system, shall be implemented.

IV.11. The generation, change or cancellation of access authorisations shall be recorded.

IV.12. The identity of operators creating, changing, confirming or deleting data shall be recorded, including the date and time where the operations occur.

IV.13. All incidents, not only system failures and data errors, shall be reported and assessed. The root cause of a critical incident shall be identified and shall form the basis for the implementation of corrective and preventive actions as appropriate.

IV.14. Electronic records may be signed electronically. Electronic signatures shall be permanently linked to their respective record and shall include the time and date when they were generated.

IV.15. When a computerised system is used for recording certification, the system shall be designed/controlled to ensure that only the Qualified Person can certify the batches.

IV.16. The continuity of operations performed by computerised systems supporting critical processes, shall be ensured in the event of a system breakdown (e.g. by means of a manual or another alternative system). The time required to bring the alternative arrangements into use shall be commensurate to the risks. The implemented arrangements shall be documented and tested.

IV.17. Data may be archived. This data shall be checked for accessibility, readability and integrity. If relevant changes are to be made to the system (e.g. computer equipment or programs), then the ability to retrieve the data shall be ensured and tested.

ANNEX V

QUALIFICATION AND VALIDATION

I. SCOPE

The requirements set out in this Annex shall apply to the qualification of equipment, facilities, utilities and systems used for the manufacture of veterinary medicinal products and the validation of the manufacturing process. Computerised systems used for the manufacture of veterinary medicinal products shall be validated according to the requirements set out in Annex IV.

II. GENERAL REQUIREMENTS

II.1. Decisions on the scope and extent of the qualification/validation shall be based on a documented risk assessment. Retrospective qualification/validation is not acceptable. Data supporting qualification/validation studies that were obtained from sources outside of the manufacturers own programmes may be used provided that this approach is justified and that there is adequate assurance of the reliability thereof to support the intended qualification/validation.

II.2. Qualification and validation activities shall take into consideration the life cycle of the relevant equipment, facilities, utilities, systems and of the veterinary medicinal product.

II.3. Any planned changes to the equipment, facilities, utilities, systems or manufacturing process that may affect the quality of the veterinary medicinal product shall be formally documented and its impact on the validated status or control strategy shall be assessed.

II.4. Qualification and validation activities shall only be performed by suitably trained personnel who follow approved procedures, including on reporting. There shall be appropriate oversight over the whole validation life cycle.

II.5. The key elements of the site qualification and validation programme shall be clearly defined and documented in a validation master plan or in an equivalent document, which – as a minimum – shall include or refer to the following:

(a) the general qualification and validation approach applied by the manufacturer;

(b) the organisational structure, including roles and responsibilities for qualification and validation activities;

(c) a summary of the equipment, facilities, utilities, systems, manufacturing processes on site and their qualification/validation status;

(d) the strategy for the implementation of changes ('change control') and management of deviations for qualification and validation;

(e) guidance on developing acceptance criteria;

(f) references to documents supporting/recording qualification and validation;

(g) the qualification and validation strategy/plan for the equipment, facilities, utilities, systems or processes, including requalification, where applicable.

II.6. A quality risk management approach shall be used for qualification and validation activities. Where required, in light of increased knowledge acquired during the life-cycle, the risk assessments shall be repeated. The way in which risk assessments are used to support qualification and validation activities shall be documented.

II.7. Appropriate checks shall be incorporated into qualification and validation work to ensure the integrity of all data obtained.

III. DOCUMENTATION

III.1. All documents generated during qualification and validation shall be approved and authorised by appropriate personnel as defined in the pharmaceutical quality system.

III.2. The inter-relationship between documents in complex qualification/validation projects shall be clearly defined.

III.3. Qualification/validation protocols defining the critical systems, attributes and parameters and the associated acceptance criteria shall be prepared.

III.4. Qualification documents may be combined together, where appropriate, e.g. installation qualification and operational qualification.

III.5. Where qualification/validation protocols and other documentation are supplied by a third party providing validation services, appropriate personnel at the manufacturing site shall confirm their suitability and compliance with internal procedures before approval. Vendor protocols may be supplemented by additional documentation/test protocols before use.

III.6. Any significant changes to the approved protocol during execution (e.g. acceptance criteria, operating parameters, etc.) shall be documented as a deviation and be scientifically justified.

III.7. Results that fail to meet the pre-defined acceptance criteria shall be recorded as a deviation and be fully investigated. Implications for the qualification/validation status shall be discussed in the report.

III.8. The review and conclusions of the qualification/validation shall be reported and the results obtained summarised against the acceptance criteria. Any subsequent changes to acceptance criteria shall be scientifically justified and a final recommendation made as to the outcome of the qualification/validation.

III.9. A formal release for the next stage in the qualification/validation process shall be authorised by the relevant responsible personnel either as part of the qualification/validation report approval or as a separate summary document. Conditional approval to proceed to the next qualification/validation stage may be given where certain acceptance criteria or deviations have not been fully addressed and there is a documented assessment supporting that there is no significant impact on the next activity.

IV. QUALIFICATION STAGES FOR EQUIPMENT, FACILITIES, UTILITIES AND SYSTEMS

IV.1. Qualification activities shall consider all stages, from the initial development of the user requirements specification up to the end use of the equipment, facility, utility or system. While the specific stages/criteria are to be adapted to the specific project characteristics, the main stages and some criteria that may be included in each stage are indicated in Sections IV.2 to IV.7 for orientation purposes.

IV.2. **User requirements specification**

Specifications for equipment, facilities, utilities or systems shall be defined in a user requirements specification or a functional specification document. The essential elements of quality shall be built in at this stage and any risks mitigated to an acceptable level. The user requirement specification is a point of reference throughout the validation life cycle.

IV.3. **Design qualification**

Design qualification is the documented verification that the proposed design of the equipment, facilities, utilities or systems is suitable for the intended purpose. Through design qualification the compliance of the design with good manufacturing practice shall also be demonstrated and documented. The requirements of the user requirements specification shall be verified during the design qualification.

IV.4. **Factory acceptance testing / Site acceptance testing**

Where applicable, equipment may be evaluated at the vendor site, prior to delivery. This may be particularly relevant in case of novel or complex technologies.

Prior to installation, the equipment shall be confirmed to comply with the user requirements specification / functional specification at the vendor site, if applicable.

Where appropriate and justified, documentation review and some tests may be performed as part of the factory acceptance testing or other stages without the need for repetition thereof on site as part of installation qualification or operational qualification, provided that it is shown that the functionality is not affected by the transport and installation.

Factory acceptance testing may be supplemented by the execution of a site acceptance testing following the receipt of equipment at the manufacturing site.

IV.5. **Installation qualification (IQ)**

Installation qualification is the documented verification that the equipment, facilities, utilities or systems, as installed or modified, comply with the approved design and the manufacturer's recommendations.

Installation qualification shall include, but is not limited to the following:

(a) verification of the correct installation of components, instrumentation, equipment, pipe work and services against the engineering drawings and specifications;

(b) verification of the correct installation against the pre-defined criteria;

(c) collection and collation of supplier operating and working instructions and maintenance requirements;

(d) calibration of instruments;

(e) verification of the materials of construction.

IV.6. **Operational qualification (OQ)**

Operational qualification is the documented verification that the equipment, facilities, utilities or systems, as installed or modified, perform as intended throughout the anticipated operating ranges. While operational qualification usually follows installation qualification, depending on the complexity of the equipment, a combined installation/operation qualification may be performed.

Operational qualification shall include, but is not limited to, the following:

— tests that have been developed from the knowledge of processes, systems and equipment to ensure the system is operating as designed;

— tests to confirm upper and lower operating limits, including worst case conditions.

IV.7. **Performance qualification**

Performance qualification is the documented verification that equipment, facilities, utilities or systems can perform effectively and reproducibly based on the approved specifications and manufacturing process. While this step shall generally take place after the successful completion of installation and operational qualification, in some cases, it may be appropriate to perform it in conjunction with operational qualification or process validation.

Performance qualification shall include tests, using production materials, qualified substitutes or a simulated product that has been demonstrated to have an equivalent behaviour under normal operating conditions with worst case batch sizes. The frequency of sampling used to confirm process control shall be justified.

Tests shall cover the operating range of the intended process, unless documented evidence from the development phases confirming the operational ranges is available.

Other requirements

IV.8. The quality of steam, water, air and other gases shall be confirmed after the installation in accordance with the approach above-referred. The period and extent of the qualification shall take due consideration of seasonal variations (where relevant) and the intended use of the utility.

IV.9. A risk assessment shall be carried out in cases where there may be a direct contact with the product (e.g. heating, ventilation and air-conditioning (HVAC) systems) or an indirect contact (e.g. through heat exchangers) to mitigate any risks of failure.

IV.10. The qualification of the equipment used for primary packaging shall be carried out at the minimum and maximum operating ranges defined for the critical process parameters such as temperature, machine speed and sealing pressure.

V. RE-QUALIFICATION

V.1. Equipment, facilities, utilities and systems shall be re-evaluated at an appropriate frequency to confirm that they remain suitable for the intended operations.

V.2. The need for re-qualification (e.g. following changes to equipment/systems) shall be evaluated on the basis of quality risk management principles.

VI. PROCESS VALIDATION

VI.1. **General requirements**

VI.1.1. Process validation is the documented evidence that the process, operated within the established parameters, can perform effectively and reproducibly to produce a veterinary medicinal product within the required specifications and quality attributes and in compliance with the terms of the marketing authorisation.

VI.1.2. Through the process validation it shall be shown that all quality attributes and process parameters that are important for ensuring the required product quality can be consistently met by the process. The classification of process parameters and quality attributes as critical or non-critical shall be conducted having regard to available product and process knowledge ([1]) and based on a risk assessment; it shall be duly documented.

VI.1.3. Manufacturing processes shall be shown to be capable of ensuring consistent production of a product of the required quality and in compliance with the requirements set in the marketing authorisation before the veterinary medicinal products are placed on the market. Retrospective validation is not acceptable.

VI.1.4. Process validation of new products shall cover all intended marketed strengths and sites of manufacture. Bracketing may be justified for new products based on extensive process knowledge from the development stage in conjunction with an appropriate ongoing verification programme.

VI.1.5. For process validation of products that are transferred from one site to another or within the same site, the number of validation batches may be reduced by the use of a bracketing approach. This approach shall be scientifically justified on the basis of existing product knowledge. Different strengths, batch sizes and pack sizes/container types may also use a bracketing approach, if justified.

VI.1.6. Batches used for process validation shall usually be of the same size as the intended commercial scale batches; the use of any other batch sizes shall be duly justified.

([1]) Adequate process knowledge is particularly relevant where the concept of design space is used as well as for the development of any mathematical models.

VI.1.7. Equipment, facilities, utilities and systems used for process validation shall be qualified. In addition, test methods used for process validation shall be validated for their intended use.

VI.1.8. Validation batches may be released to the market only if this is pre-defined and provided that they comply with good manufacturing practice (including the validation acceptance criteria or continuous process verification criteria) and with the terms of the marketing authorisation.

VI.2. **Traditional process validation**

VI.2.1. Under the so-called traditional approach, a number of batches of the finished product are manufactured under routine conditions to confirm reproducibility.

VI.2.2. While it is generally considered acceptable that a minimum of three consecutive batches manufactured under routine conditions can constitute a validation of the process, the number of batches used for process validation shall be justified on the basis of a risk assessment that takes into consideration the complexity of the process and the variability of the results from the process as well as other relevant factors.

An alternative number of batches may be justified taking into account whether standard methods of manufacture are used and whether similar products or processes are already manufactured/used at the site. An initial validation exercise with three batches may need to be supplemented with further data obtained from subsequent batches as part of an on-going process verification exercise.

VI.2.3. A process validation protocol shall be developed which shall define the critical process parameters (i.e. process parameters the variability of which have an impact on critical quality attributes and which therefore shall be monitored or controlled to ensure the desired product quality), critical quality attributes (i.e. physical, chemical, biological or microbiological characteristics that shall be controlled to ensure the desired product quality) and the associated acceptance criteria based on development data or process knowledge.

VI.2.4. Process validation protocols shall include, but are not limited to, the following:

(a) a short description of the process and a reference to the respective batch record;

(b) functions and responsibilities;

(c) a summary of the critical quality attributes to be investigated;

(d) a summary of critical process parameters and their associated limits;

(e) a summary of other (non-critical) attributes and parameters to be investigated or monitored during the validation activity, and the reasons for their inclusion;

(f) a list of the equipment/facilities to be used (including measuring/monitoring/recording equipment) together with the calibration status;

(g) a list of analytical methods and method validation, as appropriate;

(h) proposed in-process controls with acceptance criteria and the reason(s) why each in-process control is selected;

(i) additional testing to be carried out with acceptance criteria;

(j) the sampling plan and the rationale behind it;

(k) methods for recording and evaluating results;

(l) the process for release and certification of batches (if applicable).

VI.3. **Continuous process verification**

VI.3.1. Continuous process verification may be used as an alternative to traditional process validation for products developed under a quality by design approach, where it has been scientifically established during the development phase that the established control strategy provides a high degree of assurance of product quality.

VI.3.2. The method by which the process will be verified shall be defined. There shall be a science-based control strategy for the required attributes for incoming materials, critical quality attributes and critical process parameters. The control strategy shall be regularly evaluated. Process analytical technology and multivariate statistical process control may be used as tools.

VI.3.3. The number of batches necessary to demonstrate that the process is capable of consistently delivering a product of the desired quality and in compliance with the terms of the marketing authorisation shall be set case by case having regard to the specificities of the product and applying quality risk management principles.

VI.4. **Hybrid approach**

VI.4.1. A hybrid of the traditional approach and continuous process verification may be used where there is a substantial amount of product and process knowledge gained from manufacturing experience and historical batch data.

VI.4.2. This approach may also be used for any validation activities after changes or during ongoing process verification even though the product was initially validated using a traditional approach.

VI.5. **Ongoing process verification during lifecycle**

VI.5.1. Ongoing process verification (also known as continued process verification) is the documented evidence that the manufacturing process is capable of ensuring consistent production of a product of the required quality and in compliance with the requirements set in the marketing authorisation. Ongoing process verification is applicable regardless of the approach to process validation implemented (traditional, continuous or hybrid).

VI.5.2. The extent and frequency of the ongoing process verification shall be reviewed periodically having regard to the level of process understanding and process performance.

VI.5.3. Ongoing process verification shall be conducted under an approved protocol or equivalent documents and a report shall be prepared to document the results obtained. Statistical tools shall be used, where appropriate, to support any conclusions.

VI.5.4. Ongoing process verification shall be used throughout the product lifecycle to support the validated status of the product, taking into consideration the outcome of the product quality review. Incremental changes over time shall also be considered and the need for any additional actions, e.g. enhanced sampling, shall be assessed.

VI.6. **Concurrent validation**

VI.6.1. In exceptional circumstances, where there is a strong benefit-risk ratio for the treated animal, it may be acceptable not to complete a validation programme before routine production starts and concurrent validation may be used. However, the decision to carry out concurrent validation must be justified, documented and approved by authorised personnel.

VI.6.2. Where a concurrent validation approach has been adopted, there shall be sufficient data to support a conclusion that any given batch of product is uniform and meets the defined acceptance criteria. The results and conclusions shall be formally documented and available to the qualified person prior to the certification of the batch.

VII. VALIDATION OF TEST METHODS

VII.1. Analytical methods that are used for the manufacture or control of veterinary medicinal products (including those supporting validation and qualification) shall be validated. The validation shall demonstrate the suitability of the analytical methods for the intended purpose.

VII.2. Analytical procedures, which are either described in the European Pharmacopoeia, the pharmacopoeia of a Member State, or are linked to a product specific monograph, and are performed according to the monograph, are generally considered as validated. In such cases, the suitability of the validated test for the intended purpose shall be verified.

VII.3. Where microbial testing of product is carried out, the method shall be validated to confirm that the product does not influence the recovery of microorganisms.

VII.4. Where microbial testing of surfaces in clean rooms is carried out, the test method shall be validated to confirm that the use of sanitising agents does not influence the recovery of microorganisms.

VIII. CLEANING VALIDATION

VIII.1. Cleaning validation is the documented evidence that a given cleaning procedure reproducibly removes contaminants, residues from previous product and cleaning agents below a pre-defined threshold. Cleaning validation is required to confirm the effectiveness of cleaning procedures for all product contact equipment.

VIII.2. Simulating agents (i.e. materials that closely resemble the specific characteristics of the relevant product) may be used provided that it is scientifically justified.

VIII.3. The cleaning validation for similar types of equipment may be grouped together provided that it is duly justified.

VIII.4. While a visual check for cleanliness is part of the acceptance criteria for cleaning validation, this criterion alone is generally not sufficient. Moreover, repeated cleaning and retesting until acceptable residue results are obtained is not considered an acceptable approach.

VIII.5. It is recognised that cleaning validation may take some time to complete and that, in such cases, verification ([2]) after each batch is required until the validation is complete. When this approach is implemented, there shall be sufficient data from the verification to support a conclusion that the equipment is clean and available for further use.

VIII.6. Validation shall consider the level of automation in the cleaning process. Where an automatic process is used, the specified normal operating range of the utilities and equipment shall be validated.

VIII.7. An assessment shall be performed to determine the variable factors that influence the effectiveness and performance of the cleaning procedure (e.g. operators, the level of detail in procedures such as rinsing times, etc.) If variable factors have been identified, the worst case situations shall be used as the basis for the cleaning validation studies.

([2]) For the purposes of this Annex, 'cleaning verification' means the gathering of evidence through chemical analysis after each batch/campaign to show that the residues of the previous product or cleaning agents have been reduced below the scientifically set maximum limit.

VIII.8. Limits for the carryover of product residues shall be based on a toxicological evaluation ([3]), The justification for the selected limits shall be documented in a risk assessment including all the supporting references. Limits shall also be established for the removal of the cleaning agents used. Acceptance criteria shall consider the potential cumulative effect of multiple items of equipment used. The following adaptations are however possible:

(a) therapeutic macromolecules and peptides are known to degrade and denature when exposed to pH extremes and/or heat, and may become pharmacologically inactive. A toxicological evaluation may therefore not be applicable in these circumstances;

(b) if it is not feasible to test for specific product residues, other representative parameters may be selected, e.g. total organic carbon (TOC) and conductivity.

VIII.9. The risk presented by microbial and endotoxin contamination shall be considered during the development of cleaning validation protocols.

VIII.10. The influence of the time between the manufacture and the cleaning, and the time between the cleaning and the use shall be taken into account to define dirty and clean hold times for the cleaning process.

VIII.11. Where campaign manufacture is carried out, the impact on the ease of cleaning at the end of the campaign shall be considered and the maximum length of a campaign (in time and/or number of batches) shall be the basis for cleaning validation exercises.

VIII.12. Where a worst-case product approach is used as a cleaning validation model, a scientific rationale shall be provided for the selection of the worst-case product and the impact of new products assessed. Criteria for determining the worst case may include solubility, cleanability, toxicity and potency.

VIII.13. Cleaning validation protocols shall specify or make reference to the locations to be sampled and the rationale for the selection of these locations and shall define the acceptance criteria.

VIII.14. Sampling may be carried out by swabbing, rinsing or by other means depending on the production equipment. The sampling materials and method applied shall not influence the result. Recovery shall be shown to be possible from all product contact materials sampled in the equipment with the sampling methods used.

VIII.15. The cleaning procedure shall be performed an appropriate number of times based on a risk assessment and meet the acceptance criteria in order to prove that the cleaning method is validated.

VIII.16. Where a cleaning process is ineffective or is not appropriate for some equipment, dedicated equipment or other appropriate measures shall be implemented.

VIII.17. Where manual cleaning of equipment is performed, the effectiveness of the manual process shall be confirmed at a justified frequency.

([3]) See EMA Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities.

ANNEX VI

TEMPLATE FOR THE SITE MASTER FILE

Note 1: The site master file relates to the pharmaceutical activities carried out at a specific site. If only part of a manufacturing process is undertaken at a site, the site master file need only relate to such operations (e.g. analysis, packaging).

Note 2: The site master file shall contain adequate information but, as far as possible, shall not exceed 25-30 pages, plus appendices. The document shall be readable when printed on A4 paper sheets.

Note 3: The site master file shall be kept up to date and be representative of current activities. The site master file shall have an edition number, the date when it becomes effective and the date by which it has to be reviewed. Each Appendix may have an individual effective date and be subject to a specific review date.

1. GENERAL INFORMATION ON THE MANUFACTURER

1.1. **Contact information on the manufacturer**

— Name and official address of the manufacturer.

— Name and street address of the site, buildings and production units located on the site.

— Contact information of the manufacturer, including the telephone number of the personnel to be contacted in the case of product defects or recalls (this number shall be always operational, including outside business hours).

— Identification number of the site, using a geolocalisation system such as Galileo or GPS. In addition, OMS ([1]) is mandatory for submissions in the EEA.

1.2. **Authorised pharmaceutical manufacturing activities of the site**

— Copy of a valid manufacturing authorisation issued by the relevant competent authority shall be provided as Appendix 1. Alternatively, reference to the EudraGMDP database may be provided (where applicable). In cases where the relevant competent authority has not issued a manufacturing authorisation, this shall be explained.

— Brief description of the manufacture, control, storage, import, export, transport or other activities authorised by the relevant competent authority(ies), including foreign authorities, with reference to the authorised pharmaceutical forms/activities, respectively, where not covered by the manufacturing authorisation.

— A list with the type of products currently manufactured on-site shall be provided as Appendix 2, where not covered by Appendix 1 or EudraGMDP entry.

— List of GMP inspections of the site within the last 5 years, including dates and name/country of the Competent Authority having performed the inspection.

— A copy of the current GMP certificate or, alternatively, reference to the EudraGMDP database shall be provided as Appendix 3.

1.3. **Any other manufacturing activities carried out on the site**

— Description of non-pharmaceutical activities on-site, if any.

([1]) https://www.ema.europa.eu/en/human-regulatory-overview/research-development/data-medicines-iso-idmp-standards-overview/substance-product-organisation-referential-spor-master-data/organisation-management-service-oms.

2. QUALITY MANAGEMENT SYSTEM OF THE MANUFACTURER

2.1. **The quality management system of the manufacturer**

— Brief description of the quality management systems run by the company and reference to the standards used.

— Responsibilities related to the maintenance of the quality system, including for senior management.

— Information about the activities for which the site is accredited and certified, including dates and contents of accreditations and names of the accrediting bodies.

2.2. **Release procedure of finished products**

— Detailed description of the qualification requirements (education and work experience) of the authorised person(s) / qualified person(s) responsible for batch certification and releasing procedures.

— General description of batch certification and releasing procedure.

— Brief description of the batch release process, including the specific tasks of the authorised person / qualified person and arrangements for ensuring compliance with the marketing authorisation (where applicable).

— The arrangements between the authorised persons / qualified persons when several authorised persons / qualified persons are involved.

— Statement on whether the control strategy employs process analytical technology (PAT) or real time release or parametric release.

2.3. **Management of suppliers and contractors**

— A brief summary of the supply chain and the external audit programme.

— Brief description of the qualification system of contractors, manufacturers of active pharmaceutical ingredients and other suppliers of critical materials.

— Measures to ensure that products manufactured are compliant with TSE (transmissible spongiform encephalopathy) guidelines, where applicable.

— Measures to address instances when counterfeit/falsified products, bulk products (i.e. unpacked tablets), active pharmaceutical ingredients or excipients are suspected or identified.

— Use of outside scientific, analytical or other technical assistance in relation to the manufacture or control activities.

— List of contract manufacturers and laboratories, including addresses and relevant contact information, and flow charts of supply-chains for outsourced manufacturing and quality control activities (e.g. sterilisation of primary packaging material for aseptic processes, testing of starting raw materials, etc.) shall be provided as Appendix 4.

— Brief overview of the allocation of responsibilities between the contract giver and contract acceptor with respect to compliance with the marketing authorisation (where not included under 2.2).

2.4. **Quality Risk Management**

— Brief description of the quality risk management methodologies used by the manufacturer.

— Scope and focus of the quality risk management, including a brief description of any activities which are performed at corporate level and those which are performed locally. Any application of the quality risk management system to avoid disruptions of supply linked to manufacturing issues shall be mentioned.

2.5. **Product Quality Reviews**

— Brief description of the methodologies used.

3. PERSONNEL

— An organisation chart showing the arrangements for quality management, production and quality control positions/titles shall be provided as Appendix 5, including senior management and qualified person(s).

— Number of employees involved in the quality management, production, quality control and storage respectively.

4. PREMISES AND EQUIPMENT

4.1. **Premises**

— Short description of the plant, including the size of the site and list of buildings. If production for different countries takes place in different buildings on the site, the buildings shall be listed with destined markets identified (if not identified under 1.1).

— Simple plan or description of the manufacturing areas with indication of the scale (architectural or engineering drawings are not required).

— Layouts and flow charts of the production areas shall be provided as Appendix 6, showing the room classification and pressure differentials between adjoining areas and indicating the production activities (i.e. compounding, filling, storage, packaging, etc.) in the rooms.

— Layouts of warehouses and storage areas shall be provided as part of Appendix 6, with indication of special areas for the storage and handling of highly toxic, hazardous and sensitising materials, if applicable.

— Brief description of specific storage conditions if applicable, unless they are already indicated on the layouts.

4.1.1. Brief description of heating, ventilation and air conditioning (HVAC) systems:

— Principles for defining the air supply, temperature, humidity, pressure differentials and air change rates, policy of air recirculation (%).

4.1.2. Brief description of the water systems:

— Quality references of the water produced.

— Schematic drawings of the systems shall be provided as Appendix 7.

4.1.3. Brief description of other relevant utilities, such as steam, compressed air, nitrogen, etc.

4.2. **Equipment**

4.2.1. Listing of major production and control laboratory equipment with critical pieces of equipment identified shall be provided as Appendix 8.

4.2.2. Cleaning and sanitation:

— Brief description of the cleaning and sanitation methods of product contact surfaces (i.e. manual cleaning, automatic clean-in-place, etc.).

4.2.3. GMP critical computerised systems:

— Description of GMP critical computerised systems (excluding equipment specific programmable logic controllers).

5. DOCUMENTATION

— Brief description of the documentation system (i.e. electronic, manual).

— Where applicable, a list of the type of documents/records stored or archived off-site (including pharmacovigilance data, when applicable) shall be provided, as well as the name and address of storage site and an estimate of time required for retrieving documents from the off-site archive.

6. PRODUCTION

6.1. **Type of products** ([2])

— Type of products manufactured including a list of pharmaceutical forms.

— Toxic or hazardous substances handled (e.g. with high pharmacological activity and/or with sensitising properties).

— Product types manufactured in a dedicated facility or on a campaign basis, if applicable.

— Process analytical technology (PAT) used, if applicable: general statement of the relevant technology and associated computerised systems.

6.2. **Process validation**

— Brief description of the general policy for process validation.

— Brief description of the policy for reprocessing or reworking.

6.3. **Material management and warehousing**

— Brief description of the arrangements for the handling of materials used in the production, including packaging materials, bulk and finished products. Sampling, quarantine, release and storage shall also be addressed.

— Brief description of the arrangements for the handling of rejected materials and products.

7. QUALITY CONTROL (QC)

— Brief description of the quality control activities carried out on the site in terms of physical, chemical, and microbiological and biological testing.

8. TRANSPORT, COMPLAINTS, PRODUCT DEFECTS AND RECALLS

8.1. **Transport arrangements (as applicable to the role of the manufacturer)**

— Types (wholesale licence holders, manufacturing licence holders, etc.) and locations (EU/EEA, USA, etc.) of the companies to which the products are shipped from the site.

— Description of the system used to verify that each customer/recipient is legally entitled to receive the products from the manufacturer.

— Brief description of the system to ensure appropriate environmental conditions during transit, e.g. temperature monitoring/control.

— Arrangements for product distribution and methods by which product traceability is maintained.

— Measures taken to prevent manufacturers' products to fall in the illegal supply chain.

([2]) Cross-reference to information provided in Appendix 1 or 2 is acceptable.

8.2. **Complaints, product defects and recalls**

— Brief description of the system for handling complaints, product defects and recalls.

9. SELF INSPECTIONS

— Brief description of the self-inspection system with a focus on the criteria used for the selection of the areas to be covered during planned inspections, practical arrangements and follow-up activities.

Appendices

— Appendix 1: Copy of valid manufacturing authorisation.

— Appendix 2: List of pharmaceutical forms manufactured including the INN-names or common name (as available) of the active pharmaceutical ingredients (API) used.

— Appendix 3: Copy of a valid GMP certificate.

— Appendix 4: List of contract manufacturers and laboratories including the addresses and contact information, and flow-charts of the supply chains for these outsourced activities.

— Appendix 5: Organisational charts.

— Appendix 6: Layouts of production areas, including material and personnel flows and general flow charts of manufacturing processes of each product type (pharmaceutical form), and layouts of warehouse and storage areas.

— Appendix 7: Schematic drawings of water systems.

— Appendix 8: List of major production and laboratory equipment.

ANNEX VII

USE OF IONISING RADIATION IN THE MANUFACTURE OF VETERINARY MEDICINAL PRODUCTS

I. GENERAL

The requirements set out in this Annex shall apply to the use of ionising radiation in the manufacture of veterinary medicinal products. The specific requirements set forth in this Annex shall apply only to the ionising radiation process, other aspects of the manufacturing process shall comply with the requirements set forth in this Regulation as appropriate.

The required radiation dose to be applied, including relevant limits, shall be provided for in the marketing authorisation.

II. PREMISES

Premises shall be designed and operated to segregate irradiated from non-irradiated containers to avoid their cross-contamination. Where materials are handled within closed irradiation containers, it may not be necessary to segregate materials intended for use in the production of medicinal products from other type of materials, provided that there is no risk of the former being contaminated by the latter. Any possibility of contamination of the products by radionuclide from the source shall be excluded.

III. EQUIPMENT

III.1. **Dosimeters**

III.1.1. Dosimeters used shall be calibrated according to relevant standards. The period of validity of the calibration shall be documented in written with appropriate justification and be adhered to.

III.1.2. The same instrument shall normally be used to establish the calibration curve of the dosimeters and to measure the change in their absorbance after irradiation. If a different instrument is used, the absolute absorbance of each instrument shall be established.

III.1.3. Depending on the type of dosimeter used, due account shall be taken of possible causes of inaccuracy, including a change in moisture content, a change in temperature, the time elapsed between the irradiation and the measurement or the dose rate.

III.1.4. The wavelength of the instrument used to measure the change in absorbance of dosimeters and the instrument used to measure their thickness shall be subject to regular checks of calibration at intervals established having regard to the stability, purpose and usage.

III.2. **Irradiators**

III.2.1. *Qualification*

III.2.1.1. It shall be demonstrated, through appropriate documentation, that irradiators are able to perform consistently within predetermined limits when operated according to the process specifications. In this context, predetermined limits are the maximum and minimum doses designed to be absorbed by the irradiation container. It shall not be possible for variations to occur in the operation of the irradiator which give a dose to the container outside those limits without the knowledge of the operator.

III.2.1.2. When there is a change to the process or the irradiator that could affect the dose distribution to the irradiation container (e.g. change of source pencils), it shall be re-assessed whether the irradiator continues to consistently perform within the predetermined limits. The extent of the assessment needed depends on the extent of the change in the irradiator or the load that has taken place.

III.2.2. *Gamma irradiators*

III.2.2.1. Design

The irradiator shall be designed taking into account that the absorbed dose received by a particular part of an irradiation container at any specific point in the irradiator can be impacted by the following factors:

— the activity and geometry of the source;

— the distance from the source to the container;

— the duration of the irradiation controlled by the timer setting or conveyor speed;

— the composition and density of the material, including other products, between the source and the particular part of the container;

— the path of containers through a continuous irradiator or the loading pattern in a batch irradiator;

— the number of exposure cycles.

III.2.2.2. Dose mapping

The results of the dose mapping procedure shall give minimum and maximum absorbed doses in the product and on the container surface for a given set of irradiator parameters, product density and loading pattern.

For the dose mapping procedure, the following elements shall apply:

(a) The irradiator shall be filled with irradiation containers packed with dummy products or a representative product of uniform density. Dosimeters shall be placed throughout a minimum of three loaded irradiation containers which are passed through the irradiator, surrounded by similar containers or dummy products. If the product is not uniformly packed, dosimeters shall be placed in a larger number of containers.

(b) The positioning of the dosimeters shall depend on the size of the irradiation container. For example, for containers up to 1 × 1 × 0,5 m, a three-dimensional 20 cm grid throughout the container including the outside surfaces might be suitable. If the expected positions of the minimum and maximum dose are known from a previous irradiator performance characterisation, some dosimeters could be removed from regions of average dose and replaced to form a 10 cm grid in the regions of extreme dose.

(c) Ideally, reference dosimeters shall be used because of their greater precision. Routine dosimeters are permissible but it is advisable to place reference dosimeters beside them at the expected positions of minimum and maximum dose and at the routine monitoring position in each of the replicate irradiation containers. The observed values of dose will have an associated random uncertainty that can be estimated from the variations in replicate measurements.

(d) The minimum observed dose, as measured by the routine dosimeters, necessary to ensure that all irradiation containers receive the minimum required dose shall be set having regard to the random variability of the routine dosimeters used.

(e) Irradiator parameters shall be kept constant, monitored and recorded during dose mapping. The records, together with the dosimetry results and all other records generated, shall be retained.

III.2.3. *Electron irradiators*

III.2.3.1. Design

The irradiator shall be designed taking into account that the absorbed dose received by a particular portion of an irradiated product at any specific point in the irradiator can be impacted by the following factors:

— the characteristics of the beam, which are: electron energy, average beam current, scan width and scan uniformity;

— the conveyor speed;

— the product composition and density;

— the composition, density and thickness of material between the output window and the particular portion of product;

— the output window to container distance.

III.2.3.2. Dose mapping

The results of the dose mapping procedure shall give minimum and maximum absorbed doses in the product and on the container surface for a given set of irradiator parameters, product density and loading pattern.

For the dose mapping procedure, dosimeters shall be placed between layers of homogeneous absorber sheets making up a dummy product, or between layers of representative products of uniform density, such that at least ten measurements can be made within the maximum range of the electrons. Requirements set forth in points (b) to (d) of Section III.2.2.2 shall apply also.

IV. DOCUMENTATION

IV.1. The numbers of containers received, irradiated and dispatched shall be reconciled with each other and with the associated documentation. Any discrepancy shall be reported and resolved.

IV.2. The irradiator operator shall certify in writing the range of doses received by each irradiated container within a batch or delivery.

IV.3. Process and control records for each irradiation batch shall be checked and signed by a nominated responsible person and retained.

IV.4. The documentation associated with the validation/qualification of the irradiator shall be retained for one year after the expiry date or at least five years after the release of the last product processed by the irradiator, whichever is longer.

V. PROCESSING

V.1. **General**

V.1.1. Irradiation containers shall be packed in accordance with the specified loading pattern(s) established during validation.

V.1.2. During the process, the radiation dose to the irradiation containers shall be monitored using validated dosimetry procedures. The relationship between that dose and the dose absorbed by the product inside the container must have been established during process validation and as part of the qualification of the irradiator.

V.1.3. Radiation indicators shall be used as an aid to differentiate irradiated from non-irradiated containers. However, they shall neither be used as the sole means of differentiation nor be considered as an indication of satisfactory processing.

V.1.4. Processing of mixed loads of containers within the irradiation cell shall only be done when there is evidence supporting that the radiation dose received by individual containers remains within the limits specified.

V.1.5. When the required radiation dose is – by design – achieved during more than one exposure or passage, this shall be specified as part of the contract, including relevant details regarding the predetermined time period. Unplanned interruptions during irradiation that extend the irradiation process beyond the specifications set forth in the contract shall be notified to the contract giver, who shall bring the information to the attention of the qualified person.

V.1.6. Non-irradiated products shall be segregated from irradiated products at all times. Methods of achieving this objective include the use of radiation indicators and appropriate design of premises.

V.2. **Gamma irradiators**

V.2.1. For continuous processing modes ([1]), the following shall apply:

(a) dosimeters shall be placed so that at least two are exposed in the irradiation at all times;

(b) there shall be a positive indication of the correct position of the source and an interlock between source position and conveyor movement. The conveyor speed shall be monitored continuously and recorded.

V.2.2. For batch modes ([2]), the following shall apply:

(a) at least two dosimeters shall be exposed in positions related to the minimum dose position;

(b) source movement and exposure times for each batch shall be monitored and recorded.

V.2.3. For a given desired dose, the timer setting or conveyor speed shall be adjusted for source decay and source additions. The period of validity of the setting or speed shall be recorded and adhered to.

V.3. **Electron beam irradiators**

V.3.1. A dosimeter shall be placed on every container.

V.3.2. There shall be continuous recording of average beam current, electron energy, scan-width and conveyor speed. These variables, other than conveyor speed, shall be controlled within the pre-defined limits established pursuant to Section III.2.1.

VI. PROCESS VALIDATION

VI.1. Through process validation it shall be demonstrated that the delivery of the intended absorbed dose to the product will achieve the expected results.

VI.2. Validation shall include dose mapping to establish the distribution of absorbed dose within the irradiation container when packed with product in a defined configuration.

VI.3. The irradiation process specification shall include at least the following:

(a) details of the packaging of the product;

(b) the loading pattern(s) of product within the irradiation container. When a mixture of products is allowed in the irradiation container, particular care shall be taken that there is no underdosing of dense products or shadowing of other products by dense products. Each mixed product arrangement shall be specified and validated;

([1]) For the purposes of this Annex, 'continuous processing mode' means a type of irradiation process where an automatic system conveys the products into the radiation cell, past the exposed radiation source along a defined path and at an appropriate speed, and out of the cell.

([2]) For the purposes of this Annex, 'batch mode' means a type of irradiation process where the product is arranged at fixed locations around the radiation source and cannot be loaded or unloaded while the radiation source is exposed.

(c) the loading pattern of irradiation containers around the source (batch mode) or the pathway through the cell (continuous mode);

(d) the maximum and minimum limits of absorbed dose to the product, as well as the associated routine dosimetry;

(e) the maximum and minimum limits of absorbed dose to the irradiation container and the associated routine dosimetry to monitor this absorbed dose;

(f) other process parameters, including dose rate, maximum time of exposure, number of exposures, etc.

When irradiation is outsourced to a third party, items (d) and (e) shall form part of the contract.

VII. MICROBIOLOGICAL MONITORING

Microbiological monitoring is the responsibility of the manufacturer of the veterinary medicinal product. Environmental monitoring and bioburden monitoring prior to irradiation may be required as specified in the marketing authorisation.

VIII. SUBCONTRACTING

VIII.1. When treatment by irradiation is subcontracted, the subcontractor shall hold an appropriate manufacturing authorisation.

VIII.2. The manufacturer of the veterinary medicinal product bears the responsibility for the quality of the product, including the attainment of the objective of irradiation. The sub-contractor for the radiation process shall ensure that the dose of radiation required by the manufacturer is delivered to the irradiation container (i.e. the outermost container in which the products are irradiated).

ANNEX VIII

I. **Model for confirmation of partial manufacturing**

[LETTER HEAD OF MANUFACTURER WHO CARRIED OUT THE MANUFACTURING ACTIVITY]

1. Name of the product and description of the manufacturing stage (e.g. paracetamol tablets, primary packaging into blister packs).

2. Batch number.

3. Name and address of the site carrying out the partial manufacturing.

4. Reference to the written agreement detailing the responsibilities between both parties (in accordance with Article 43).

5. Confirmation statement:

   I hereby confirm that the manufacturing stages referred to in the written agreement referred to in Section 4 have been carried out in full compliance with good manufacturing practice requirements applicable in the EU and the terms described in the agreement as provided by [Contract Giver/manufacturer certifying and releasing the batch].

6. Name of the qualified person confirming the partial manufacturing.

7. Signature of qualified person confirming the partial manufacturing.

8. Date of signature.

II. **Model for batch release certificate**

[LETTER HEAD OF THE MANUFACTURER CERTIFYING AND RELEASING THE BATCH]

1. Name, strength/potency, dosage form and package size (identical to the text on the finished product package).

2. Batch number of the finished product.

3. Name of the destination country/countries of the batch, at least when within the EU.

4. Certification statement:

   I hereby certify that all the manufacturing stages of this batch of finished product have been carried out in full compliance with the good manufacturing practice requirements applicable in the EU and with the requirements of the marketing authorisation *[to be added only when batch is exported:* of the destination country/countries].

5. Name of the qualified person certifying the batch.

6. Signature of the qualified person certifying the batch.

7. Date of signature.

ANNEX IX

REAL TIME RELEASE TESTING AND PARAMETRIC RELEASE

I. REAL TIME RELEASE TESTING

I.1. Under a real time release testing approach, a combination of in-process monitoring and controls may replace end-product testing in the context of the batch release. This approach may only be implemented if it is authorised in the marketing authorisation.

I.2. When designing the real time release testing strategy, the following minimum criteria shall be considered:

— the proposed real time measurement and control of the relevant in-process material attributes and process parameters shall be accurate predictors of the corresponding finished product attributes;

— the suitability of the combination of the relevant assessed material attributes and process controls to replace end-product testing shall be scientifically demonstrated;

— the combined process measurements (process parameters and material attributes) and any other test data generated during the manufacturing process shall provide a robust basis for the batch release decision.

I.3. A real time release testing strategy shall be integrated and controlled as part of the pharmaceutical quality system, in particular with respect to:

(a) personnel: the implementation of real time release testing requires input from a cross-functional/multi-disciplinary team with relevant experience on topics, such as engineering, analytics, chemometric modelling or statistics;

(b) control strategy: when implementing real time release testing, it is paramount to ensure the robustness of controls applied during the manufacturing process and their suitability to ensure the quality of the product and consistent production. The control strategy shall be adapted through the life-cycle in light of acquired knowledge and in accordance with quality risk management principles;

(c) management of changes: requirements set forth in Article 26(3) are particularly relevant when implementing real time release testing;

(d) validation and qualification policy: the qualification and validation of in-line [1] and on-line [2] analytical methods is particularly relevant when real time release testing is implemented, especially when advanced analytical methods are used. Particular attention shall be paid to the location where the sampling probe is placed within the manufacturing equipment;

(e) any deviation or process failure shall be thoroughly investigated and any adverse trending indicating a change in the state of control of the process, equipment or facilities shall be followed up appropriately;

(f) continuous learning through data collection and analysis over the life cycle of a product is important. Manufacturers shall scientifically evaluate data (including data trends), to assess opportunities to improve quality and/or consistency. For the implementation of changes, Article 26(3) applies.

[1] The testing equipment is integrated into the process line, where the analysis is implemented under the process conditions. After the measurement, the sample moves forward continuously along the flow. This was the original method for real-time analysis.

[2] The sample is extracted from the process line in a statistically representative way and introduced to the measurement zone. The measurement conditions are similar to those of the process line. After the measurement, the sample may be drained as waste or introduced back to the process line.

I.4. When real time release testing has been approved in the marketing authorisation, this approach shall be routinely used for batch release and may not be replaced by end-product testing (unless the terms of the marketing authorisation are amended). In the event that the results from real time release testing fail or are trending toward failure, there shall be a thorough investigation. The results of the investigation shall be duly considered for a decision on batch release (release may only take place if it is ascertained that the product complies with the terms of the marketing authorisation and good manufacturing practice). Trends shall be followed up appropriately.

I.5. Attributes (e.g. uniformity of content) that are indirectly controlled by approved real time release testing shall appear in the certificate of analysis for batches. The approved method for end-product testing shall be mentioned and the results given as 'Complies if tested' with a footnote: 'Controlled by approved real time release testing'.

II. PARAMETRIC RELEASE

II.1. Parametric release for terminally sterilised products is the release of a batch based on a review of critical process control parameters instead of relying on end-product testing for sterility. Requirements set forth in Annex I regarding terminal sterilisation shall apply.

II.2. An end-product test for sterility is limited in its ability to detect contamination as it utilises only a small number of samples in relation to the overall batch size, and also because culture media may only stimulate growth of some, but not all, microorganisms. Therefore, an end-product testing for sterility only provides an opportunity to detect major failures in the sterility assurance system (i.e. a failure that results in the contamination of a large number of product units or that result in contamination by the specific microorganisms whose growth is supported by the prescribed media). In contrast, data derived from in-process controls (e.g. pre-sterilisation product bioburden or environmental monitoring) and by monitoring relevant sterilisation parameters can provide more accurate and relevant information to support sterility assurance of the product.

II.3. Parametric release may only be applied to products sterilised in their final container using either moist heat, dry heat or ionising radiation (dosimetric release), according to European Pharmacopoeial requirements. Additionally, it is required that the manufacturer has a good record of compliance with good manufacturing practice and a robust sterility assurance programme in place to demonstrate a consistent process control and process understanding.

II.4. The sterility assurance programme shall be documented and include, at least, the identification and monitoring of the critical process parameters, the steriliser cycle development and the validation thereof, the container/packaging integrity validation, the bioburden control, the environmental monitoring programme and relevant aspects concerning personnel, premises, equipment and utilities.

II.5. Risk management is an essential aspect of parametric release and shall focus on mitigating the factors that increase the risk of failure to achieve and maintain sterility in each unit of every batch. If a new product or process is being considered for parametric release, a risk assessment shall be conducted during the process development, including an evaluation of production data from existing products if applicable. If an existing product or process is being considered, the risk assessment shall include an evaluation of historical data.

II.6. Personnel involved in the parametric release process shall have experience in the following areas: microbiology, sterility assurance, engineering, production and sterilisation. The qualifications, experience and training of personnel involved in parametric release shall be documented.

II.7. Any proposed change that may impact on sterility assurance shall be handled in accordance with Article 26(3) by appropriate personnel who are qualified and experienced in sterility assurance.

II.8. A pre-sterilisation bio-burden monitoring programme for the product and primary packaging material shall be developed to support parametric release. The monitoring shall be performed for each batch and the sampling locations of filled units before sterilisation shall be based on a worst-case scenario and be representative of the batch. Any organisms found shall be identified to confirm that they are not spore forming, which may be more resistant to the sterilising process.

II.9. Appropriate measurement of critical process parameters during sterilisation is a critical requirement in a parametric release programme. The standards used for process measuring devices shall be specified and the calibration shall be traceable to national or international standards.

II.10. Critical process parameters shall be established, defined and undergo periodic re-evaluation. The operating ranges shall be developed based on the sterilisation process, the process capability, the calibration tolerance limits and parameter criticality.

II.11. Routine monitoring of the steriliser shall demonstrate that the validated conditions necessary to achieve the specified process is achieved in each cycle. Critical processes shall be specifically monitored during the sterilisation phase.

II.12. A sterilisation record shall be kept which shall include all the critical process parameters. Sterilisation records shall be checked for compliance with the specifications by at least two independent systems. These systems may consist of two people or a validated computer system plus a person.

II.13. Once parametric release has been approved as part of the marketing authorisation, decisions for release or rejection of a batch shall be based on the approved specifications and the review of critical process control data. Routine checks of the steriliser, changes, deviations, unplanned and routine planned maintenance activities shall be recorded, assessed and approved before releasing the products to the market. Non-compliance with the specification for parametric release may not be overruled by a sterility test.