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Veterinary Medicines Division

Advice on the implementing measures under Article 93(2) of Regulation (EU) 2019/6 of the European Parliament and of the Council on Veterinary Medicinal Products, as regards the GMP for veterinary medicinal products and active substances used as starting materials

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Introduction

According to Article 93(2) of Regulation (EU) 2019/6, the European Commission shall adopt, by means of implementing acts, measures on good manufacturing practice for veterinary medicinal products and active substances used as starting materials.

On 28 July 2022 the European Commission requested the European Medicines Agency (EMA) to provide scientific advice on:

- GMP for active substances used as starting materials in veterinary medicinal products;
- GMP for veterinary medicinal products.

In this regard, the GMP/GDP Inspectors Working Group (GMDP IWG) agreed that one expert group should be constituted to provide recommendations in relation to the two requests by December 2023. The call for nomination of experts for the expert group was performed by the Heads of Medicines Agencies (HMA) upon EMA request. The expert group membership was endorsed by the GMDP IWG. The group was composed of 13 experts selected from the European network of experts, on the basis of recommendations from the national competent authorities, one Agency staff member and one European Commission representative.

When addressing this request on GMP for veterinary medicinal products, the European Commission asked the Agency to take into account:

- the policy reasoning and purpose of GMP to ensure a quality warranty system on the manufacturing of veterinary medicinal products;
- the experience gained with the application of the current EU system of principles and guidelines of GMP as established in Directive 91/412/EEC and the detailed guidelines contained in EudraLex - Volume 4 – Good Manufacturing Practice (GMP) guidelines;
- the ongoing work on the revision of Annexes 4 and 5 to EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines, as well as the relevant PIC/S concept papers;
- existing international standards and guidelines on GMP of medicinal products, e.g. WHO Good Manufacturing Practices for Pharmaceutical Products: Main principles, Annex 2, WHO Technical Report Series 986, 2014, WHO Good Manufacturing Practices for Sterile Pharmaceutical Products, Annex 6, WHO Technical Report Series 961, 2011, WHO Good Manufacturing Practices For Biological Products (Jointly with The Expert Committee on Biological Standardization), Annex 3, WHO Technical Report Series 996, 2016, WHO Good Manufacturing Practices for Pharmaceutical Products Containing Hazardous Substances, Annex 3 WHO Technical Report Series 957, 2010 and the PIC/S GMP Guide; and ICH guidelines in the area of quality risk management (ICH Q9) and pharmaceutical quality systems (ICH Q10);
- the similarities and potential differences between the requirements towards GMP for veterinary medicinal products and medicinal products for human use;
- the fact that veterinary medicinal products and medicinal products for human use are sometimes produced on the same manufacturing sites and that more often than not GMP inspections are to be performed by the same experts for both types of medicines and therefore, in order to avoid unnecessary administrative burden and cost, it is not desirable to deviate significantly from the human side, unless practical needs dictate otherwise;

- the need to ensure that the compilation of Union procedures for inspections and exchange of information should serve as a basis for competent authorities to carry out their controls;
- if the GMP requirements need to be adapted for the manufacturing of novel therapy veterinary medicinal products as defined in Article 4(43), taking into account the specific nature of those products;
- if the GMP requirements need to be adapted for the manufacturing of homeopathic veterinary medicinal products registered in accordance with Article 86 considering the specific nature of those products;
- if the GMP requirements need to be adapted for the manufacturing of inactivated autogenous vaccines in order to ensure their manufacturing and availability since they are prepared in a way that is different from industrially prepared products, reviewing, where possible, existing recommendations, e.g. the Recommendations for the manufacture, control and use of inactivated autogenous veterinary vaccines within the EEA issued by the Coordination group for mutual recognition and decentralised procedures for veterinary medicinal products (CMDv) in March 2017, the European Manufacturers of Autogenous Vaccines and Sera (EMAV) EMAV Proposal: EU-GMP-Annex for Autogenous vaccines in 2021.
- the Union and international standards of animal welfare when active substances are prepared from animals;
- measures to prevent or minimise discharge of active substances into the environment following an evaluation of the impact of such measures.

The expert group submitted their recommendations to the GMP/GDP Inspectors Working Group for comments on 20 June 2023 and 20 July 2023.

The GMP/GDP Inspectors Working Group adopted the scientific advice on 30 October 2023.

Considerations and rationale for the recommendations

Article 93(2) of the VMP Regulation introduces provisions for measures on Good Manufacturing Practice (‘GMP’) for veterinary medicinal products and active substances used as starting materials indicating that the European Commission shall by means of implementing acts adopt such measures.

Good Manufacturing Practice measures have been adopted for decades at EU level for both human and veterinary medicines[1]. The experience gained with the application of the current EU system on both human and veterinary medicines sides as well as experience with GMP inspections for veterinary medicinal products conducted under existing EU and national legislation were therefore taken into account and constitutes the basis for the recommendations made in relation to veterinary medicines.

Due to the short time available for developing the advice, the wide scope of the Veterinary Medicinal Products (VMP) covered and the necessity for some GMP areas to be updated on regular basis in order to reflect changes in technological progress and not hinder innovation, the expert group has decided:

[1] EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines

- to dedicate some sections of the scientific advice for specific productions (i.e. active substances, veterinary medicinal products, novel therapy products, autogenous vaccines);
- to limit the scope of the advice to general GMP requirements, more specific technical requirements, likely to be subject to regular updates, should be covered by future guidelines published by the European Commission;
- to address in separate sections the request to evaluate the impact of potential inclusion in GMP of measures for taking into account the Union and international standards of animal welfare when active substances are prepared from animals and for preventing or minimising discharge of active substances into the environment.

The expert group recommends to manage these GMP areas which have to be updated on regular basis in order to reflect changes in technological progress and not hinder innovation through guidelines published by the European Commission. Current GMP annexes of Eudralex Vol. 4 applicable to veterinary medicinal products and active substances used as starting material in veterinary medicinal products (e.g. Annex 1 on manufacture of sterile medicinal products, Annex 4 on Manufacture of Veterinary Medicinal Products other than Immunological Veterinary Medicinal Products) fall within this category as technical guidelines complementary to Part I and Part II and are dedicated to specific dosage forms (e.g. sterile, medical gases or herbal products) or manufacturing operation (e.g. sampling operation, use of ionising radiation, qualification and validation, certification...). Once the implementing act is published, they could be re-evaluated in line with it and Regulation 2019/6 and then republished by the European Commission as ad hoc GMP related guidelines. Afterwards, significant development and innovation in veterinary product manufacture, technologies, product types or dosage form could be addressed by regular update or extension of the scope of these guidelines.

For the preparation of the advice, international standards and guidelines on GMP for medicinal products such as the WHO guidelines and PIC/S ones were taken into account.

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

Recommendations

The recommendations provided in the Agency's advice to the European Commission are based on the current EU system of principles and guidelines of GMP as established in Directive 91/412/EEC and the detailed guidelines contained in EudraLex - Volume 4 – Good Manufacturing Practice (GMP) guidelines taking into account the specificities of the veterinary field.

Homeopathic products

Authorised and registered homeopathic veterinary medicinal products are prepared from synthetic origin or from various natural source materials like mineral, chemical, botanical, animal source and need to be carefully handled from the very beginning of the collection process. Their quality is mainly determined by the authenticity and the origin of the starting materials according to the homeopathic tradition (i.e. European Pharmacopoeia or, the pharmacopoeias used officially in Member States), and by the

manufacturing and control procedure which prevent or mitigate the risks of misidentification, impurity of starting material, cross-contamination or incidental contamination (residue).

Homeopathic veterinary medicinal products are prepared from homeopathic stocks in accordance with a homeopathic manufacturing procedure described by the Pharmacopoeias. Because definitions may vary between pharmacopoeias, and because of the wide range of processing techniques and manufacturing methods in the various pharmacopoeias, the final homeopathic veterinary medicinal products may show marked variability which can impact their quality.

Moreover, Article 2 (5) of Regulation 2019/6 defines the scope for homeopathic veterinary medicinal products which are registered in accordance with Article 86. Article 95 of Regulation 2019/6 being not applicable to this category of products, the expert group understands that GMP for active substances used as starting material in veterinary medicinal products is not required to them.

Therefore, in order to answer to these unique characteristics, the expert group recommends, taking in account recital 90 and article 2 (5) of Regulation 2019/6 that:

- the manufacture of homeopathic veterinary medicinal products **with MA** shall be undertaken in accordance with the measures of Good Manufacturing Practice for veterinary medicinal products, and Good Manufacturing Practice for active substances used as starting material in veterinary medicinal products and, where applicable ad hoc related guidelines published by European Commission,
- the manufacture of homeopathic veterinary medicinal products **which are registered** in accordance with Article 86 shall be undertaken in accordance with the measures of Good Manufacturing Practice for veterinary medicinal products only and, where applicable ad hoc related guidelines published by European Commission."

Please note that regarding the measures of Good Manufacturing Practice for veterinary medicinal products, point 5.71 is not applicable to these types of products.

Veterinary medicinal products intended for animals which are exclusively kept as pets as per Article 5 (6) of Regulation 2019/6

Article 5 (6) of Regulation 2019/6 covers veterinary medicinal products intended for animals which are exclusively kept as pets: aquarium or pond animals, ornamental fish, cage birds, homing pigeons, terrarium animals, small rodents, ferrets and rabbits.

Member States may allow exemptions from this Marketing Authorisation, provided that such veterinary medicinal products are not subject to a veterinary prescription and that all necessary measures are in place in the Member State to prevent unauthorised use of those veterinary medicinal products for other animals.

Article 2 (4) highlights the scope of requirements from Regulation 2019/6 applicable to those veterinary medicinal products for other animals. Article 95 of Regulation 2019/6 being not applicable to this category of products, the expert group understands that GMP for active substances used as starting material in veterinary medicinal products is not required to them.

Therefore, in order to answer to these unique characteristics, the expert group recommends, taking into account article 2 (4) of Regulation 2019/6 that the manufacture of veterinary medicinal products **which fall within article 5 (6)** shall be undertaken in accordance with the measures of Good Manufacturing Practice for veterinary medicinal products only and, where applicable ad hoc related guidelines published

by European Commission. Please note that regarding the measures of Good Manufacturing Practice for veterinary medicinal products, points 1.11, 5.35, 5.71, 6.26 to 6.31, 7.3 and all points of chapter 8 are not applicable to these types of products.

Novel therapy products

According to article 4 (43) of Regulation 2019/6, novel therapy veterinary medicinal product means:

(a) a veterinary medicinal product specifically designed for gene therapy, regenerative medicine, tissue engineering, blood product therapy, phage therapy;

(b) a veterinary medicinal product issued from nanotechnologies;

Or (c) any other therapy which is considered as a nascent field in veterinary medicine;

In the Annex II of regulation 2019/6, Section V Requirements for marketing authorisation applications for particular veterinary medicinal products, item V.1.1.3. it is stated that "The manufacturing processes for novel therapy veterinary medicinal products shall comply with the principles of Good Manufacturing Practice (GMP) adapted where necessary, to reflect the specific nature of those products. Guidelines specific to novel therapy veterinary products shall be drawn up, to properly reflect the particular nature of their manufacturing process."

The expert group has taken into account the most current advanced therapy GMP guidance relating to this topic as a starting point for drafting the GMP for veterinary novel therapy products (NT): Part IV of Eudralex vol. 4: Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products (ATMP). However, the scope of products falling into ATMP and in NT are not fully congruent. Furthermore, in the case of products issued from nanotechnologies, such products have already been authorised without a need for adaptation of any specific GMP requirements and therefore no provision for these products need be included in the GMP principles for novel therapy veterinary medicinal products.

Taking into account the need to develop specific requirements for novel therapy veterinary medicinal products while avoiding major overhaul of the GMP provisions, in particular not altering the structure, the expert group recommends the manufacture of veterinary NT shall be undertaken:

- In accordance with the measures of Good Manufacturing Practice for veterinary medicinal products, and Good Manufacturing Practice for active substances used as starting material in veterinary medicinal products.

  and

- In accordance with complementary specific GMP principles for veterinary novel therapy products

  and

- Where applicable ad hoc related guidelines published by European Commission,

Autogenous vaccines

According to article 2 (3) of Regulation (EU) 2019/6 inactivated Veterinary Autogenous Vaccines (AV) are 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.

The article 2 (3) lays down that only the articles 94, 105, 108, 117, 120, 123 and 134 apply to inactivated autogenous vaccines. In article 106 (5) it is stated that inactivated immunological veterinary medicinal products referred to in Article 2 (3) shall only be used in the animals referred to therein in exceptional circumstances, in accordance with a veterinary prescription, and if no immunological veterinary medicinal product is authorised for the target animal species and the indication.

Article 94 regulates the certificates of good manufacturing practice and article 159 says that without prejudice to the date of application of this Regulation, the obligations regarding certificates of good manufacturing practice for 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 shall only start to apply from the date of application of the implementing acts laying down specific measures on good manufacturing practice for those veterinary medicinal products referred to in Article 93(2).

Taking into account the wording of article 159 regarding specific measures on good manufacturing practice and recital 70 that - although inactivated immunological veterinary medicinal products referred to in Article 2 (3) should be manufactured in accordance with the principles of good manufacturing practice, detailed guidelines of good manufacturing practice should specifically be prepared for those products since they are manufactured in a way that is different from industrially prepared products – as well as available existing guidelines and national legislation: the expert group recommends that the manufacture of inactivated veterinary AV shall be undertaken:

- in accordance with the adapted specific Good Manufacturing Practice Principles for inactivated veterinary AV only
- and, where applicable ad hoc related specific guidelines published by the European Commission.

That would preserve their quality without hindering their manufacturing and availability.

Structure of the implementing act

During the whole drafting process, the expert group have taken care to maintain a certain alignment of the recommendations and structure (sections names, chapters numbering, chapters names and numbering, even if this results in some blank sections. This is specifically recommended to allow interchange of reports and documentation between human and veterinary inspections and facilitate harmonised training, etc.) with the corresponding measures established for the good manufacturing practice of human medicinal products. This approach is mainly driven by the fact that Good Manufacturing Practice inspections for both types of medicine will often be carried out by the same inspectors and that the same manufacturer may produce both veterinary and human medicinal products. This would also contribute to maintain the existing equivalency recognition of EU GMP by MRA partners and more largely at international level (PIC/s). For this purpose, the expert group recommends to maintain this design during the elaboration of the Implementing Act.

In addition, the expert group proposes the following structure for the future implementing acts:

Implementing Act on GMP for veterinary medicinal products

Recitals

Section I - Definitions

Section II - GMP for veterinary medicinal products (including homeopathic products, products authorised under Article 5 (6) and novel therapy products)

Section III - Specific GMP principles for novel therapy veterinary medicinal products

Section IV - Adapted GMP principles for inactivated veterinary autogenous vaccines

Implementing Act on GMP for active substances used as starting material in veterinary medicinal products

Recitals

Section I - Definitions

Section II - GMP for active substances used as starting materials in veterinary medicinal products including homeopathic products holding a Marketing Authorisation and Novel Therapy Products (not including AV homeopathic products registered under article 86 of Regulation 2019/6 and products authorised under Article 5 (6))

An overview of the recommendations provided in the Agency's advice to the European Commission is provided in the table below:

		Veterinary Medicinal Products other than homeopathic VMPs, novel therapy VMPs, autogenous vaccines or VMPs issued in accordance with Article 5(6)	Homeopathic Veterinary Medicinal Products with Marketing Authorisation	Homeopathic Veterinary Medicinal Products registered in accordance with Article 86 of Regulation 2019/6	Veterinary medicinal products as per Article 5 (6) of Regulation 2019/6	Novel Therapy Veterinary Medicinal Products	Autogenous Vaccines
GMP for active substances used as starting materials in veterinary medicinal products		☑	☑			☑	
GMP veterinary medicinal products		☑	☑	☑	☑	☑	
Specific GMP principles for novel therapy veterinary medicinal products						☑	
Adapted GMP principles for inactivated veterinary autogenous vaccines							☑
Additional GMP Guidelines published by the European Commission (existing and/or future)		☑	☑	☑	☑	☑	☑

Note: *For Veterinary medicinal products as per Article 5(6) of Regulation 2019/6, regarding the measures of Good Manufacturing Practice for veterinary medicinal products, points 1.11, 5.35, 5.71, 6.26 to 6.31, 7.3 and all points of chapter 8 are not applicable.*

For Homeopathic veterinary medicinal products, regarding the measures of Good Manufacturing Practice for veterinary medicinal products, point 5.71 is not applicable to these types of products.

Veterinary medicinal products used in clinical trial

Veterinary medicinal products can be tested or used as a reference, including as a placebo, in a veterinary clinical trial in order to examine under field conditions their safety or efficacy (or both) under normal conditions of animal husbandry or as part of normal veterinary practice for the purpose of obtaining a marketing authorisation or a change thereof. In these clinical trials, there may be added risk to the subjects compared to animals treated with authorised medicinal products.

In the recital (5) of Directive 91/412/EEC laying down the principles and guidelines of good manufacturing practice for veterinary medicinal products, it is stated that "in accordance with national legislation, Member States may require compliance with these principles of good manufacturing practice during the manufacture of products intended for use in clinical trials".

Moreover, the article 9 of Regulation 2019/6 requires an application for any clinical trial according to national law, following by an approval by national competent authority. It states also that clinical trials shall be carried out taking into account the international guidelines on good clinical practice (GCP) of the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products ('VICH'). At item 2.7 of VICH GL 9 on GCP, it is said that "2.7. Wherever possible, investigational veterinary products should be prepared, handled and stored in accordance with the concepts of good manufacturing practice (GMP) of the relevant regulatory authorities. Details of preparation, handling and storage of investigational veterinary products should be documented and the products should be used in accordance with the study protocol".

For this reason, even if article 2 (7) d excludes veterinary medicinal products intended for research and development from the scope of the regulation 2019/6, the expert group recommends to maintain the sentence from recital (5) of Directive 91/412/EEC in the recital of the implementing act. This would allow competent authority, when it is required by national law, to ensure that subjects and users involved in approved clinical trial are not placed at undue risk, and that the results of clinical trials are unaffected by inadequate quality, safety or efficacy arising from unsatisfactory manufacture or import such as:

- inconsistency between batches of the same investigational medicinal product used in the same or different clinical trials,
- changes during the development of an investigational medicinal product inadequately documented and justified,
- increased risk of product cross-contamination and mix-up due to randomisation and blinding process, or
- incomplete knowledge of the potency and toxicity of the product and a lack of full process validation.

Additional recommendations and points to note

In addition to the recommendations made, the matters below were addressed and are brought to the Commission's attention for consideration in the development of the implementing acts.

Control, Inspection and conformity with good manufacturing practice

Supervision by Controls and Inspections

The expert group recommends to recall, as an important element of the context for the implementing act, the requirements relating of the controls and inspections the competent authorities are responsible to carry out on European territory and outside Europe:

By means of controls referred to in Article 123 of Regulation 2019/6, the Competent Authorities shall ensure that manufacturers authorised in accordance with Article 88 (1) of Regulation 2019/6, the manufacturers of autogenous vaccines as per Article 2 (3) of Regulation 2019/6 or manufacturers / importers registered in accordance with Article 95 (1) of Regulation 2019/6 respect their manufacturing authorisation, if applicable, and the good manufacturing practice laid down by in this Implementing Act and the associated guidelines. This provision shall also apply to medicinal products intended only for export.

These controls shall be carried out regularly, on a risk-basis, in order to verify that manufacturers comply with the Regulation. Inspections may be carried out as part of these controls. Without prejudice to any arrangements which may have been concluded between the Union and third countries, a competent authority, the Commission or the Agency may require a manufacturer established to a third country to undergo an inspection as referred in article 94 (1) and article 95 (7). The competent authorities shall ensure that the products have been manufactured in accordance with standards which are at least equivalent to the good manufacturing practice standards laid down in the Union and that such products have been manufactured by manufacturers duly authorised to do so.

Due to the change of the legal level of the future GMP guidance for veterinary domain, the expert group wants to stress out the following point which can impact the effective implementation of this new regulation when assessing the compliance of a manufacturer with GMP: To avoid creating more stringent supervision and compliance assessment procedures for veterinary medicines, the difference between the regulatory level of GMP standards applying to human medicines (i.e. GMP Guidance in Eudralex Volume 4) and veterinary medicines (Implementing Acts) should not have impact on the outcome of an inspection (e.g. issuance of GMP certificate, inspection report). Thus, a deviation from the veterinary GMP Implementing Act should not be more aggravating than a deviation from a human GMP Guide.

Cooperation and coordination of controls and inspections

The competent authorities shall cooperate with each other and with the Agency in relation to controls and inspections. They shall share information with the Agency on both controls and inspections planned and conducted.

The competent authorities shall also take into account the compilation, published by the Commission, of Union procedures on controls and inspections and exchange of information.

Controls and inspection may also be carried out on the request of a competent authority of another Member State, the European Commission or the Agency.

Control, Inspection and compliance with marketing authorisation

The expert group recommends to remind the global principles for compliance with marketing authorisation detailed further in the good manufacturing practice:

The competent authorities shall ensure that all manufacturing or import operations for veterinary medicinal products subject to a marketing authorisation are carried out by manufacturers in accordance with the information provided in the application for that marketing authorisation.

The competent authorities shall oblige the marketing authorisation holder and the manufacturer(s) if different to regularly review his manufacturing methods in the light of scientific and technical progress in accordance with article 58 of regulation 2019/6.

If a variation to the marketing authorisation dossier is necessary, the variation shall take place by the arrangements established in accordance with the procedures laid down in Section 3 of Regulation 2019/6.

In the case of Homeopathic veterinary medicinal products registered in accordance with Article 86 of Regulation 2019/6 or products falling under Article 5(6) of Regulation 2019/6, reference to the Marketing authorisation holder (MAH), throughout the Implementing act should be understood to refer to the legal entity responsible for placing the product on the market and reference to the Marketing authorisation

(MA),where applicable, should be understood to refer to the registration or other authorisation granted by EU or national competent authority.

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GMP for veterinary medicinal products (including homeopathic products, products authorised under Article 5 (6) and novel therapy products)

1. Pharmaceutical quality system

The holder of a Manufacturing Authorisation must manufacture medicinal products so as to ensure that they are fit for their intended use, comply with the requirements of the Marketing Authorisation, as appropriate and do not place animals or humans at risk due to inadequate safety, quality or efficacy. The same applies to manufacturers in third countries. The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment by staff in many different departments and at all levels within the company, by the company's suppliers and by its distributors. To achieve this quality objective reliably there must be a comprehensively designed and correctly implemented Pharmaceutical Quality System incorporating Good Manufacturing Practice, Quality Management Quality Management and Quality Risk Management. When using electronical systems these should be validated and clearly controlled in a transparent way and approved locally. It should be fully documented and its effectiveness monitored. All systems should be transparent and clearly structured.

The manufacturing authorization holder has the obligation to supply all parts of production and quality units with competent personnel, and suitable and sufficient premises, equipment and facilities. There are additional legal responsibilities for the holder of the Manufacturing Authorisation and for the Qualified Person(s).

Pharmaceutical quality system

1.1 deleted.

1.2 GMP applies to the lifecycle stages from the manufacture of registration batches, technology transfer, commercial manufacturing through to product discontinuation. The principles of vICH guidelines should be considered.

1.3 The size and complexity of the company's activities should be taken into consideration when developing a new Pharmaceutical Quality System or modifying an existing one. The design of the system should incorporate appropriate risk management principles including the use of appropriate tools. All aspects of the system should refer to the site and be adapted, controlled and approved on site level as an obligation, so the effectiveness has to be shown on site level.

1.4 A Pharmaceutical Quality System appropriate for the manufacture of veterinary medicinal products should ensure that:

(i) Product realisation is achieved by designing, planning, implementing, maintaining and continuously improving a system that allows the consistent delivery of products with appropriate quality attributes;

(ii) Product and process knowledge is managed throughout all lifecycle stages;

(iii) Medicinal products are designed and developed in a way that takes account of the requirements of Good Manufacturing Practice;

(iv) Production and control operations are clearly specified and Good Manufacturing Practice adopted;

(v) Managerial responsibilities are clearly specified;

(vi) Arrangements are made for the manufacture, supply and use of the correct starting and packaging materials, the selection and monitoring of suppliers and for verifying that each delivery is from the approved supply chain;

(vii) Processes are in place to assure the management of outsourced activities.

(viii) A state of control is established and maintained by developing and using effective monitoring and control systems for process performance and product quality.

(ix) The results of product and processes monitoring are taken into account in batch release, in the investigation of deviations, and, with a view to taking preventive action to avoid potential deviations occurring in the future.

(x) All necessary controls on intermediate products, and any other in-process controls and validations are carried out;

(xi) Continual improvement is facilitated through the implementation of quality improvements appropriate to the current level of process and product knowledge.

(xii) Arrangements are in place for the prospective evaluation of planned changes and their approval prior to implementation taking into account regulatory notification and approval where required;

(xiii) After implementation of any change, an evaluation is undertaken to confirm the quality objectives were achieved and that there was no unintended deleterious impact on product quality;

(xiv) An appropriate level of root cause analysis should be applied during the investigation of deviations, suspected product defects and other problems. This can be determined using Quality Risk Management principles. In cases where the true root cause(s) of the issue cannot be determined, consideration should be given to identifying the most likely root cause(s) and to addressing those. Where human error is suspected or identified as the cause, this should be justified having taken care to ensure that process, procedural or system- based errors or problems have not been overlooked, if present. Appropriate corrective actions and/or preventative actions (CAPAs) should be identified and taken in response to investigations. The effectiveness of such actions should be monitored and assessed, in line with Quality Risk Management principles.

(xv) 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 any other regulations relevant to the production, control and release of medicinal products;

(xvi) Satisfactory arrangements exist to ensure, as far as possible, that the medicinal products are stored, distributed and subsequently handled so that quality is maintained throughout their shelf life;

(xvii) There is a process for self-inspection and/or quality audit, which regularly appraises the effectiveness and applicability of the Pharmaceutical Quality System.

1.5 Senior management has the ultimate responsibility to ensure an effective Pharmaceutical Quality System is in place, adequately resourced and that roles, responsibilities, and authorities are defined, communicated and implemented throughout the organisation. Senior management's leadership and active participation in the Pharmaceutical Quality System is essential. This leadership should ensure the support and commitment of staff at all levels and sites within the organisation to the Pharmaceutical Quality System.

1.6 There should be periodic management review, with the involvement of senior management, of the operation of the Pharmaceutical Quality System to identify opportunities for continual improvement of products, processes and the system itself.

1.7 The Pharmaceutical Quality System should be defined and documented. A Quality Manual or equivalent documentation should be established and should contain a description of the quality management system including management responsibilities.

1.8 Good Manufacturing Practice is that part of the Pharmaceutical Quality System which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the Marketing Authorisation or product specification. Good Manufacturing Practice is concerned with both production and quality control.

The basic requirements of GMP are that:

(i) All manufacturing processes are clearly defined, systematically reviewed in the light of experience and shown to be capable of consistently manufacturing medicinal products of the required quality and complying with their specifications;

(ii) Critical steps of manufacturing processes and significant changes to the process are validated;

(iii) All necessary facilities for GMP are provided including:

- Appropriately qualified and trained personnel;
- Adequate premises and space;
- Suitable equipment and services;
- Correct materials, containers and labels;
- Approved procedures and instructions, in accordance with the Pharmaceutical Quality System;
- Suitable storage and transport;

(iv) Instructions and procedures are written in an instructional form in clear and unambiguous language, specifically applicable to the facilities provided;

(v) Procedures are carried out correctly and operators are trained to do so;

(vi) Records are made, manually and/or by recording instruments, during manufacture which demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the product was as expected.

(vii) Any significant deviations are fully recorded, investigated with the objective of determining the root cause and appropriate corrective and preventive action implemented;

(viii) Records of manufacture including distribution which enable the complete history of a batch to be traced are retained in a comprehensible and accessible form;

(ix) The distribution of the products minimises any risk to their quality and takes account of Good Distribution Practice;

(x) A system is available to recall any batch of product, from sale or supply;

(xi) Complaints about products are examined, the causes of quality defects investigated and appropriate measures taken in respect of the defective products and to prevent reoccurrence.

Quality control

1.9 Quality Control is that part of Good Manufacturing Practice which is concerned with sampling, specifications and testing, and with the organisation, documentation and release procedures which ensure that the necessary and relevant tests are actually 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 basic requirements of Quality Control are regulated in chapter 6. More details are to be found in the annexes for quality control respectively in the guidelines for specific products.

Product quality review

1.10 Regular periodic or rolling quality reviews of all authorised veterinary medicinal products, including export only products, should be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished product, to highlight any trends and to identify product and process improvements. Such reviews should be conducted and documented annually (at minimum), taking into account previous reviews, and should include at least:

i) A review of starting materials including packaging materials used in the product, especially those from new sources and in particular the review of supply chain traceability of active substances.

(ii) A review of critical in-process controls and finished product results.

(iii) A review of all batches that failed to meet established specification(s) and their investigation.

(iv) A review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventive actions taken.

(v) A review of all changes carried out to the processes or analytical methods.

(vi) A review of Marketing Authorisation variations submitted, granted or refused, including those for third country (export only) dossiers.

(vii) A review of the results of the stability monitoring programme and any adverse trends.

(viii) A review of all quality-related returns, complaints and recalls and the investigations performed at the time.

(ix) A review of adequacy of any other previous product process or equipment corrective actions.

(x) For new marketing authorisations and variations to marketing authorisations, a review of post-marketing commitments.

(xi) The qualification status of relevant equipment and utilities, e.g. HVAC, water, compressed gases, etc.

(xii) A review of any contractual arrangements of outsourced activities to ensure that they are up to date.

1.11 The manufacturer and, where different, marketing authorisation holder should evaluate the results of the review and an assessment made as to whether corrective and preventive action or any revalidation should be undertaken, under the Pharmaceutical Quality System. There should be management procedures for the ongoing management and review of these actions and the effectiveness of these procedures verified during self-inspection. Quality reviews may be grouped by product type, e.g. solid dosage forms, liquid dosage forms, sterile products, etc. where scientifically justified.

Where the marketing authorisation holder is not the manufacturer, there should be a technical agreement in place between the various parties that defines their respective responsibilities in producing the product quality review.

Quality risk management

1.12 Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively.

1.13 The principles of quality risk management are that:

i) The evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient

ii) The level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk

Examples of the processes and applications of quality risk management can be found inter alia in ICH Q9.

2. Personnel

The correct manufacture of veterinary medicinal products relies upon people. For this reason there must be sufficient qualified personnel to carry out all the tasks which are the responsibility of the manufacturer. Individual responsibilities should be clearly understood by the individuals and recorded. All personnel should be aware of the principles of Good Manufacturing Practice that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs.

General

2.1 The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience. Senior management should determine and provide adequate and appropriate resources (human, financial, materials, facilities and equipment) to implement and maintain the quality management system and continually improve its effectiveness. The responsibilities placed on any one individual should not be so extensive as to present any risk to quality.

2.2 The manufacturer must have an organisation chart in which the relationships between the key management personnel and in particular, where applicable, the heads of Production, Quality Control and Head of Quality Assurance or Quality Unit and the position of the Qualified Person(s), where required by Regulation 2019/6, are clearly shown in the managerial hierarchy.

2.3 People in responsible positions should have specific duties recorded in written job descriptions and adequate authority to carry out their responsibilities. Their duties may be delegated to designated deputies of a satisfactory qualification level. There should be no gaps or unexplained overlaps in the responsibilities of those personnel concerned with the application of Good Manufacturing Practice.

2.4 Senior management has the ultimate responsibility to ensure an effective quality management system is in place to achieve the quality objectives, and, that roles, responsibilities, and authorities are defined, communicated and implemented throughout the organisation. Senior management should establish a quality policy that describes the overall intentions and direction of the company related to

quality and should ensure continuing suitability and effectiveness of the quality management system and GMP compliance through participation in management review.

Key personnel

2.5 Senior Management should appoint Key Management Personnel including the head of Production, where applicable, the head of Quality Control, and if at least one of these persons is not responsible for the duties described in Article 97 of Regulation 2019/6, an adequate number, but at least one, Qualified Person(s) designated for the purpose, where requested by Regulation 2019/6. Normally, key posts should be occupied by full-time personnel. The heads of Production and Quality Control must be independent from each other. In large organisations, it may be necessary to delegate some of the functions listed in 2.7, 2.8 and 2.9. 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. Where such a function exists usually some of the responsibilities described in 2.7, 2.8 and 2.9 are shared with the Head of Quality Control and Head of Production and senior management should therefore take care that roles, responsibilities, and authorities are defined.

2.6 The duties of the Qualified Person(s) are described in Article 97 of Regulation 2019/6. The responsibilities of a Qualified Person may be delegated, but only to other Qualified Person(s). Additional guidance regarding the role of the Qualified Person to be defined in specific guidelines to be adopted by the European Commission.

2.7 The head of the Production Department has at least the following responsibilities:

i. To ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality;

ii. To approve the instructions relating to production operations and to ensure their strict implementation;

iii. To ensure that the production records are evaluated and signed by an authorised person;

iv. To ensure the qualification and maintenance of his department, premises and equipment;

v. To ensure that the appropriate validations are done;

vi. To ensure that the required initial and continuing training of his department personnel is carried out and adapted according to need.

2.8 The head of Quality Control has at least the following responsibilities:

i. To approve or reject, , starting materials, packaging materials, intermediate, bulk and finished products;

ii. To ensure that all necessary testing is carried out and the associated records evaluated;

iii. To approve specifications, sampling instructions, test methods and other Quality Control procedures;

iv. To approve and monitor any contract analysts;

v. To ensure the qualification and maintenance of his department, premises and equipment;

vi. To ensure that the appropriate validations are done;

vii. To ensure that the required initial and continuing training of his department personnel is carried out and adapted according to need.

Other duties of Quality Control are summarised in additional sections of the advice.

2.9 The heads of Production, Quality Control and where relevant, Head of Quality Assurance or Head of Quality Unit, generally have some shared, or jointly exercised, responsibilities relating to quality including

in particular the design, effective implementation, monitoring and maintenance of the quality management system. These may include, subject to any national regulations:

i. The authorisation of written procedures and other documents, including amendments;

ii. The monitoring and control of the manufacturing environment;

iii. Plant hygiene;

iv. Process validation;

v. Training;

vi. The approval and monitoring of suppliers of materials;

vii. The approval and monitoring of contract manufacturers and providers of other GMP related outsourced activities;

viii. The designation and monitoring of storage conditions for materials and products;

ix. The retention of records;

x. The monitoring of compliance with the requirements of Good Manufacturing Practice;

xi. The inspection, investigation, and taking of samples, in order to monitor factors which may affect product quality;

xii. Participation in management reviews of process performance, product quality and of the quality management system and advocating continual improvement

xiii. Ensuring that a timely and effective communication and escalation process exists to raise quality issues to the appropriate levels of management.

Training

2.10 The manufacturer should provide training for all the personnel whose duties take them into production and storage areas or into control laboratories (including the technical, maintenance and cleaning personnel), and for other personnel whose activities could affect the quality of the product.

2.11 Besides the basic training on the theory and practice of the Pharmaceutical quality management system and Good Manufacturing Practice, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given, and its practical effectiveness should be periodically assessed. Training programmes should be available, approved by relevant persons in accordance with the quality management system. Training records should be kept.

2.12 Personnel working in areas where contamination is a hazard, e.g. clean areas or areas where highly active, toxic, infectious or sensitising materials are handled, should be given specific training.

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

2.14 The pharmaceutical quality system and good manufacturing practice and all the measures capable of improving its understanding and implementation should be thoroughly discussed during the training sessions.

Personnel Hygiene

2.15 Detailed hygiene programmes should be established and adapted to the different needs within the factory. They should include procedures relating to the health, hygiene practices and clothing of personnel. These procedures should be understood and followed in a very strict way by every person

whose duties take him into the production and control areas. Hygiene programmes should be promoted by management and widely discussed during training sessions.

2.16 All personnel should receive medical examination upon recruitment. It must be the manufacturer's responsibility that there are instructions ensuring that health conditions that can be of relevance to the quality of products come to the manufacturer's knowledge. After the first medical examination, examinations should be carried out when necessary for the work and personal health.

2.17 Manufacturer should ensure as far as is practicable that no person affected by an infectious disease or having open lesions on the exposed surface of the body is engaged in the manufacture of veterinary medicinal products.

2.18 Every person entering the manufacturing areas should wear protective garments appropriate to the operations to be carried out.

2.19 Eating, drinking, chewing or smoking, or the storage of food, drink, smoking materials or personal medication in the production and storage areas should be prohibited. In general, any unhygienic practice within the manufacturing areas or in any other area where the product might be adversely affected should be forbidden.

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

2.21 Personnel should be instructed to use the hand-washing facilities.

2.22 Any specific requirements for the manufacture of special groups of products, for example sterile preparations, are included in specific guidelines to be adopted by the European Commission.

Consultants

2.23 Consultants should have adequate education, training, and experience, or any combination thereof, to advise on the subject for which they are retained. Records should be maintained stating the name, address, qualifications, and type of service provided by these consultants.

3. Premises and equipment

Premises and equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. Their layout and design must aim to minimise the risk of errors and permit effective cleaning and maintenance in order to avoid contamination and cross-contamination, build-up of dust or dirt and, in general, any adverse effect on the quality of products.

Premises

General

3.1 Premises should be situated in an environment which, when considered together with measures to protect the manufacture, presents minimal risk of causing contamination of materials or products.

3.2 Premises should be carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the quality of products. They should be cleaned and, where applicable, disinfected according to detailed written procedures.

3.3 Lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the medicinal products during their manufacture and storage, or the accurate functioning of equipment.

3.4 Premises should be designed and equipped so as to afford maximum protection against the entry of insects or other animals.

3.5 Steps should be taken in order to prevent the entry of unauthorised people. Production, storage and quality control areas should not be used as a right of way by personnel who do not work in them.

Production area

3.6 Cross-contamination should be prevented for all products by appropriate design and operation of manufacturing facilities. The measures to prevent cross-contamination should be commensurate with the risks. Quality Risk Management principles should be used to assess and control the risks.

Depending of the level of risk, it may be necessary to dedicate premises and equipment for manufacturing and/or packaging operations to control the risk presented by some medicinal products.

Dedicated facilities are required for manufacturing when a medicinal product presents a risk because:

i. the risk cannot be adequately controlled by operational and/ or technical measures,

ii. scientific data from the toxicological evaluation does not support a controllable risk (e.g. allergenic potential from highly sensitising materials such as beta lactams) or

iii. relevant residue limits, derived from the toxicological evaluation, cannot be satisfactorily determined by a validated analytical method.

Further guidance can be found in Chapter 5 and in guidelines published by European commission.

3.7 Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.

3.8 The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimise the risk of confusion between different medicinal products or their components, to avoid cross- contamination and to minimise the risk of omission or wrong application of any of the manufacturing or control steps.

3.9 Where starting and primary packaging materials, intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors and ceilings) should be smooth, free from cracks and open joints, and should not shed particulate matter and should permit easy and effective cleaning and, if necessary, disinfection.

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

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

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

3.13 Weighing of starting materials usually should be carried out in a separate weighing room designed for such use.

3.14 In cases where dust is generated (e.g. during sampling, weighing, mixing and processing operations, packaging of dry products), specific provisions should be taken to avoid cross-contamination and facilitate cleaning.

3.15 Premises for the packaging of medicinal products should be specifically designed and laid out so as to avoid mix-ups or cross-contamination.

3.16 Production areas should be well lit, particularly where visual on-line controls are carried out.

3.17 In-process controls may be carried out within the production area provided they do not carry any risk to production.

Storage areas

3.18 Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products: starting and packaging materials, intermediate, bulk and finished products, products in quarantine, released, rejected, returned or recalled.

3.19 Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these should be provided, checked and monitored.

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

3.21 Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorised personnel. Any system replacing the physical quarantine should give equivalent security.

3.22 There should normally be a separate sampling area for starting materials. If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination.

3.23 Segregated areas should be provided for the storage of rejected, recalled or returned materials or products.

3.24 Materials or products when they present a risk according to the approach detailed in 3.6 should be stored in safe and secure areas.

3.25 Printed packaging materials are considered critical to the conformity of the medicinal product and special attention should be paid to the safe and secure storage of these materials.

Quality control areas

3.26 Normally, Quality Control laboratories should be separated from production areas. This is particularly important for laboratories for the control of biologicals, microbiologicals and radioisotopes, which should also be separated from each other.

3.27 Control laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix-ups, contamination and cross-contamination. There should be adequate suitable storage space for samples and records.

3.28 Separate rooms may be necessary to protect sensitive instruments from vibration, electrical interference, humidity, etc.

3.29 Special requirements are needed in laboratories handling hazardous substances, such as biological or other health risk samples.

Ancillary Areas

3.30 Rest and refreshment rooms should be separate from other areas.

3.31 Facilities for changing clothes and for washing and toilet purposes should be easily accessible and appropriate for the number of users. Toilets should not directly communicate with production or storage areas.

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

3.33 Animal houses should be well isolated from other areas, with separate entrance (animal access) and air handling facilities.

Equipment

3.34 Manufacturing equipment should be designed, located and maintained to suit its intended purpose.

3.35 Repair and maintenance operations should not present any hazard to the quality of the products.

3.36 Manufacturing equipment should be designed so that it can be easily and thoroughly cleaned. It should be cleaned according to detailed and written procedures and stored only in a clean and dry condition.

3.37 Washing and cleaning equipment should be chosen and used in order not to be a source of contamination.

3.38 Equipment should be installed in such a way as to prevent any risk of error or of contamination.

3.39 Production equipment should not present any hazard to products. Parts of production equipment that come into contact with the product must not be reactive, additive or absorptive to such an extent that it will affect the quality of the product and thus present any hazard.

3.40 Balances and measuring equipment of an appropriate range and precision should be available for production and control operations.

3.41 Measuring, weighing, recording and control equipment should be calibrated and checked at defined intervals by appropriate methods. Adequate records of such tests should be maintained.

3.42 Fixed pipework should be clearly labelled to indicate the contents and, where applicable, the direction of flow.

3.43 Distilled, deionised and, where appropriate, other water pipes should be sanitised according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.

3.44 Defective equipment should, if possible, be removed from production and quality control areas, or at least be clearly labelled as defective.

4. Documentation

Good documentation constitutes an essential part of the quality assurance system and is key to operating in compliance with GMP requirements. The various types of documents and media used should be fully defined in the manufacturer's Quality Management System. Documentation may exist in a variety of forms, including paper-based, electronic or photographic media. The main objective of the system of documentation utilized must be to establish, control, monitor and record all activities which directly or indirectly impact on all aspects of the quality of veterinary medicinal products. The Quality Management System should include sufficient instructional detail to facilitate a common understanding of the requirements, in addition to providing for sufficient recording of the various processes and evaluation of any observations, so that ongoing application of the requirements may be demonstrated.

There are two primary types of documentation used to manage and record GMP compliance: instructions (directions, requirements) and records/reports. Appropriate good documentation practice should be applied with respect to the type of document.

Suitable controls should be implemented to ensure the accuracy, integrity, availability and legibility of documents. Instruction documents should be free from errors and available in writing. The term 'written' means recorded, or documented on media from which data may be rendered in a human readable form.

Required GMP documentation (by type):

Site Master File: A document describing the GMP related activities of the manufacturer.

Instructions (directions, or requirements) type:

Specifications: Describe in detail the requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

Manufacturing Formulae, Processing, Packaging and Testing Instructions: Provide detail all the starting materials, equipment and computerised systems (if any) to be used and specify all processing, packaging, sampling and testing instructions. In- process controls and process analytical technologies to be employed should be specified where relevant, together with acceptance criteria.

Procedures: (Otherwise known as Standard Operating Procedures, or SOPs), give directions for performing certain operations.

Protocols: Give instructions for performing and recording certain discreet operations.

Technical Agreements: Are agreed between contract givers and acceptors for outsourced activities.

Record/Report type:

Records: Provide evidence of various actions taken to demonstrate compliance with instructions, e.g. activities, events, investigations, and in the case of manufactured batches a history of each batch of product, including its distribution. Records include the raw data which is used to generate other records. For electronic records regulated users should define which data are to be used as raw data. At least, all data on which quality decisions are based should be defined as raw data

Certificates of Analysis: Provide a summary of testing results on samples of products or materials (Alternatively the certification may be based, in-whole or in-part, on the assessment of real time data (summaries and exception reports) from batch related process analytical technology (PAT), parameters or metrics as per the approved marketing authorisation dossier.) together with the evaluation for compliance to a stated specification.

Reports: Document the conduct of particular exercises, projects or investigations, together with results, conclusions and recommendations.

Generation and Control of Documentation

4.1 All types of documents should be defined and adhered to. The requirements apply equally to all forms of document media types. Complex systems need to be understood, well documented, validated, and adequate controls should be in place. Many documents (instructions and/or records) may exist in hybrid forms, i.e. some elements as electronic and others as paper based. Relationships and control measures for master documents, official copies, data handling and records need to be stated for both hybrid and homogenous systems. Unnecessary, overlapping of content should be avoided. The documentation system should be clearly structured and transparent. Appropriate controls for documentation, electronic or in any other form, such as templates, forms, and master documents should be implemented. Appropriate controls should be in place to ensure the integrity of the documents and records throughout the lifecycle, including the retention period.

4.2 Documents should be designed, prepared, reviewed, and distributed with care. They should comply with the relevant parts of Product Specification Files, Manufacturing and Marketing Authorisation dossiers, as where applicable. The reproduction of working documents from master documents should not allow any error or unauthorized change to be introduced through the reproduction process.

4.3 Documents containing instructions should be approved, signed and dated by appropriate and authorised persons. Documents should have unambiguous contents and be uniquely identifiable. The contents should contain complete and correct instructions and descriptions. The effective date should be defined.

4.4 Documents containing instructions should be laid out in an orderly fashion and be easy to check. The style and language of documents should fit with their intended use. Standard Operating Procedures, Work Instructions and Methods should be written in an imperative mandatory style.

4.5 Documents within the Quality Management System should be regularly reviewed and kept up-to-date.

4.6 Documents should not be hand-written; although, where documents require the entry of data, sufficient space should be provided for such entries.

Good Documentation Practices

4.7 Handwritten entries should be made in clear, legible, indelible way.

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

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

Retention of Documents

4.10 It should be clearly defined which record is related to each manufacturing activity and where this record is located. Secure controls must be in place to ensure the integrity of the record throughout the retention period and validated where appropriate.

4.11 Specific requirements apply to batch documentation which must be kept for one year after expiry of the batch to which it relates or at least five years after certification of the batch by the Qualified

Person, whichever is the longer. Other requirements for retention of documentation may be described in legislation in relation to specific types of product (e.g. Novel Therapies Products) and specify that longer retention periods be applied to certain documents.

4.12 For other types of documentation, the retention period will depend on the business activity which the documentation supports. Critical documentation, including raw data (for example relating to validation or stability), which supports information in the Marketing Authorisation should be retained whilst the authorization remains in force. It may be considered acceptable to retire certain documentation (e.g. raw data supporting validation reports or stability reports) where the data has been superseded by a full set of new data. Justification for this should be documented and should take into account the requirements for retention of batch documentation; for example, in the case of process validation data, the accompanying raw data should 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.

The following section gives some examples of required documents. The quality management system should describe all documents required to ensure product quality and patient safety.

Specifications

4.13 There should be appropriately authorised and dated specifications for starting and packaging materials, and finished products.

Specifications for starting and packaging materials

4.14 Specifications for starting and primary or printed packaging materials should include or provide reference to, if applicable:

a) A description of the materials, including:

- The designated name and the internal code reference;

- The reference, if any, to a pharmacopoeial monograph;

- The approved suppliers and, if reasonable, the original producer of the material;

- A specimen of printed materials;

b) Directions for sampling and testing;

c) Qualitative and quantitative requirements with acceptance limits;

d) Storage conditions and precautions;

e) The maximum period of storage before re-examination.

Specifications for intermediate and bulk products

4.15 Specifications for intermediate and bulk products should be available for critical steps or if these are purchased or dispatched. The specifications should be similar to specifications for starting materials or for finished products, as appropriate.

Specifications for finished products

4.16 Specifications for finished products should include or provide reference to:

a) The designated name of the product and the code reference where applicable;

b) The formula;

c) A description of the pharmaceutical form and package details;

d) Directions for sampling and testing

e) The qualitative and quantitative requirements, with the acceptance limits;

f) The storage conditions and any special handling precautions, where applicable;

g) The shelf-life.

Manufacturing Formula and Processing Instructions

Approved, written Manufacturing Formula and Processing Instructions should exist for each product and batch size to be manufactured.

4.17 The Manufacturing Formula should include:

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

b) A description of the pharmaceutical form, strength of the product and batch size;

c) A list of all starting materials to be used, with the amount of each, described; mention should be made of any substance that may disappear in the course of processing;

d) A statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable

4.18 The Processing Instructions should include:

a) A statement of the processing location and the principal equipment to be used;

b) The methods, or reference to the methods, to be used for preparing the critical equipment (e.g. cleaning, assembling, calibrating, sterilising);

c) Checks that the equipment and work station are clear of previous products, documents or materials not required for the planned process, and that equipment is clean and suitable for use;

d) Detailed stepwise processing instructions [e.g. checks on materials, pre-treatments, sequence for adding materials, critical process parameters (time, temp etc)];

e) The instructions for any in-process controls with their limits;

f) Where necessary, the requirements for bulk storage of the products; including the container, labeling and special storage conditions where applicable;

g) Any special precautions to be observed.

Packaging Instructions

4.19 Approved Packaging Instructions for each product, pack size and type should exist. These should include, or have a reference to, the following:

a) Name of the product; including the batch number of bulk and finished product

b) Description of its pharmaceutical form, and strength where applicable;

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

d) A complete list of all the packaging materials required, including quantities, sizes and types, with the code or reference number relating to the specifications of each packaging material;

e) Where appropriate, an example or reproduction of the relevant printed packaging materials, and specimens indicating where to apply batch number references, and shelf life of the product;

f) Checks that the equipment and work station are clear of previous products, documents or materials not required for the planned packaging operations (line clearance), and that equipment is clean and suitable for use.

g) Special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before operations begin;

h) A description of the packaging operation, including any significant subsidiary operations, and equipment to be used;

i) Details of in-process controls with instructions for sampling and acceptance limits.

Batch Processing Record

4.20 A Batch Processing Record should be kept for each batch processed. It should be based on the relevant parts of the currently approved Manufacturing Formula and Processing Instructions, and should contain the following information:

a) The name and batch number of the product;

b) Dates and times of commencement, of significant intermediate stages and of completion of production;

c) Identification (initials) of the operator(s) who performed each significant step of the process and, where appropriate, the name of any person who checked these operations;

d) The batch number and/or analytical control number as well as the quantities of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);

e) Any relevant processing operation or event and major equipment used;

f) A record of the in-process controls and the initials of the person(s) carrying them out, and the results obtained;

g) The product yield obtained at different and pertinent stages of manufacture;

h) Notes on special problems including details, with signed authorisation for any deviation from the Manufacturing Formula and Processing Instructions;

i) Approval by the person responsible for the processing operations.

Note: Where a validated process is continuously monitored and controlled, then automatically generated reports may be limited to compliance summaries and exception/ out-of- specification (OOS) data reports.

Batch Packaging Record

4.21 A Batch Packaging Record should be kept for each batch or part batch processed. It should be based on the relevant parts of the Packaging Instructions.

The batch packaging record should contain the following information:

a) The name and batch number of the product,

b) The date(s) and times of the packaging operations;

c) Identification (initials) of the operator(s) who performed each significant step of the process and, where appropriate, the name of any person who checked these operations;

d) Records of checks for identity and conformity with the packaging instructions, including the results of in-process controls;

e) Details of the packaging operations carried out, including references to equipment and the packaging lines used;

f) Whenever possible, samples of printed packaging materials used, including specimens of the batch coding, expiry dating and any additional overprinting;

g) Notes on any special problems or unusual events including details, with signed authorisation for any deviation from the Packaging Instructions;

h) 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. Where there are there are robust electronic controls in place during packaging there may be justification for not including this information

i) Approval by the person responsible for the packaging operations

Procedures and records

Receipt

4.22 There should be written procedures and records for the receipt of each delivery of each starting material, (including bulk, intermediate or finished goods), primary, secondary and printed packaging materials.

4.23 The records of the receipts should include:

a) The name of the material on the delivery note and the containers;

b) The "in-house" name and/or code of material (if different from a);

c) Date of receipt;

d) Supplier’s name and, manufacturer’s name;

e) Manufacturer’s batch or reference number;

f) Total quantity and number of containers received;

g) The batch number assigned after receipt;

h) Any relevant comment.

4.24 There should be written procedures for the internal labelling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

Sampling

4.25 There should be written procedures for sampling, which include the methods and equipment to be used, the amounts to be taken and any precautions to be observed to avoid contamination of the material or any deterioration in its quality.

Testing

4.26 There should be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used. The tests performed should be recorded.

Other

4.27 Written release and rejection procedures should be available for materials and products, and in particular for the certification for sale of the finished product by the Qualified Person(s). All records should be available to the Qualified Person. A system should be in place to indicate special observations and any changes to critical data.

4.28 Records should be maintained for the distribution of each batch of a product in order to facilitate recall of any batch, if necessary.

4.29 There should be written policies, procedures, protocols, reports and the associated records of actions taken or conclusions reached, where appropriate, for the following examples:

- Validation and qualification of processes, equipment and systems;

- Equipment assembly and calibration;

- Technology transfer;

- Maintenance, cleaning and sanitation;

- Personnel matters including signature lists, training in GMP and technical matters, clothing and hygiene and verification of the effectiveness of training.

- Environmental monitoring;

- Pest control;

- Complaints;

- Recalls;

- Returns;

- Change control;

- Investigations into deviations and non-conformances;

- Internal quality/GMP compliance audits;

- Summaries of records where appropriate (e.g. product quality review);

- Supplier audits.

4.30 Clear operating procedures should be available for major items of manufacturing and test equipment.

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

4.32 An inventory of documents within the Quality Management System should be maintained.

5. Production

Production operations must follow clearly defined procedures; they must comply with the Good Manufacturing Practice in order to obtain products of the requisite quality and, where applicable, be in accordance with the relevant manufacturing and marketing authorisations.

General

5.1 Production should be performed and supervised by competent people.

5.2 All handling of materials and products, such as receipt and quarantine, sampling, storage, labelling, dispensing, processing, packaging and distribution should be done in accordance with written procedures or instructions and, where necessary, recorded.

5.3 All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labelled with the prescribed data.

5.4 Damage to containers and any other problem which might adversely affect the quality of a material should be investigated, recorded and reported to the Quality Control Department.

5.5 Incoming materials and finished products should be physically or administratively quarantined immediately after receipt or processing, until they have been released for use or distribution.

5.6 Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials.

5.7 All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation (physical and/or electronic) and stock rotation.

5.8 Checks on yields, and reconciliation of quantities, should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.

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

5.10 At every stage of processing, products and materials should be protected from microbial and other contamination.

5.11 When working with dry materials and products, special precautions should be taken to prevent the generation and dissemination of dust. This applies particularly to the handling of highly active or sensitising materials.

5.12 At all times during processing, all materials, bulk containers, major items of equipment and where appropriate rooms used should 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 should also mention the stage of production.

5.13 Labels applied to containers, equipment or premises should be clear, unambiguous and in the company's agreed format. It is often helpful in addition to the wording on the labels to use colours to indicate status (for example, quarantined, accepted, rejected, clean).

5.14 Checks should be carried out to ensure that pipelines and other pieces of equipment used for the transportation of products from one area to another are connected in a correct manner.

5.15 Any deviation from instructions or procedures should be avoided as far as possible. If a deviation occurs, it should be approved in writing by a competent person, with the involvement of the Quality Control department when appropriate.

5.16 Access to production premises should be restricted to authorised personnel.

Prevention of cross-contamination in production

5.17 Normally, the production of non-medicinal products should be avoided in areas and with equipment destined for the production of veterinary medicinal products but, where justified, could be allowed where the measures to prevent cross-contamination with medicinal products described below and in section *Premises and equipment* can be applied. The production and/or storage of technical substances, such as those used in biocides (except where the same substance and its grade is also used for manufacture of such medicinal product) and plant protection products, should not be allowed in areas used for the manufacture and / or storage of medicinal products.

5.18 Contamination of a starting material or of a product by another material or product should be prevented. This risk of accidental cross-contamination resulting from, for example, the uncontrolled release of dust, gases, vapours, aerosols, genetic material or organisms from active substances, other starting materials, and products in process, from residues on equipment, and from operators' clothing should be assessed. The significance of this risk varies with the nature of the contaminant and that of the product being contaminated. Products in which cross-contamination is likely to be most significant are those administered by injection and those given over a long time. However, contamination of all products poses a risk to patient safety dependent on the nature and extent of contamination.

5.19 Cross-contamination should be prevented by attention to design of the premises and equipment as described in section *Premises and equipment*. This should be supported by attention to process design and implementation of any relevant technical or organizational measures, including effective and reproducible cleaning processes to control risk of cross- contamination.

5.20 A Quality Risk Management process, which includes a potency and toxicological evaluation, should be used to assess and control the cross-contamination risks presented by the products manufactured. Factors including; facility/equipment design and use, personnel and material flow, microbiological controls, physico-chemical characteristics of the active substance, process characteristics, cleaning processes and analytical capabilities relative to the relevant limits established from the evaluation of the products should also be taken into account. The outcome of the Quality Risk Management process should be the basis for determining the necessity for and extent to which premises and equipment should be dedicated to a particular product or product family. This may include dedicating specific product contact parts or dedication of the entire manufacturing facility. It may be acceptable to confine manufacturing activities to a segregated, self contained production area within a multiproduct facility, where justified.

5.21 The outcome of the Quality Risk Management process should be the basis for determining the extent of technical and organisational measures required to control risks for cross-contamination. These could include where applicable, but are not limited to, the following:

Technical Measures

i. Dedicated manufacturing facility (premises and equipment);

ii. Self-contained production areas having separate processing equipment and separate heating, ventilation and air-conditioning (HVAC) systems. It may also be desirable to isolate certain utilities from those used in other areas;

iii. Design of manufacturing process, premises and equipment to minimize opportunities for cross-contamination during processing, maintenance and cleaning;

iv. Use of "closed systems" for processing and material/product transfer between equipment;

v. Use of physical barrier systems, including isolators, as containment measures;

vi. Controlled removal of dust close to source of the contaminant e.g. through localised extraction;

vii. Dedication of equipment, dedication of product contact parts or dedication of selected parts which are harder to clean (e.g. filters), dedication of maintenance tools;

viii. Use of single use disposable technologies;

ix. Use of equipment designed for ease of cleaning;

x. Appropriate use of air-locks and pressure cascade to confine potential airborne contaminant within a specified area;

xi. Minimising the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;

xii. Use of automatic clean in place systems of validated effectiveness;

xiii. For common general wash areas, separation of equipment washing, drying and storage areas.

Organisational Measures

i. Dedicating the whole manufacturing facility or a self contained production area on a campaign basis (dedicated by separation in time) followed by a cleaning process of validated effectiveness;

ii. Keeping specific protective clothing inside areas where products with high risk of cross-contamination are processed;

iii. Cleaning verification after each product campaign should be considered as a detectability tool to support effectiveness of the Quality Risk Management approach for products deemed to present higher risk;

iv. Depending on the contamination risk, verification of cleaning of non product contact surfaces and monitoring of air within the manufacturing area and/or adjoining areas in order to demonstrate effectiveness of control measures against airborne contamination or contamination by mechanical transfer;

v. Specific measures for waste handling, contaminated rinsing water and soiled gowning;

vi. Recording of spills, accidental events or deviations from procedures;

vii. Design of cleaning processes for premises and equipment such that the cleaning processes in themselves do not present a cross-contamination risk;

viii. Design of detailed records for cleaning processes to assure completion of cleaning in accordance with approved procedures and use of cleaning status labels on equipment and manufacturing areas;

ix. Use of common general wash areas on a campaign basis;

x. Supervision of working behaviour to ensure training effectiveness and compliance with the relevant procedural controls.

5.22 Measures to prevent cross-contamination and their effectiveness should be reviewed periodically according to set procedures.

Validation

5.23 Validation studies should reinforce Good Manufacturing Practice and be conducted in accordance with defined procedures. Results and conclusions should be recorded.

5.24 When any new manufacturing formula or method of preparation is adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, should be shown to yield a product consistently of the required quality.

5.25 Significant amendments to the manufacturing process, including any change in equipment or materials, which may affect product quality and/or the reproducibility of the process, should be validated.

5.26 Processes and procedures should undergo periodic critical re-validation to ensure that they remain capable of achieving the intended results.

Starting materials

5.27 The selection, qualification, approval and maintenance of suppliers of starting materials, together with their purchase and acceptance, should be documented as part of the pharmaceutical quality system. The level of supervision should be proportionate to the risks posed by the individual materials, taking account of their source, manufacturing process, supply chain complexity and the final use to which the material is put in the medicinal product. The supporting evidence for each supplier / material approval should be maintained. Staff involved in these activities should have a current knowledge of the suppliers, the supply chain and the associated risks involved. Where possible, starting materials should be purchased directly from the manufacturer of the starting material.

5.28 The quality requirements established by the manufacturer for the starting materials should be discussed and agreed with the suppliers. Appropriate aspects of the production, testing and control, including handling, labelling, packaging and distribution requirements, complaints, recalls and rejection procedures should be documented in a formal quality agreement or specification.

5.29 For the approval and maintenance of suppliers of active substances and excipients, the following is required:

Active substances

Supply chain traceability should be established and the associated risks, from active substance starting materials to the finished medicinal product, should be formally assessed and periodically verified. Appropriate measures should be put in place to reduce risks to the quality of the active substance.

The supply chain and traceability records for each active substance (including active substance starting materials) should be available and be retained by the EEA based manufacturer or importer of the medicinal product.

Audits at the manufacturers and distributors of active substances should be conducted based on risk to confirm that they comply with the relevant good manufacturing practice and good distribution practice requirements. The holder of the manufacturing authorisation shall verify such compliance either by himself or through an entity acting on his behalf under a contract.

Audits should be of an appropriate duration and scope to ensure that a full and clear assessment of GMP is made; consideration should be given to potential cross-contamination from other materials on site.

The report should fully reflect what was done and seen on the audit with any deficiencies clearly identified. Any required corrective and preventive actions should be implemented.

Further audits should be undertaken at intervals defined by the quality risk management process to ensure the maintenance of standards and continued use of the approved supply chain.

5.30 For each delivery of starting material the containers should be checked for integrity of package, including tamper evident seal where relevant, and for correspondence between the delivery note, the purchase order, the supplier's labels and approved manufacturer and supplier information maintained by the medicinal product manufacturer. The receiving checks on each delivery should be documented.

5.31 If one material delivery is made up of different batches, each batch must be considered as separate for sampling, testing and release.

5.32 Starting materials in the storage area should be appropriately labelled (see section 13). Labels should bear at least the following information:

i. The designated name of the product and the internal code reference where applicable;

ii. A batch number given at receipt;

iii. Where appropriate, the status of the contents (e.g. in quarantine, on test, released, rejected);

iv. Where appropriate, an expiry date or a date beyond which retesting is necessary.

When fully computerised storage systems are used, all the above information need not necessarily be in a legible form on the label.

5.33 There should be appropriate procedures or measures to assure the identity of the contents of each container of starting material. Bulk containers from which samples have been drawn should be identified (see section *Quality Control*).

5.34 Only starting materials which have been released by the Quality Control department and which are within their retest period should be used.

5.35 Manufacturers of finished products are responsible for any testing of starting and packaging materials as described in the marketing authorisation dossier where applicable. They can utilise partial or full test results from the approved starting material and packaging manufacturer but must, as a minimum, perform identification testing of each batch of starting material according to guidelines published by European commission.

5.36 The rationale for the outsourcing of this testing should be justified and documented and the following requirements should be fulfilled:

i. Special attention should be paid to the distribution controls (transport, wholesaling, storage and delivery) in order to maintain the quality characteristics of the starting materials and to ensure that test results remain applicable to the delivered material;

ii. The veterinary medicinal product manufacturer should perform audits, either itself or via third parties, at appropriate intervals based on risk at the site(s) carrying out the testing (including sampling) of the starting materials in order to assure compliance with Good Manufacturing Practice and with the specifications and testing methods described in the marketing authorisation dossier, where applicable;

iii. The certificate of analysis provided by the starting material manufacturer/supplier should be signed by a designated person with appropriate qualifications and experience. The signature assures that each batch has been checked for compliance with the agreed product specification unless this assurance is provided separately;

iv. The veterinary medicinal product manufacturer should have appropriate experience in dealing with the starting material manufacturer (including experience via a supplier) including assessment of batches previously received and the history of compliance before reducing in-house testing. Any significant change in the manufacturing or testing processes should be considered;

v. The veterinary medicinal product manufacturer should also perform (or via a separately approved contract laboratory) a full analysis at appropriate intervals based on risk and compare the results with the material manufacturer or supplier's certificate of analysis in order to check the reliability of the latter. Should this testing identify any discrepancy then an investigation should be performed and appropriate measures taken. The acceptance of certificates of analysis from the material manufacturer or supplier should be discontinued until these measures are completed.

5.37 Starting materials should only be dispensed by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers.

5.38 Each dispensed material and its weight or volume should be independently checked and the check recorded.

5.39 Materials dispensed for each batch should be kept together and conspicuously labelled as such.

Processing operations: intermediate and bulk products

5.40 Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues or documents not required for the current operation.

5.41 Intermediate and bulk products should be kept under appropriate conditions.

5.42 Critical processes should be validated (see *Validation* in this section).

5.43 Any necessary in-process controls and environmental controls should be carried out and recorded.

5.44 Any significant deviation from the expected yield should be recorded and investigated.

Packaging materials

5.45 The selection, qualification, approval and maintenance of suppliers of primary and printed packaging materials shall be accorded attention similar to that given to starting materials.

5.46 Particular attention should be paid to printed materials. They should be stored in adequately secure conditions such as to exclude unauthorised access. Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix-ups. Packaging materials should be issued for use only by authorised personnel following an approved and documented procedure.

5.47 Each delivery or batch of printed or primary packaging material should be given a specific reference number or identification mark.

5.48 Outdated or obsolete primary packaging material or printed packaging material should be destroyed and this disposal recorded.

Packaging operations

5.49 When setting up a programme for the packaging operations, particular attention should be given to minimising the risk of cross-contamination, mix-ups or substitutions. Different products should not be packaged in close proximity unless there is physical segregation.

5.50 Before packaging operations are begun, steps should be taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents previously used, if these are not required for the current operation. The line-clearance should be performed according to an appropriate check-list.

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

5.52 All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity and conformity with the Packaging Instructions.

5.53 Containers for filling should be clean before filling. Attention should be given to avoid and remove any contaminants such as glass fragments and metal particles.

5.54 Normally, filling and sealing should be followed as quickly as possible by labelling. If it is not the case, appropriate procedures should be applied to ensure that no mix-ups or mislabelling can occur.

5.55 The correct performance of any printing operation (for example code numbers, expiry dates) to be done separately or in the course of the packaging should be checked and recorded. Attention should be paid to printing by hand which should be re-checked at regular intervals.

5.56 Special care should be taken when using cut-labels and when over-printing is carried out off-line. Roll-feed labels are normally preferable to cut-labels, in helping to avoid mix-ups.

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

5.58 Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.

5.59 On-line control of the product during packaging should include at least checking the following:

i. General appearance of the packages;

ii. Whether the packages are complete;

iii. Whether the correct products and packaging materials are used;

iv. Whether any over-printing is correct;

v. Correct functioning of line monitors.

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

5.60 Products which have been involved in an unusual event should only be reintroduced into the process after special inspection, investigation and approval by authorised personnel. Detailed record should be kept of this operation.

5.61 Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced should be investigated and satisfactorily accounted for before release.

5.62 Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded. A documented procedure should be followed if un-coded printed materials are returned to stock.

Finished products

5.63 Finished products should be held in quarantine until their final release under conditions established by the manufacturer.

5.64 The evaluation of finished products and documentation which is necessary before release of product for sale is described in section *Quality Control*.

5.65 After release, finished products should be stored as usable stock under conditions established by the manufacturer.

Rejected, recovered and returned materials

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

5.67 The reprocessing of rejected products should be exceptional. It is only permitted if the quality of the final product is not affected, if the specifications are met and if it is done in accordance with a defined and authorised procedure after evaluation of the risks involved. Record should be kept of the reprocessing.

5.68 The recovery of all or part of earlier batches which conform to the required quality by incorporation into a batch of the same product at a defined stage of manufacture should be authorised beforehand. This recovery should be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf life. The recovery should be recorded.

5.69 The need for additional testing of any finished product which has been reprocessed, or into which a recovered product has been incorporated, should be considered by the Quality Control Department.

5.70 Products returned from the market and which have left the control of the manufacturer should be destroyed unless without doubt their quality is satisfactory; they may be considered for re-sale, re-labelling or recovery in a subsequent batch only after they have been critically assessed by the Quality Control Department in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for re-issue or re-use, although basic chemical reprocessing to recover active ingredient may be possible. Any action taken should be appropriately recorded.

Product shortage due to manufacturing constraints

5.71 The manufacturer should report to the marketing authorisation holder (MAH) any constraints in manufacturing operations which may result in abnormal restriction in the supply. This should be done in a timely manner to facilitate reporting of the restriction in supply by the MAH, to the relevant competent authorities, in accordance with its legal obligations (Article 58 (2) of Regulation 2019/6).

6. Quality Control

Quality Control is concerned with sampling, specifications and testing as well as the organisation, documentation and release procedures which ensure that the necessary and 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 satisfactory. Quality Control is not confined to laboratory operations, but must be involved in all decisions which may concern the quality of the product. The independence of Quality Control from Production is considered fundamental to the satisfactory operation of Quality Control.

General

6.1 Each manufacturer of veterinary medicinal products should have a Quality Control Department. This department should be independent from other departments, and under the authority of a person with appropriate qualifications and experience, who has one or several control laboratories at his disposal. Adequate resources must be available to ensure that all the Quality Control arrangements are effectively and reliably carried out.

6.2 The principal duties of the head of Quality Control are summarised Article xx. The Quality Control Department is responsible, at least, for establishing validation and implementation of all quality control procedures, for overseeing the control of the reference and/or retention samples of materials and products when applicable, for ensuring the correct labelling of containers of materials and products, for ensuring the monitoring of the stability of the products, participate in the investigation of complaints related to the quality of the product. All these operations should be carried out in accordance with written procedures and, where necessary, recorded.

6.3 Finished product assessment should embrace all relevant factors, including production conditions, results of in-process testing, a review of manufacturing (including packaging) documentation, compliance with Finished Product Specification and examination of the final finished pack.

6.4 Quality Control personnel should have access to production areas for sampling and investigation as appropriate.

Good Quality Control Laboratory Practice

6.5 Control laboratory premises and equipment should meet the general and specific requirements for Quality Control areas given in the *Premises and equipments* specific section. Laboratory equipment should not be routinely moved between high risk areas to avoid accidental cross-contamination. In particular, the microbiological laboratory should be arranged so as to minimize risk of cross-contamination.

6.6 The personnel, premises, and equipment in the laboratories should be appropriate to the tasks imposed by the nature and the scale of the manufacturing operations. The use of outside laboratories, in conformity with the principles detailed in the *Outsourced activities* section, is accepted and this should be stated in the Quality Control records.

Documentation

6.7 Laboratory documentation should follow the principles given in the *Documentation* section. An important part of this documentation deals with Quality Control and the following details should be readily

available to the Quality Control Department:

i. Specifications;

ii. Procedures describing sampling, testing, records (including test worksheets and/or laboratory notebooks), recording and verifying;

iii. Procedures for and records of the calibration/qualification of instruments and maintenance of equipment;

iv. A procedure for the investigation of Out of Specification and Out Of Trend results;

v. Testing reports and/or certificates of analysis;

vi. Data from environmental (air, water and other utilities) monitoring, where required;

vii. Validation records of test methods, where applicable.

6.8 Any Quality Control documentation relating to a batch record should be retained following the principles given in the *Documentation* section on retention of batch documentation.

6.9 The data (including test results, yields and environmental controls) as required in the implementing act and Commission guidelines, and any additional data selected using quality risk management principles, should be recorded in a manner permitting trend evaluation. Any out of trend or out of specification data should be addressed and subject to investigation.

6.10 In addition to the information which is part of the batch documentation, other raw data such as laboratory notebooks and/or records should be retained and readily available

Sampling

6.11 The sample taking should be done and recorded in accordance with approved written procedures that describe:

i. The method of sampling;

ii. The equipment to be used;

iii. The amount of the sample to be taken;

iv. Instructions for any required sub-division of the sample;

v. The type and condition of the sample container to be used;

vi. The identification of containers sampled;

vii. Any special precautions to be observed, especially with regard to the sampling of sterile or noxious materials;

viii. The storage conditions;

ix. Instructions for the cleaning and storage of sampling equipment.

6.12 Samples should be representative of the batch of materials or products from which they are taken. The sampling plan used should be appropriately justified and based on a risk management approach, ensuring adequate coverage of the starting materials, batch unit operation/process step, intermediate, bulk, finished product.

6.13 Sample containers should bear a label indicating the contents, with the batch number, the date of sampling and the containers from which samples have been drawn. They should be managed in a manner to minimize the risk of mix-up and to protect the samples from adverse storage conditions.

6.14 Further guidance on reference and retention samples is given in specific guidelines to be adopted by the European Commission.

Testing

6.15 Testing methods should be validated. A laboratory that is using a testing method and which did not perform the original validation, should verify the appropriateness of the testing method. All testing operations described in the marketing authorisation or technical dossier should be carried out according to the approved methods.

6.16 The results obtained should be recorded. Results of critical quality attributes and other attributes based on quality risk management principles, should be trended and checked to make sure that they are consistent with each other. Any calculations should be critically examined.

6.17 The tests performed should be recorded and the records should include at least the following data:

i. Name of the material or product and, where applicable, dosage form;

ii. Batch number and, where appropriate, the manufacturer and/or supplier;

iii. References to the relevant specifications and testing procedures;

iv. Test results, including observations and calculations, and reference to any certificates of analysis;

v. Dates of testing;

vi. Identification of the persons who performed the testing;

vii. Identification of the persons who verified the testing and the calculations, where appropriate;

viii. A clear statement of approval or rejection (or other status decision) and the dated signature of the designated responsible person;

ix. Reference to the equipment used.

6.18 All the in-process controls, including those made in the production area by production personnel, should be performed according to methods approved by Quality Control and the results recorded.

6.19 Laboratory materials like, but not restricted to, reagents, solutions, glassware, reference standards and culture media should have the appropriate quality. They should be prepared and controlled in accordance with written procedures and based on a risk management approach taking into account their use and available stability data.

6.20 Reference standards should be established as suitable for their intended use. Their qualification and certification should be clearly stated and documented. Whenever compendial reference standards from an officially recognised source exist, these should preferably be used as primary reference standards unless justified. The use of secondary standards must be documented and their traceability to primary standards must be demonstrated. These compendial materials should be used for the purpose described in the appropriate monograph unless otherwise authorised by the National Competent Authority.

6.21 Laboratory reagents, solutions, reference standards and culture media should be marked with the preparation and opening date and the signature of the person who prepared them. The expiry date of reagents and culture media should be indicated on the label, together with specific storage conditions. In addition, for volumetric solutions, the last date of standardisation and the last current factor should be indicated.

6.22 Where necessary, the date of receipt of any substance used for testing operations (e.g. reagents, solutions and reference standards) should be indicated on the container. Instructions for use and storage should be followed. In certain cases it may be necessary to carry out an identification test and/or other testing of reagent materials upon receipt or before use.

6.23 Culture media should be prepared in accordance with the media manufacturer's requirements unless scientifically justified. The performance of all culture media should be verified prior to use.

6.24 Used microbiological media and strains should be decontaminated according to a standard procedure and disposed of in a manner to prevent the cross-contamination and retention of residues. The in-use shelf life of microbiological media should be established, documented and scientifically justified.

6.25 Animals used for testing components, materials or products, should, where appropriate, be quarantined before use. They should be maintained and controlled in a manner that assures their suitability for the intended use. They should be identified, and adequate records should be maintained, showing the history of their use.

On-going stability programme

6.26 The stability of released medicinal product should be monitored according to a continuous appropriate programme that will permit the detection of any stability issue (e.g. changes in levels of impurities or dissolution profile) associated with the formulation in the marketed package.

6.27 The purpose of the on-going stability programme is to monitor the product over its shelf life and to determine that the product remains, and can be expected to remain, within specifications under the labelled storage conditions.

6.28 This mainly applies to the medicinal product in the package in which it is sold, however, based on a risk management approach, it may also be relevant for bulk product or/and intermediates, which encounter particular processes or situations that could impact on the stability of the medicinal product. Stability studies on reconstituted product is not required to be monitored on an on-going basis, except if relevant.

6.29 The on-going stability programme should be described in a written protocol following the general rules of the *Documentation* section and results formalised as a report. The equipment used for the on-going stability programme (stability chambers among others) should be qualified and maintained following the general rules of *Premises and equipment* section and specific guidelines to be adopted by the European Commission.

6.30 The protocol for an on-going stability programme should extend to the end of the shelf life period and should include, but not be limited to, the following parameters:

i. Number of batch(es) per strength and different batch sizes, if applicable;

ii. Relevant physical, chemical, microbiological and biological test methods;

iii. Acceptance criteria;

iv. Reference to test methods;

v. Description of the container closure system(s);

vi. Testing intervals (time points);

vii. Description of the conditions of storage (standardised ICH/VICH conditions for long term testing, consistent with the product labelling, should be used);

viii. Other applicable parameters specific to the medicinal product.

6.31 The protocol for the on-going stability programme can be different from that of the initial long-term stability study as submitted in the marketing authorisation dossier provided that this is justified and documented in the protocol (for example the frequency of testing, or when updating to ICH/VICH recommendations).

6.32 The number of batches and frequency of testing should provide a sufficient amount of data to allow for trend analysis. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every primary packaging type, if relevant, should be included in the stability programme (unless none are produced during that year). The testing should be carried out in the final packaging described in the marketing authorisation (including, as appropriate, any secondary packaging and container label), when applicable and practicable. Because of the large volume of certain veterinary medicinal products in their final packaging, the use of smaller comparable containers simulating the actual market packaging may be considered, if scientifically justified and based on a risk management approach in the protocol. For products where on-going stability monitoring would normally require testing using animals and no appropriate alternative, validated techniques are available, the frequency of testing may take account of a risk-benefit approach. The principle of bracketing and matrixing designs may be applied if scientifically justified in the protocol.

6.33 In certain situations, additional batches should be included in the on-going stability programme taking into account any significant change or significant deviation to the process or package, reworking, reprocessing or recovery operation should also be considered on the basis of risk management approach.

6.34 Results of on-going stability studies should be made available to key personnel and, in particular, to the Qualified Person(s). Where on-going stability studies are carried out at a site other than the site of manufacture of the bulk or finished product, there should be a written agreement between the parties concerned. Results of on-going stability studies should be available at the site of manufacture for review by the competent authority.

6.35 Out of specification or significant atypical trends should be investigated. Any confirmed out of specification result, or significant negative trend, affecting product batches released on the market should be reported to the relevant competent authorities. The possible impact on batches on the market should be considered in accordance with the *Complaints and product recall* section and in consultation with the relevant competent authorities.

6.36 A summary of all the data generated, including any interim conclusions on the programme, should be written and maintained. This summary should be subjected to periodic review.

Technical transfer of testing methods

6.37 Prior to transferring a test method, the transferring site should verify that the test method(s) comply with those as described in the Marketing Authorisation or the relevant technical dossier. The original validation of the test method(s) should be reviewed to ensure compliance with current ICH/VICH requirements. A gap analysis should be performed and documented to identify any supplementary validation that should be performed, prior to commencing the technical transfer process.

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

6.39 The transfer protocol should include, but not be limited to, the following parameters:

i. Identification of the testing to be performed and the relevant test method(s) undergoing transfer;

ii. Identification of the additional training requirements;

iii. Identification of standards and samples to be tested;

iv. Identification of any special transport and storage conditions of test items;

v. The acceptance criteria which should be based upon the current validation study of the methodology and with respect to ICH/VICH requirements.

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

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

6.41 Where appropriate, specific requirements described in other European Commission published Guidelines, should be addressed for the transfer of particular testing methods (e.g Near Infrared Spectroscopy).

7. Outsourced operations

Any activity covered by the GMP Implementing Act relevant to the medicinal product(s) in question, that is outsourced should be appropriately defined, agreed and controlled in order to avoid misunderstandings which could result in a product or operation of unsatisfactory quality. There must be a written Contract between the Contract Giver and the Contract Acceptor which clearly establishes the duties of each party. The Quality Management System of the Contract Giver must clearly state the way that the Qualified Person certifying each batch of product for release exercises his full responsibility.

Note: This Chapter deals with the responsibilities of manufacturers towards the Competent Authorities of the Member States with respect to the granting of marketing and manufacturing authorizations, where applicable. It is not intended in any way to affect the respective liability of Contract Acceptors and Contract Givers to consumers; this is governed by other provisions of Community and national law.

General

7.1 There should be a written Contract covering the outsourced activities, the products or operations to which they are related, and any technical arrangements made in connection with it.

7.2 All arrangements for the outsourced activities including any proposed changes in technical or other arrangements should be in accordance with regulations in force, and the Marketing Authorisation for the product concerned, where applicable.

7.3 Where the marketing authorization holder and the manufacturer are not the same, appropriate arrangements should be in place, taking into account the principles described in this chapter.

The Contract Giver

7.4 The pharmaceutical quality system of the Contract Giver should include the control and review of any outsourced activities. The Contract Giver is ultimately responsible to ensure processes are in place

to assure the control of outsourced activities. These processes should incorporate quality risk management principles and notably include 7.5 to 7.8 as listed below.

7.5 Prior to outsourcing activities, the Contract Giver is responsible for assessing the legality, suitability and the competence of the Contract Acceptor to carry out successfully the outsourced activities. The Contract Giver is also responsible for ensuring by means of the Contract that GMP and associated guidelines are followed.

7.6 The Contract Giver should provide the Contract Acceptor with all the information and knowledge necessary to carry out the contracted operations correctly in accordance with regulations in force, and the Marketing Authorisation for the product concerned, where applicable. The Contract Giver should ensure that the Contract Acceptor is fully aware of any problems associated with the product or the work which might pose a hazard to his premises, equipment, personnel, other materials or other products.

7.7 The Contract Giver should monitor and review the performance of the Contract Acceptor and the identification and implementation of any needed improvement.

7.8 The Contract Giver should be responsible for reviewing and assessing the records and the results related to the outsourced activities. In the context of manufacturing operations, he should also ensure, either by himself, or based on the confirmation of the Contract Acceptor's Qualified Person, that all products and materials delivered to him by the Contract Acceptor have been processed in accordance with GMP and the marketing authorisation, where applicable.

The Contract Acceptor

7.9 The Contract Acceptor must be able to carry out satisfactorily the work ordered by the Contract Giver such as having adequate premises, equipment, knowledge, experience, and competent personnel.

7.10 The Contract Acceptor should ensure that all products, materials and knowledge delivered to him are suitable for their intended purpose.

7.11 The Contract Acceptor should not subcontract to a third party any of the work entrusted to him under the Contract without the Contract Giver's prior evaluation and approval of the arrangements. Arrangements made between the Contract Acceptor and any third party should ensure that information and knowledge, including those from assessments of the suitability of the third party, are made available in the same way as between the original Contract Giver and Contract Acceptor.

7.12 The Contract Acceptor should not make unauthorized changes, outside the terms of the Contract, which may adversely affect the quality of the outsourced activities for the Contract Giver.

7.13 The Contract Acceptor should understand that outsourced activities, including contract analysis, may be subject to inspection by the competent authorities.

The Contract

7.14 A Contract should be drawn up between the Contract Giver and the Contract Acceptor which specifies their respective responsibilities and communication processes (for example in the scope of deviations or complaints) relating to the outsourced activities. Technical aspects of the Contract should be drawn up by competent persons suitably knowledgeable in related outsourced activities and Good Manufacturing Practice. All arrangements for outsourced activities must be in accordance with regulations in force and the Marketing Authorisation, where applicable, for the product concerned and agreed by both parties.

7.15 The Contract should describe clearly who undertakes each step of the outsourced activity, e.g. knowledge management, technology transfer, supply chain, subcontracting, quality and purchasing of materials, testing and releasing materials, undertaking production and quality controls (including in-process controls, sampling and analysis).

7.16 All records related to the outsourced activities, e.g. manufacturing, analytical and distribution records, and reference samples, should be kept by, or be available to, the Contract Giver. Any records relevant to assessing the quality of a product in the event of complaints or a suspected defect or to investigating in the case of a suspected falsified product must be accessible and specified in the relevant procedures of the Contract Giver.

7.17 The Contract should permit the Contract Giver to audit outsourced activities, performed by the Contract Acceptor or his mutually agreed subcontractors.

8. Complaints, Quality Defects and Product Recalls

In order to protect consumer and animal health, a system and appropriate procedures should be in place to record, assess, investigate and review complaints including potential quality defects, and if necessary, to effectively and promptly recall medicinal products for veterinary use from the distribution network. Quality Risk Management principles should be applied to the investigation and assessment of quality defects and to the decision-making process in relation to product recalls corrective and preventative actions and other risk-reducing actions. Requirements in relation to these principles are provided in the *Pharmaceutical quality system* section.

All concerned competent authorities should be informed in a timely manner in case of a confirmed quality defect (faulty manufacture, product deterioration, detection of falsification, non-compliance with the marketing authorisation or product specification file, or any other serious quality problems) with a medicinal or which may result in the recall of the product or an abnormal restriction in the supply. In situations where product on the market is found to be non-compliant with the marketing authorisation, there is no requirement to notify concerned competent authorities provided the degree of non-compliance satisfies the European Commission GMP Guidelines restrictions regarding the handling of unplanned deviations.

In case of outsourced activities, a contract should describe the role and responsibilities of the manufacturer, the marketing authorisation holder and any other relevant third parties in relation to assessment, decision-making, and dissemination of information and implementation of risk-reducing actions relating to a defective product. Guidance in relation to contracts is provided in the *Outsourced activities* section. Such contracts should also address how to contact those responsible at each party for the management of quality defect and recall issues.

Personnel and Organisation

8.1 Appropriately trained and experienced personnel should be responsible for managing complaint and quality defect investigations and for deciding the measures to be taken to manage any potential risk(s) presented by those issues, including recalls. These persons should be independent of the sales and marketing organisation, unless otherwise justified. If these persons do not include the Qualified Person involved in the certification for release of the concerned batch or batches, the latter should be made formally aware of any investigations, any risk-reducing actions and any recall operations, in a timely manner.

8.2 Sufficient trained personnel and resources should be made available for the handling, assessment, investigation and review of complaints and quality defects and for implementing any risk-reducing actions. Sufficient trained personnel and resources should also be available for the management of interactions with competent authorities.

8.3 The use of inter-disciplinary teams should be considered, including appropriately trained Quality Management personnel.

8.4 In situations in which complaint and quality defect handling is managed centrally within an organisation, the relative roles and responsibilities of the concerned parties should be documented. Central management should not, however, result in delays in the investigation and management of the issue.

8.5 There should be written procedures describing the actions to be taken upon receipt of a complaint. All complaints should be documented and assessed to establish if they represent a potential quality defect or other issue.

8.6 Special attention should be given to establishing whether a complaint or suspected quality defect relates to falsification.

8.7 As not all complaints received by a company may represent actual quality defects, complaints which do not indicate a potential quality defect should be documented appropriately and communicated to the relevant group or person responsible for the investigation and management of complaints of that nature, such as suspected adverse events.

8.8 There should be procedures in place to facilitate a request to investigate the quality of a batch of a medicinal product in order to support an investigation into a reported suspected adverse event.

8.9 When a quality defect investigation is initiated, procedures should be in place to address at least the following:

i. The description of the reported quality defect.

ii. The determination of the extent of the quality defect. The checking or testing of reference and/or retention samples should be considered as part of this, and in certain cases, a review of the batch production record, the batch certification record and the batch distribution records (especially for temperature-sensitive products) should be performed.

iii. The need to request a sample, or the return, of the defective product from the complainant and, where a sample is provided, the need for an appropriate evaluation to be carried out.

iv. The assessment of the risk(s) posed by the quality defect, based on the severity and extent of the quality defect.

v. The decision-making process that is to be used concerning the potential need for risk- reducing actions to be taken in the distribution network, such as batch or product recalls, or other actions.

vi. The assessment of the impact that any recall action may have on the availability of the medicinal product to patients/animals in any affected market, and the need to notify the relevant authorities of such impact.

vii. The internal and external communications that should be made in relation to a quality defect and its investigation.

viii. The identification of the potential root cause(s) of the quality defect.

ix. The need for appropriate Corrective and Preventative Actions (CAPAs) to be identified and implemented for the issue, and for the assessment of the effectiveness of those CAPAs.

Investigation and Decision-making

8.10 The information reported in relation to possible quality defects should be recorded, including all the original details. The validity and extent of all reported quality defects should be documented and assessed in accordance with Quality Risk Management principles in order to support decisions regarding the degree of investigation and action taken.

8.11 If a quality defect is discovered or suspected in a batch, consideration should be given to checking other batches and in some cases other products, in order to determine whether they are also affected. In particular, other batches which may contain portions of the defective batch or defective components should be investigated.

8.12 Quality defect investigations should include a review of previous quality defect reports or any other relevant information for any indication of specific or recurring problems requiring attention and possibly further regulatory action.

8.13 The decisions that are made during and following quality defect investigations should reflect the level of risk that is presented by the quality defect as well as the seriousness of any non-compliance with respect to the requirements of the marketing authorisation/product specification file or GMP. Such decisions should be timely to ensure that user, consumer and animal safety is maintained, in a way that is commensurate with the level of risk that is presented by those issues.

8.14 As comprehensive information on the nature and extent of the quality defect may not always be available at the early stages of an investigation, the decision-making processes should still ensure that appropriate risk-reducing actions are taken at an appropriate time- point during such investigations. All the decisions and measures taken as a result of a quality defect should be documented.

8.15 Quality defects should be reported in a timely manner by the manufacturer to the marketing authorisation holder/sponsor and all concerned Competent Authorities in cases where the quality defect may result in the recall of the product or in an abnormal restriction in the supply of the product.

Root Cause Analysis and Corrective and Preventative Actions

8.16 An appropriate level of root cause analysis work should be applied during the investigation of quality defects. In cases where the true root cause(s) of the quality defect cannot be determined, consideration should be given to identifying the most likely root cause(s) and to addressing those.

8.17 Where human error is suspected or identified as the cause of a quality defect, this should be formally justified and care should be exercised so as to ensure that process, procedural or system-based errors or problems are not overlooked, if present.

8.18 Appropriate CAPAs should be identified and taken in response to a quality defect. The effectiveness of such actions should be monitored and assessed.

8.19 Quality defect records should be reviewed and trend analyses should be performed regularly for any indication of specific or recurring problems requiring attention.

Product Recalls and other potential risk-reducing actions

8.20 There should be established written procedures, regularly reviewed and updated when necessary, in order to undertake any recall activity or implement any other risk-reducing actions.

8.21 After a product has been placed on the market, any retrieval of it from the distribution network as a result of a quality defect should be regarded and managed as a recall. (This provision does not apply to the retrieval (or return) of samples of the product from the distribution network to facilitate an investigation into a quality defect issue/report).

8.22 Recall operations should be capable of being initiated promptly and at any time. In certain cases recall operations may need to be initiated to protect consumer or animal health prior to establishing the root cause(s) and full extent of the quality defect

8.23 The batch/product distribution records should be readily available to the persons responsible for recalls, and should contain sufficient information on wholesalers and directly supplied customers (with addresses, phone and/or fax numbers inside and outside working hours, batches and amounts delivered), including those for exported products and medical samples.

8.24 *deleted*

8.25 Consideration should be given following consultation with the concerned Competent Authorities, as to how far into the distribution network a recall action should extend, taking into account the potential risk to public or animal health and any impact that the proposed recall action may have. The Competent Authorities should also be informed in situations in which no recall action is being proposed for a defective batch because the batch has expired (such as with short shelf-life products).

8.26 All concerned Competent Authorities should be informed in advance in cases where products are intended to be recalled. For very serious issues (i.e. those with the potential to seriously impact upon user and consumer or animal health), rapid risk-reducing actions (such as a product recall) may have to be taken in advance of notifying the Competent Authorities. Wherever possible, attempts should be made to agree these in advance of their execution with the concerned Competent Authorities

8.27 It should also be considered whether the proposed recall action may affect different markets in different ways, and if this is the case, appropriate market-specific risk-reducing actions should be developed and discussed with the concerned competent authorities. Taking account of its therapeutic use the risk of shortage of a medicinal product which has no authorised alternative should be considered before deciding on a risk-reducing action such as a recall. Any decisions not to execute a risk-reducing action which would otherwise be required should be agreed with the competent authority in advance.

8.28 Recalled products should be identified and stored separately in a secure area while awaiting a decision on their fate. A formal disposition of all recalled batches should be made and documented. The rationale for any decision to rework recalled products should be documented and discussed with the relevant competent authority. The extent of shelf- life remaining for any reworked batches that are being considered for placement onto the market should also be considered.

8.29 The progress of the recall process should be recorded until closure and a final report issued, including a reconciliation between the delivered and recovered quantities of the concerned products/batches.

8.30 The effectiveness of the arrangements in place for recalls should be periodically evaluated to confirm that they remain robust and fit for use. Such evaluations should extend to both within office-hour situations as well as out-of-office hour situations and, when performing such evaluations, consideration should be given as to whether mock-recall actions should be performed. This evaluation should be documented and justified.

8.31 In addition to recalls, there are other potential risk-reducing actions that may be considered in order to manage the risks presented by quality defects. Such actions may include the issuance of

cautionary communications to healthcare professionals in relation to their use of a batch that is potentially defective. These should be considered on a case- by-case basis and discussed with the concerned competent authorities.

9. Self inspection

Self inspections should be conducted in order to monitor the implementation and compliance with Good Manufacturing Practice and to propose necessary corrective measures.

9.1 Personnel matters, premises, equipment, documentation, production, quality control, distribution of the veterinary medicinal products, arrangements for dealing with complaints and recalls, and self inspection, should be examined at intervals following a prearranged programme in order to verify their conformity with the Pharmaceutical Quality System.

9.2 Self inspections should be conducted in an independent and detailed way by designated competent person(s) from the company. Independent audits by external experts may also be useful.

9.3 All self inspections should be recorded. Reports should contain all the observations made during the inspections and, where applicable, proposals for corrective measures. Statements on the actions subsequently taken should also be recorded.

Specific GMP principles for novel therapy veterinary medicinal products

Introduction

According to article 4 (43) of Regulation 2019/6, novel therapy veterinary medicinal product means:

(a) a veterinary medicinal product specifically designed for gene therapy, regenerative medicine, tissue engineering, blood product therapy, phage therapy;

(b) a veterinary medicinal product issued from nanotechnologies;

Or (c) any other therapy which is considered as a nascent field in veterinary medicine;

In the Annex II of regulation 2019/6, Section V Requirements for marketing authorisation applications for particular veterinary medicinal products, item V.1.1.3. it is stated that "The manufacturing processes for novel therapy veterinary medicinal products shall comply with the principles of Good Manufacturing Practice (GMP) adapted where necessary, to reflect the specific nature of those products. Guidelines specific to novel therapy veterinary products shall be drawn up, to properly reflect the particular nature of their manufacturing process"".

The expert group has taken in account the most current advanced therapy GMP guidance relating to this topic as a starting point for drafting the GMP for veterinary novel therapy products (NT): Part IV of Eudralex vol. 4: Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products (ATMP). However, the scope of products falling into ATMP and in NT are not fully congruent. Furthermore, in the case of products issued from nanotechnologies, such products have already been authorised without a need for adaptation of any specific GMP requirements and therefore no provision for these products need be included in the GMP principles for novel therapy veterinary medicinal products.

Taking into account the need to develop specific requirements for novel therapy veterinary medicinal products while avoiding major overhaul of the GMP provisions, in particular not altering the structure, the expert group recommends the manufacture of veterinary NT shall be undertaken:

- In accordance with the measures of Good Manufacturing Practice for veterinary medicinal products, and Good Manufacturing Practice for active substances used as starting material in veterinary medicinal products,

and

- In accordance with complementary specific GMP principles for veterinary novel therapy products,

and

- Where applicable, ad hoc related guidelines published by European Commission.

1. Scope

1.1 Product scope:

• These principles apply to NT products and active substances used in NT products other than those issued from solely nanotechnologies. For those products classified as NTs solely by virtue of the use of nanotechnologies, these principles do not apply and only GMP requirements in accordance with Good

Manufacturing Practice for veterinary medicinal products, and Good Manufacturing Practice for active substances used as starting material in veterinary medicinal products apply.

• For combined VMPs including elements that are considered novel, the appropriate level of GMP applied should be commensurate with the nature of the material /product and should be determined on a case-by-case basis using a quality risk management approach as described in section 4.

1.2 No provision in these principles (including the quality risk management approach) can be regarded as derogation to the terms of the marketing authorisation.

1.3 Allogenic and autologous cell/tissue therapies that have not been subjected to an industrial process are outside the scope of Regulation (EU) 2019/6. Nevertheless, where appropriate the principles detailed herein may be used by MS Competent Authorities to support their manufacture.

1.4 These principles do not intend to place any restraint on the development of new concepts of new technologies. While this document describes the standard expectations, alternative approaches may be implemented by manufacturers if it is demonstrated that the alternative approach is capable of meeting the same outcome. Any adaptation applied must be compatible with the need to ensure the quality, safety, efficacy and traceability of the product. Additionally, it is stressed that the terms of the marketing authorisation should be complied with.

2. General principles

Quality plays a major role in the safety and efficacy profile of NTs. It is the responsibility of the NT manufacturer to ensure that appropriate measures are put in place to safeguard the quality of the product (so-called "pharmaceutical quality system"). In particular adequate systems are implemented to ensure traceability of the NTs and of their starting and critical raw materials.

3. Quality risk management

3.1 NTs are complex products and risks may differ according to the type of product, nature/characteristics of the starting materials and level of complexity of the manufacturing process. It is also acknowledged that the finished product may entail some degree of variability due to the nature of the materials and/or complex manipulation steps. The flexible nature and complexity of NTs increase the need to apply life cycle management and knowledge management to maintain a high level of control over time and to ensure product improvement.

3.2 NTs are at the forefront of scientific innovation and the field is experiencing technological change that also impacts on the manufacturing processes. For instance, new manufacturing models may emerge to address the specific challenges of NTs.

3.3 In laying down the GMP principles applicable to NTs, it is necessary to recognise a certain level of flexibility so that the NT manufacturer can implement the measures that are most appropriate having regard to specific characteristics of the manufacturing process and of the product.

3.4 The quality Risk Management approach ("QRM") is applicable to all type of NTs within the scope of this implementing act. The quality, safety and efficacy attributes of the NTs and compliance with GMP should be ensured for all NTs.

3.5 Manufacturers are responsible for the quality of the NTs they produce. The quality risk management approach permits the manufacturer to design the organisational, technical and structural measures that

are put in place to comply with GMP and thus to ensure quality according to the specific risks of the product and the manufacturing process. While the quality risk management approach brings flexibility, it also implies that the manufacturer is responsible to put in place the control/mitigation measures that are necessary to address the specific risks of the product and of the manufacturing process.

3.6 The quality risks associated with an NT are highly dependent on the characteristics and origin of the starting materials/product, the biological characteristics (for cell, tissue or bacteriophage based products), the level and characteristics of the expressed protein (for gene therapy products), the specific properties of non-cellular components (raw materials, matrixes), and the manufacturing process.

3.7 When identifying the control/mitigation measures that are most appropriate in each case, the NT manufacturer should consider all the potential risks related to the product or the manufacturing process on the basis of all information available, including an assessment of the potential implications for the quality, safety and efficacy profile of the product, as well as other related risks to animal and human health or to the environment. When new information emerges which may affect the risks, an assessment should be made whether the control strategy (i.e. the totality of the control and mitigation measures applied) continues to be adequate.

3.8 The evaluation of the risks and the effectiveness of the control/mitigation measures should be based on current scientific knowledge and the accumulated experience.

3.9 The level of effort and documentation should be commensurate with the level of risk. It is neither always appropriate nor always necessary to use a formal risk management process (using recognized tools and/ or internal procedures). The use of informal risk management processes (using empirical tools and/or internal procedures) can also be considered acceptable.

3.10 The application of a quality risk management approach can facilitate compliance but does not obviate the manufacturer's obligation to comply with relevant regulatory requirements and to demonstrate that it is able to adequately manage the risks of the product/manufacturing process. It likewise does not replace appropriate communications with the authorities.

3.11 The application of the quality risk management approach should be consistent with the terms of the marketing authorisation. When providing the description of the manufacturing process and process controls in the marketing authorisation application (or, as appropriate, in the context of the submission of a variation), account can be taken of the specific characteristics of the product/manufacturing process to justify adaptation/deviation from standard expectations. Thus, the strategy to address specific limitations that may exist in connection with product development, the manufacturing process, including controls of raw materials and starting materials, the manufacturing facilities and equipment, tests and acceptance criteria, process validation, release specifications, or stability data should be agreed as part of the marketing authorisation.

3.12 For aspects that are not specifically covered by the marketing authorisation, it is incumbent upon the manufacturer to document the reasons for the approach implemented when the quality risk management approach is applied, and to justify that the totality of the measures applied are adequate to ensure the quality of the product. In this regard, it is recalled that alternative approaches to the requirements explained in this act are only acceptable if they are capable of meeting the same outcome.

3.13 Main Applications of the quality risk management approach:

a) QRM in connection with raw materials

- The application of the quality risk management approach requires that the manufacturer has a good understanding of the role of the raw material in the manufacturing process and, in

particular, of the properties of the raw materials that are key to the manufacturing process and final quality of the product.

- Additionally, it is important to take into account the level of risk of the raw material due to the intrinsic properties thereof or the use thereof in the manufacturing process where the risk is higher if the raw material comes into contact with the starting materials.
- Finally, it needs to be assessed if the control strategy including qualification of suppliers and performance of suitable functional testing is sufficient to eliminate the risks or to mitigate them to an acceptable level.

b) QRM in connection with the testing strategy. It is stressed that the release testing strategy should always be performed in accordance with the marketing authorisation. It is acknowledged that in some cases, it may not be possible to perform the release tests on the active substance or the finished product. This may be the case for technical reasons, due to time restraints or when the amount of available product is limited to the clinical dose. In these cases, an adequate control strategy should be designed, and consideration can be given to the following options:

- Testing of key intermediates (instead of the finished product) or in-process controls (instead of batch release testing) if the relevance of the results from these tests to the critical quality attributes of the finished product can be demonstrated.
- Real time testing in case of short shelf-life materials/products.
- Increased reliance on process validation. When the scarcity of materials or the very short shelf-life limits the possibilities for release controls, the limitations should be compensated by a reinforced process validation and/or knowledge from other very similar products.
- The application of the sterility test or other microbiological tests to the finished product in accordance with the European Pharmacopoeia may not always be possible due to the scarcity of materials available, or it may not be possible to wait for the final result of the test before the product is released due to short shelf-life or medical need. In these cases, the strategy regarding sterility/microbiological quality assurance has to be adapted.
- The use of validated alternative rapid microbiological methods may also be considered. Alternative microbiological methods according to the European Pharmacopoeia may be acceptable when this is justified having regard to the specific characteristics of the product and the related risks, and provided that the suitability of the method for the specific product has been demonstrated.
- If the results of the sterility test or other microbiological tests of the product are not available at release, appropriate mitigation measures should be implemented, including informing the treating veterinarian.
- As products may be suspensions rather than clear solutions, it is acceptable to replace the particulate matter test by an appearance test, provided that alternative measures are put in place, such as controls of particles from materials and equipment used during manufacturing, or the verification of the ability of the manufacturing process to produce low particle products with simulated samples.
- It may be justified to waive the on-going stability program for products with shorter shelf-life or products produced in small batch sizes that do not produce sufficient volumes for stability studies.

3.14 Additional considerations relevant for cell based NTs that are not subject to substantial manipulation:

- Manufacturing processes of NTs not involving substantial manipulation of the cells/tissues are typically associated with lower risks than the manufacturing of NTs involving complex substantial

manipulations. However, it cannot be inferred that processes that are not qualified as "substantial manipulation" are risk-free, notably if the processing of the cells entails long exposure of the cells/tissues to the environment. Accordingly, an analysis of the risks of the specific manufacturing process should be performed in order to identify the measures that are necessary to ensure the quality of the product.

- Certain elements of GMP are intended to ensure the quality, safety and efficacy of the NTs, and should follow the requirements in this act, also when the manufacturing process does not involve substantial manipulation. In particular, the requirements on product characterisation (through the setting of adequate specifications), process validation, quality controls (in accordance with the terms of the marketing authorisation), and QP certification should be complied with.

4. Raw materials

4.1 Raw materials should be of suitable quality having regard to the intended use.

4.2 Raw materials used in the manufacturing of NTs should, take into consideration the monographs of the European Pharmacopoeia. While raw materials should be of pharmaceutical grade, it is acknowledged that, in some cases, only materials of research grade are available. The risks of using research grade materials should be understood (including the risks to the continuity of supply when larger amounts of product are manufactured). Additionally, the suitability of such raw materials for the intended use should be ensured, including –where appropriate– by means of testing. The quality of raw materials should comply with the marketing authorization.

4.3 In the case of critical raw materials, the specifications should include quality requirements to ensure suitability for the intended use, as well as the acceptance criteria. These quality requirements should be agreed with the supplier(s) ("agreed specifications"). The assessment whether a specific raw material is critical should be done by the manufacturer (or marketing authorisation holder) having regard to the specific risks. The decisions taken should be documented. The agreed specifications should cover aspects of the production, testing and control, and other aspects of handling and distribution as appropriate. The specifications set should be in compliance with the terms of the marketing authorisation.

4.4 The NT manufacturer should verify compliance of the supplier's materials with the agreed specifications. The level of supervision and further testing by the NT manufacturer should be proportionate to the risks posed by the individual materials. Reliance on the certificate of analysis of the supplier is acceptable if all the risks are duly understood and measures are put in place to eliminate the risks or mitigate them to an acceptable level.

4.5 The risk of contamination of raw materials of biological origin during their passage along the supply chain must be assessed, with particular emphasis on viral safety, microbial safety and infectious proteinopathies including Transmissible Spongiform Encephalopathy ("TSE"). Compliance with "Ph. Eur. 5.2.8 Minimising the Risk of Transmitting Animal Spongiform Encephalopathy (TSE) Agents via Human and Veterinary Medicinal Products and Chapter 5.2.5. of Ph Eur: Management of extraneous agents in IVMPS is required.2

[2] Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003700.pdf (updated as appropriately).

4.6 The risk of contamination from other materials that come into direct contact with manufacturing equipment or the product (such as media used for process simulation tests and lubricants that may contact the product) should also be taken into account.

4.7 Only raw materials that have been released by the person responsible for quality control should be used.

4.8 The NT manufacturer should put in place appropriate measures to ensure that critical raw materials can be traced in order to facilitate recall of products if necessary.

5. Starting materials

5.1 The NT manufacturer (or marketing authorisation holder) should establish quality requirements for the starting materials (specifications) which should be agreed with the supplier(s). These agreed specifications should cover aspects of the production, testing and control, storage, and other aspects of handling and distribution as appropriate. The agreed specifications should be in compliance with the terms of the marketing authorisation.

5.2 The NT manufacturer should verify compliance of the supplier's materials with the agreed specifications. The level of supervision and further testing by the NT manufacturer should be proportionate to the risks posed by the individual materials.

5.3 It is recommended that the agreement between the NT manufacturer and the suppliers foresees the possibility for the NT manufacturer to audit the supplier establishment. Adequate supervision in respect of the activities conducted at the supplier establishment should be carried out.

5.4 The agreement between the NT manufacturer (or marketing authorisation holder) and the supplier should contain clear provisions about the transfer of information regarding the starting materials that may become available after the supply of the starting material and which may have an impact on the quality or safety of the NTs manufactured therefrom.

5.5 The risk of contamination of the starting materials during their passage along the supply chain must be assessed, with particular emphasis on viral and microbial safety and Transmissible Spongiform Encephalopathy ("TSE"). Compliance with the latest version of the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy (TSE) Agents via Human and Veterinary Medicinal Products is required. [3]

5.6 Only starting materials that have been released by the person responsible for quality control should be used.

5.7 Where the results from the test(s) required to release the starting materials take a long time, it may be permissible to process the starting materials before the results of the test(s) are available. The risk of using a potentially failed material and its potential impact on other batches should be clearly assessed and understood. In such cases, the finished product should only be released if the results of these tests are satisfactory, unless appropriate risk mitigation measures are implemented.

[3] Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003700.pdf (updated as appropriately).

5.8 Where steps like initial processing are needed to make the starting materials available, this can take place at the suppliers or an area outside of GMP facility.

5.9 It may be acceptable that the manufacture of an NT starts from materials where some initial processing/manufacturing steps have been performed outside of the GMP environment, provided it is impossible to replace such material with GMP-compliant material. The use of starting materials that have been collected/separated/isolated/ preserved outside a GMP environment for the manufacture of an NT should be accompanied by a risk assessment to identify the testing and other requirements necessary to ensure the quality of the starting material. The overall responsibility for the quality – as well as the impact thereof on the safety and efficacy profile of the product- lies with the NT manufacturer (and/or, marketing authorisation holder), even if the activities have been outsourced. The release of such starting materials for use in the manufacturing process should be done by the person responsible for quality control after verifying the quality and safety thereof. Additionally, the competent authorities should agree to the control strategy in the context of the assessment of the marketing authorisation application.

5.10 In the case of vectors and naked plasmids used as starting materials for the manufacturing of gene therapy medicinal products, the principles of GMP apply from the bank system used to manufacture the vector or plasmid used for gene transfer. In the case of bacteriophage used as starting materials for the manufacturing of phage therapy products, the principles of GMP apply from the bank system used to manufacture both phage and targeted bacterial host.

6. Specific considerations relevant for cell based raw materials and starting materials

6.1 The donation, procurement and testing of animal/human tissues and cells used as starting materials for cell based products should be controlled in line with Regulation 2019/6. The NT manufacturer (or marketing authorisation holder) should take appropriate steps to ensure the quality, safety and traceability thereof, in accordance with the terms of the marketing authorization.

6.2 The growth promoting properties of culture media should be demonstrated to be suitable for its intended use.

6.3 Specifications related to the product (such as those in Pharmacopoeia monographs, marketing authorisation), will dictate whether and at what stage substances and materials can have a defined level of bioburden or need to be sterile. Prior to introduction in the manufacturing process, the conformity to the relevant requirements should be checked.

6.4 The use of antimicrobials may be necessary to reduce bioburden associated with the procurement of living tissues and cells. However, it is stressed that the use of antimicrobials does not replace the requirement for aseptic manufacturing. When antimicrobials are used, they should be removed as soon as possible, unless the presence thereof in the finished product is specifically foreseen in the marketing authorisation as is the case for antibiotics that are part of the matrix of the finished product. Additionally, it is important to ensure that antibiotics or antimicrobials do not interfere with the sterility testing, and that they are not present in the finished product (unless specifically foreseen in the marketing authorisation).

6.5 The selection of donor animals must be strictly controlled. Source/donor animals should be healthy and included in health monitoring programs.

6.6 The agreement between the NT manufacturer (or marketing authorisation holder) and the supplier should contain clear provisions about the transfer of information regarding the starting materials, in particular, on tests results performed by the supplier, traceability data, and transmission of health donor information that may become available after the supply of the starting material and which may have an impact on the quality or safety of the NTs manufactured therefrom.

6.7 Appropriate measures should be implemented to detect, identify and prevent incidents that negatively affect the health of the source/donor animals or that could negatively impact on the barrier facility or the SPF status, if relevant, of the source/donor animals. In addition to compliance with TSE regulations, other adventitious agents that are of concern (diseases of source animals) should be monitored and recorded. Specialist advice should be obtained in establishing the monitoring program.

6.8 Instances of ill-health occurring in the herd should be investigated with respect to the suitability of in-contact animals for continued use (in manufacture, as sources of starting and raw materials, in quality control and safety testing). The decisions taken must be documented.

6.9 The withdrawal period of therapeutic agents used to treat source/donor animals must be documented and used to determine the removal of those animals from the programme for defined periods.

Adapted GMP principles for inactivated veterinary autogenous vaccines

Considerations and Rationale

Inactivated Veterinary Autogenous Vaccines (AV) are 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. (article 2 (3) of Regulation 2019/6). Although inactivated immunological veterinary medicinal products (AV) should be manufactured in accordance with the principles of good manufacturing practice, detailed guidelines of good manufacturing practice should specifically be prepared for those products since they are manufactured in a way that is different from industrially prepared products. That would preserve their quality without hindering their manufacturing and availability. (Recital 70 of Regulation (EU) (EU) 2019/6).

The separation of measures of GMP for AVs takes into account recital 70. The aims named in recital 5 of Regulation (EU) 2019/6 to reduce the administrative burden, enhance the internal market and increase the availability of veterinary medicinal products, while guaranteeing the highest level of public and animal health and environmental protection, support this approach.

According to art. 106 paragraph 5 of the Regulation (EU)2019/6 inactivated immunological veterinary medicinal products referred to in Article 2 (3) of Regulation (EU)2019/6 shall only be used in the animals referred to therein in exceptional circumstances, in accordance with a veterinary prescription, and if no immunological veterinary medicinal product is authorised for the target animal species and the indication.

For animal welfare reasons and reasons of reduction of the use of antibiotics article 106 paragraph 5 of the Regulation (EU)2019/6 should be interpreted in a way which meets the aims of recitals 8 and 25:

The treatment with AV is needed as one option for therapy of the broad range of diseases animals can suffer from and which need to be prevented or treated by veterinary medicinal products for both animal health and welfare reasons (recital 8) considering the broad range of animal species which need treatment, too. There may be, however, situations where no suitable authorised veterinary medicinal product is available. In those situations, by way of exception, veterinarians should be allowed to prescribe other medicinal products to the animals under their responsibility in conformity with strict rules and only in the interest of animal health or animal welfare (recital 25).

It is therefore appropriate to develop a regulatory framework addressing the characteristics and specificities of the veterinary sector and here specially of AV (recital 4).

The active substances for AV isolated from infected animals shall not originate from or contain agents which are notifiable diseases in the EU according to art. 4 of Commission delegated Regulation (EU) 2023/361.

Prices for single batch production on prescription are typically quite high and must be affordable for animal welfare reasons.

The recognized differences between licensed products and AV leads clearly to the need of differentiation between the appropriate GMP-requirements.

Licensed products	AV
Needs marketing authorization	Marketing authorization not required by Regulation 2019/6
Dossiers required for license	No dossier necessary
Needs manufacturing authorization/GMP Certificate	Manufacturing authorisation not required by Regulation 2019/6. AV specific GMP Certificate is required.
Batch release by qualified person	Qualified person for batch release not required
Registration obligatory in union product database and Database on manufacturing and wholesale distribution	No registration in the union data bases
Union pharmacovigilance database applicable	No pharmacovigilance
Import regulated	Importation prohibited
Life cycle surveillance for product	No development, production and postmarketing surveillance life cycle
Production of uniformed, defined batches according to license	Production of single batches on veterinary prescription (custom-made) Usually, one batch = one product
Ongoing stability until expiry date	Usually, for use immediately after delivery
Product related manufacturing processes including validation	Manufacturing step related processes General validation
Documents are product related	No single product related specifications, manufacturing formulae and processing instructions, packaging instructions possible
Automated processing possible and in use	Because of the small size most batches are handmade (it starts with batches for one animal only)
Reworking and reprocessing possible	Not possible

So, the GMP requirements need to be adapted for the manufacturing of inactivated autogenous vaccines in order to ensure their manufacturing and availability since they are prepared in a way that is different from industrially prepared products, existing recommendations and national legislation have been reviewed, where possible:

- Recital 48 of Regulation (EU) 2019/6
- the Recommendations for the manufacture, control and use of inactivated autogenous veterinary vaccines within the EEA issued by the Coordination group for mutual recognition and decentralised procedures for veterinary medicinal products (CMDv) in March 2017
- the European Manufacturers of Autogenous Vaccines and Sera (EMAV) Proposal "EU-GMP-Annex for Autogenous vaccines in 2021"

- the Austrian Ordinance of the Federal Minister for Health concerning establishments producing, controlling or placing on the market stock-specific vaccines for animals (stock-specific vaccines – farm rules 2010 – BIBO 2010)
- the German Ordinance on Sera, Vaccines and Antigens under the Animal Health Act
- German Q & A paper on monitoring the production of autogenic immunological veterinary medicinal products published by the EFG 16 of the ZLG and the Department of Veterinary Medicine of the Paul-Ehrlich Institute in 2022, first published in 2015
- CHAPTER 1.1. 8. PRINCIPLES OF VETERINARY VACCINE PRODUCTION and section 2.3 veterinary vaccines of the Manual of Diagnostic Tests and Vaccines for Terrestrial Animals 2022, WOAH
- 9CFR 113.52, 9CFR 113.113, 9CFR 114.9, VSM 800.69 of USDA
- Recommendations on Use of stock-specific vaccines by the German Standing Committee on Veterinary Vaccines, 01.04.2020
- French Order of March 6, 2008 on good practices for the preparation of autovaccines for veterinary use
- Italian Proposal of the Experimental Zooprophylactic Institutes: EU-GMP Annex for Autogenic Veterinary Vaccines

General

This section lays down the principles (and guidelines) of good manufacturing practice in respect of Inactivated Veterinary Autogenous Vaccines whose manufacture requires the certification referred to in Article 94 of Regulation (EU) 2019/6.

The manufacturers of AV shall ensure that the manufacturing operations are carried out in accordance with the specific principles of good manufacturing practice in the following. These provisions shall also apply to AV intended only for export.

Autogenous Vaccines are not authorised VMP, and Article 88 of Regulation (EU) 2019/6 is not applicable. Therefore, the import of Autogenous Vaccines for distribution or use in the Union is not allowed.

1. Pharmaceutical quality system

1.1 The manufacturer of veterinary autogenous vaccines (AV) shall establish, implement and maintain an effective pharmaceutical quality system appropriate to the type of production that shall include sufficient production and control procedures referring to scientifically recognised standard performance.

1.2 The system consists of quality management, quality risk management and good manufacturing practice for autogenous vaccines. It shall be fully documented and its effectiveness monitored.

1.3 Good manufacturing practice for autogenous vaccines includes production and quality control.

1.4 The implemented system should ensure the following:

- Covering of all stages of manufacture, testing, release and distribution;
- Establishment of appropriate quality risk management including the use of appropriate tools commensurate with the level of risk;
- Use of GMP for autogenous vaccines for all stages of production and testing;
- Responsibilities and active participation of senior management;
- Periodic quality and management reviews;
- Establishment of quality controls of all stages;

- Adequate definition, description and documentation of the quality management system including quality assurance;
- implementation of self-inspection to monitor the implementation and compliance with Good Manufacturing Practice principles at intervals following a prearranged programme and to propose necessary corrective measures;

1.5 Senior management has the ultimate responsibility to ensure an effective Pharmaceutical Quality System is in place, adequately resourced and that roles, responsibilities and authorities are defined, communicated and implemented throughout the organisation. Senior management shall designate a person(s) responsible for the release of the batches and quality assurance. The person designated for batch release should have adequate qualification and training.

1.6 Suitable requirements of GMP for autogenous vaccines have to be in place and have to insure the following:

- Definition of all processes in the manufacture, testing, storage and quality assurance;
- Validation of critical steps of manufacturing processes and analytical methods as well as significant changes to the process.

1.7 All necessary facilities for GMP for autogenous vaccines are provided including:

- Appropriately qualified and trained personnel;
- Adequate premises and space;
- Suitable equipment and services;
- Correct materials, containers and labels;
- Approved procedures, instructions and records, in accordance with the Pharmaceutical Quality System;
- Suitable storage and transport;
- Adequate sampling, testing and release;
- A system available to take back any delivered batch of product in case of severe defects;
- Management of change control, deviations, corrective and preventive actions and suppliers.

2. Personnel

2.1 The correct manufacture of autogeneous vaccines relies much more than licensed products upon people. For this reason, there must be a sufficient number of competent and appropriate qualified personnel with practical experience to carry out all the tasks which are the responsibility of the manufacturer.

2.2 The duties of the managerial and supervisory staff including the batch releasing head of quality assurance shall be defined in job descriptions including the given authority and responsibilities. Their hierarchical relationships shall be defined in an organisation chart. The head of quality control shall be independent of the head of production. Organisation charts and job descriptions shall be approved in accordance with the manufacturer's internal procedures.

2.3 The duties of key personnel may be delegated to designated deputies of a satisfactory qualification level. Key personnel consist of the heads of production, quality control and quality assurance.

2.4 All personnel shall receive initial and ongoing training, the effectiveness of which shall be verified, covering in particular the theory and application of the concept of quality assurance, good manufacturing practice and microbiology. For visitors and untrained personnel appropriate procedures should be foreseen.

2.5 Hygiene programmes adapted to the activities to be carried out shall be established and observed. These programmes shall, in particular, include procedures relating to health, hygiene practice and clothing of personnel.

2.6 All personnel shall receive appropriate medical examination upon recruitment and ongoing where relevant. Personnel should be protected against possible infection with the biological agents used in manufacture.

3. Premises and equipment

3.1 In terms of the premises for production, testing, storage and quality departments as well as manufacturing and testing equipment the manufacturer shall ensure that they are located, designed, constructed, adapted and maintained to suit the intended operations.

3.2 Their layout and design must aim to minimise the risk of errors and permit effective cleaning and maintenance in order to avoid contamination and cross-contamination, build-up of dust or dirt and, in general, any adverse effect on the quality of products.

3.3 Premises and equipment to be used for manufacturing or quality control operations, which are critical to the quality of the products, shall be subjected to appropriate qualification and validation. Measuring, weighing, recording and control equipment should be calibrated and checked at defined intervals by appropriate methods. Adequate records of such tests should be maintained.

3.4 Rest and refreshment rooms as well as technical rooms should be separate from other areas.

3.5 All operations performed have to follow written procedures.

3.6 The measures to prevent cross-contamination should be commensurate with the risks. Quality Risk Management principles should be used to assess and control the risks. Depending of the level of risk, it may be necessary to dedicate premises and equipment for manufacturing and/or packaging operations to control the risk presented by some autogenous vaccines, in case the risk cannot be adequately controlled by operational and/ or technical measures.

4. Documentation

4.1 The manufacturer shall establish, control and maintain a documentation system based upon but not limited to specifications, manufacturing formulae and processing and packaging instructions, procedures and records covering the various manufacturing operations performed following good documentation practice.

4.2 The documentation system shall ensure data quality and integrity. Documents shall be clear, free from error and kept up to date and easy to check. Pre-established procedures for general manufacturing operations and conditions including release for delivery to the prescribing veterinarian and rejection shall be kept available, together with specific documents for the manufacture of each batch. The various types of documents and media used should be fully defined in the manufacturer's Quality Management System.

4.3 Batch processing and batch packaging records are to be kept for every single batch. The manufacturer shall be required to retain the batch documentation for at least 1 year after the expiry date of the batches.

4.4 When electronic, photographic or other data processing systems are used instead of written documents, the manufacturer shall be required to first validate the systems by showing that the data will be appropriately stored during the anticipated period of storage. Data stored by those systems shall be made readily available in legible form and shall be provided to the competent authorities upon request.

The electronically stored data shall be protected, by techniques such as duplication or back-up and transfer to another storage system, against unauthorized access, loss or damage of data, and audit trails shall be maintained. Systems shall be located and controlled onsite.

4.5 The different types of specifications, manufacturing formulae, processing instructions, packaging instructions should have a sufficient grade of detail where necessary.

4.6 Good documentation constitutes an essential part of the pharmaceutical quality system and is key to operating in compliance with GMP requirements. Good documentation practice includes:

- Generation and Control of Documentation
- Proper design, preparation, review and distribution of documents
- Approval, signing and dating of documents by appropriate and authorised persons
- Retention of Documents
- Logbooks where necessary
- Inventory of documents

5. Production

5.1 The manufacturer shall ensure that the different production operations are carried out in accordance with specifications, manufacturing formulas, pre-established instructions and procedures and in accordance with good manufacturing practice for autogenous vaccines. Adequate and sufficient resources shall be made available by the manufacturer for the in-process controls. All process deviations and product defects shall be documented and thoroughly investigated and evaluated before the release. All handling of materials and products should be recorded.

5.2 The manufacturers shall take appropriate technical and organisational measures to avoid contaminations, cross contamination and mix-ups at all stages based on an adequate quality risk management process, at least:

- Performance and supervision of production by competent people
- Checks on incoming and self-produced materials
- Quarantine of incoming materials, intermediate, bulk products and finished products until release for use or delivery by designated persons
- Storage under appropriate conditions of all materials and products
- Prevention of material and products from dust or dirt or hazardous materials
- Appropriate labelling of any materials, containers, equipment and rooms at any stage of production
- Checks of the connections of pipelines and equipment used for transport
- Implementation of a deviation management
- Restrictions of access to manufacturing and testing areas
- Effective and reproducible cleaning and disinfection processes
- Determination of the necessity for and extent to which premises and equipment should be dedicated to a particular product family or self-contained
- Use of closed systems or physical barriers where necessary
- Appropriate design and use of air-locks, air filtration, area classification, physical separation, flows and pressure cascade to confine potential airborne contaminant within a specified area where necessary
- Performance and recording of necessary in-process controls and environmental controls
- Appropriate separation of process steps (where necessary)
- Specific measures for waste handling, contaminated rinsing water and soiled gowning

- Supervision of working behaviour to ensure training effectiveness and compliance with the relevant procedural controls
- Checks on line-clearance before starting any processing operations
- Periodical review of all measures

5.3 Any critical processes and new manufacturing or important modification of a manufacturing process of an autogenous vaccine shall be validated adequately. Critical phases of manufacturing processes shall be regularly revalidated where necessary.

5.4 An adequate level of supervision of suppliers for starting and primary packaging materials including selection, qualification, approval and maintenance based on a quality risk management process and a formal quality agreement or specification should be assured.

5.5 Rejected materials and products should be clearly marked as such and stored separately in restricted areas. They should either be returned to the suppliers or destroyed. Whatever action is taken should be approved and recorded by authorised personnel.

5.6 Reprocessing is not permitted except new labelling in case of wrong labelling before delivery.

6. Quality control

6.1 The manufacturer shall establish and maintain a quality control system placed under the authority of a person who has the requisite qualifications and experience and is independent of production.

6.2 That person shall have at his or her disposal, or shall have access to, one or more quality control laboratories appropriately staffed and equipped to carry out the necessary sampling, examination and testing of starting as well as packaging materials and the testing of intermediate and finished medicinal products according to the specifications and testing respectively release procedures. All activities have to be documented sufficiently.

6.3 Adequate resources must be available to ensure that all the Quality Control arrangements are effectively and reliably carried out.

6.4 For autogenous vaccines contract laboratories may be used if authorised by the manufacturer based on a quality risk management process and a formal quality agreement.

6.5 During the final control of the finished medicinal product before its release for delivery, the quality control system shall take into account, in addition to analytical results, essential information such as the production conditions, the results of in-process controls, the examination of the manufacturing documents and the conformity of the product to its specifications, including the final finished pack.

6.6 Samples of each batch of finished autogenous vaccine shall be retained for at least 1 year after the expiry date.

6.7 Samples of starting materials, other than solvents, gases or water, used in the manufacturing process shall be retained for at least 1 year after the release of the product. All those samples shall be maintained at the disposal of the competent authorities. Other conditions may be defined, by agreement with the competent authority, for the sampling and retaining of starting materials and products.

6.8 Sampling, testing and recording has to be performed according to good quality laboratory practice, at least:

- Appropriate premises and equipment
- Establishing validation and implementation of all quality control procedures
- Control of the reference and/or retention samples of materials and products
- Ensuring the correct labelling of containers of samples, materials and products
- Participate in the investigation of out-of-specification and complaints related to the quality of the product
- Appropriate sampling
- Appropriate preparation, labelling, use and control of laboratory materials, reagents, solutions, glassware, reference standards and culture media as well as decontamination where necessary
- Investigation of out of specification results
- Good documentation practice
- No use of animals for in-process control nor release testing carried out on manufacturing site
- Adequate transfer of testing methods when necessary

7. Outsourced operations

7.1 The manufacturer shall assure that any manufacturing operation or operation linked thereto (e.g. distribution, quality control) which is outsourced is the subject of a written contract and is appropriately defined, agreed and controlled.

7.2 The contract shall clearly define the responsibilities and duties of each party and shall define, in particular, the observance of the specific good manufacturing practice for autogenous vaccines to be followed by the contract-acceptor and the manner in which the batch releasing person is to discharge his responsibilities.

7.3 The written contract should cover at least but not limited to the following:

- All relevant outsourced activities, products or operations clearly described
- All relevant technical arrangements
- Relevant assessment control and review of outsourced activities based on a quality risk management process
- Specification of the relevant responsibilities and communication processes
- Relevant regulations in force
- Keeping of relevant records and retentions samples
- Right for audits by the contract-giver at the contract acceptor or subcontractors

7.4 The contract-acceptor shall not subcontract any of the work entrusted to him under the contract without written authorisation from the contract-giver.

7.5 The contract-acceptor shall comply with the principles and guidelines of good manufacturing practice applicable to autogenous vaccines, at least but not limited to:

- Adequate premises, equipment, knowledge, experience and competent personnel
- Acceptance of inspection by the competent authorities

7.6 The contract-giver has at least the following responsibilities:

- Assessment of the legality, suitability and the competence of the contract-acceptor
- Provision of the contract-acceptor with relevant information and knowledge
- Monitoring and review of the performance of the contract-acceptor
- Review and assessment of the relevant results and records

- Ensuring of compliance with relevant GMP

8. Complaints, quality defects, product recalls

8.1 The manufacturers shall ensure that a system for recording and reviewing complaints including potential quality defects is implemented together with an effective system for recalling, promptly and at any time, medicinal products in the distribution network. Any complaint concerning a defect shall be recorded, assessed, investigated and reviewed by the manufacturer.

8.2 Quality Risk Management principles should be applied to the investigation and assessment of quality defects and to the decision-making process in relation to product recalls, corrective and preventative actions and other risk-reducing actions.

8.3 The manufacturer shall inform the competent veterinarian of any defect that could result in a recall or any other serious quality problems.

8.4 In case of situations where the distribution could lead to problems for the animal health concerning diseases of the categories A, B or C the competent veterinary authorities have to be informed.

8.5 In case of outsourced activities, the manufacturer should assure via contract that relevant third parties are obliged to necessary actions.

8.6 The system for recording and reviewing complaints including potential quality defects should assure the following:

- Appropriately trained, experienced and from sales independent personnel should be responsible for managing complaint and quality defect investigations and for deciding the measures to be taken to manage any potential risk(s) presented by those issues, including recalls. The batch releasing person should be involved.
- Appropriate documentation system including written procedures for handling and investigating complaints including possible quality defects
- Organisation of sufficient communication within the different departments of the manufacturer
- Use of an appropriate risk-based management process to take necessary corrective and preventive actions (like retesting retention samples or returned product, choice of the relevant antigens or adjuvants or change of processes)
- Assessment of the effectiveness of CAPAs

Concluding remarks

The detailed guidelines of good manufacturing practice for autogenous vaccines should specifically be prepared as a guideline. This offers the possibility to publish the implementing act right in time and have already basic obligations while developing the more detailed guidelines which could be published later.

Definitions

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

"Air-lock" means an enclosed space with two or more doors, and which is interposed between two or more rooms, e.g. of differing class of cleanliness, for the purpose of controlling the air-flow between those rooms when they need to be entered. An air-lock is designed for and used by either people or goods.

"Area" means a space. A specific set of rooms within a building associated with the manufacturing of any one product or multiple products that has a common air handling unit is considered as a single area. "Clean area" means an area designed, maintained, and controlled to prevent particle and microbiological contamination.

"Batch" means a defined quantity of starting material, packaging material or product processed in one process or series of processes so that it could be expected to be homogeneous. To complete certain stages of manufacture, it may be necessary to divide a batch into a number of sub batches, which are later brought together to form a final homogeneous batch. In the case of continuous manufacture, the batch must correspond to a defined fraction of the production, characterised by its intended homogeneity. 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 material 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. (ref. Reg. 2019/6 Annex II chapter II.2.E. (1))

"Batch number" means a distinctive combination of numbers and/or letters which specifically identifies a batch.

"Biological Agents" means micro-organisms, including genetically engineered micro-organisms, cell cultures and endoparasites, whether pathogenic or not.

"Bulk Product" means any product which has completed all processing stages up to, but not including, final packaging.

"Calibration" means the set of operations which establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system, or values represented by a material measure, and the corresponding known values of a reference standard.

"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 provided that appropriate control measures are applied.

"Closed system" means a process 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 sanitization or sterilization step prior to process use.

"Computerised System" means a system including the input of data, electronic processing and the output of information to be used either for reporting or automatic control.

"Cross Contamination" means the contamination of a material or of a product with another material or product.

"Deviation" means departure from approved documentation or an established standard.

"Documentation" means written procedures, instructions, contracts, records and data, in paper or in electronic form.

"Expiry Date" means the date placed on the packaging of a veterinary medicinal product designating the time during which that veterinary medicinal product is expected to remain within established shelf life specifications if stored under defined conditions written on the packaging or container label, and after which it should not be used.

"Finished Product" means a veterinary medicinal product which has undergone all stages of production, including packaging in its final container.

"Good manufacturing practice" means the part of the quality assurance which ensures that veterinary medicinal products are consistently produced, imported and controlled in accordance with the quality standards appropriate to their intended use.

"Infected" means contaminated with extraneous biological agents and therefore capable of spreading infection.

"In-Process Controls" means the checks performed during production in order to monitor and if necessary to adjust the process to ensure that the product conforms its specification. The control of the environment or equipment may also be regarded as a part of in-process control.

"Intermediate Product" means partly processed material which must undergo further manufacturing steps before it becomes a bulk product.

"Manufacture" means all operations of purchase of materials and products, Production, Quality Control, release, storage, distribution of medicinal products and the related controls.

"Manufacturer" means any person engaged in activities for which the authorisation referred to in Article 88 of Regulation (EU) 2019/6 is required.

"Packaging" means all operations, including filling and labelling, which a bulk product has to undergo in order to become a finished product. Note Sterile filling would not normally be regarded as part of packaging, the bulk product being the filled, but not finally packaged, primary containers.

"Packaging Material" means any material employed in the packaging of a medicinal product, excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

"Quality assurance" means the sum total of the organized arrangements made with the object of ensuring that veterinary medicinal products are of the quality required for their intended use.

"Pharmaceutical Quality System" means the total sum of the organised arrangements made with the objective of ensuring that veterinary medicinal products are of the quality required for their intended use.

"Procedures" means the description of the operations to be carried out, the precautions to be taken and measures to be applied directly or indirectly related to the manufacture of a veterinary medicinal product.

"Production" means all operations involved in the preparation of a medicinal product, from receipt of materials, through processing and packaging, to its completion as a finished product.

"Qualification" means the action of proving that any equipment works correctly and actually leads to the expected results. The word validation is sometimes widened to incorporate the concept of qualification.

"Qualification of suppliers" means a process designed to ensure the suitability of suppliers.

"Qualified person" means the person referred to in Article 97 of Regulation (EU) 2019/6.

"Quality Control" means that part of Good Manufacturing Practice which is concerned with sampling, specifications and testing, and with the organisation, documentation and release procedures which ensure that the necessary and relevant tests are actually 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.

"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.

"Quarantine" means the status of starting or packaging materials, intermediate, bulk or finished products isolated physically or by other effective means whilst awaiting a decision on their release or refusal.

"Raw Material" means a general term used to denote materials, intended for use in the production of intermediates or active substance.

"Reconciliation" means a comparison, making due allowance for normal variation, between the amount of product or materials theoretically and actually produced or used

"Record" means providing evidence of various actions taken to demonstrate compliance with instructions, e.g. activities, events, investigations, and in the case of manufactured batches a history of each batch of product, including its distribution. Records include the raw data which is used to generate other records…

"Recovery" means the introduction of all or part of previous batches of the required quality into another batch at a defined stage of manufacture.

"Reprocessing" means the reworking 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.

"Return" means sending back to the manufacturer or distributor of a medicinal product which may or may not present a quality defect.

"Segregated area" means a segregated area within a manufacturing site requires separate storage, separate production suite with separate HVAC, restrictions on the movement of personnel and equipment (without appropriate decontamination measures) and dedicated equipment reserved solely for the production of one type of product with a specific risk profile.

"Segregation" means the separation of activities or products according to their property in order to ensure the quality, security or efficacy of the final product.

"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 Council10;

"Specification" means to describe in detail the requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

"Starting Material" means any substance used in the production of a medicinal product, but excluding packaging materials.

"Sterility" means the absence of living organisms. The conditions of the sterility test are given in the European Pharmacopoeia.

"Substantial manipulation" means the cells or tissue(s) have been manipulated during the manufacturing process so that their biological characteristics, physiological functions or structural properties have been modified to be relevant for their intended function.

"System" means the used in the sense of a regulated pattern of interacting activities and techniques which are united to form an organised whole.

"User/consumer" means the intended target animal of the Veterinary medicinal product. In the context of this act, it should also be taken to include the user of the VMP and the consumer of products derived from the VMP.

"Validation" means the action of proving, in accordance with the principles of Good Manufacturing Practice, that any procedure, process, equipment, material, activity or system actually leads to the expected results (see also qualification).

GMP for active substances used as starting material in veterinary medicinal products

1. Introduction

This section place the obligations on manufacturing authorisation holders to use only active substances that have been manufactured in accordance with Good Manufacturing Practice for starting materials. In the following, the measures of Good Manufacturing Practice for active substances are laid down.

1.1 Objective

This implementing act is intended to provide guidance regarding Good Manufacturing Practice (GMP) for the manufacture of active substances under an appropriate system for managing quality. It is also intended to help ensure that active substances meet the requirements for quality and purity that they purport or are represented to possess.

In this implementing act "manufacturing" includes all operations of receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control, release, storage and distribution of active substances and the related controls. The term "should" indicates recommendations that are expected to apply unless shown to be inapplicable, modified in any relevant GMP guidelines published by European Commission, or replaced by an alternative demonstrated to provide at least an equivalent level of quality assurance.

This implementing act as a whole does not cover safety aspects for the personnel engaged in manufacture of the active substance.

This implementing act is not intended to define registration requirements or modify pharmacopoeial requirements and do not affect the ability of the responsible competent authority to establish specific registration requirements regarding active substances within the context of marketing/manufacturing authorizations. All commitments in registration documents must be met.

1.2 Scope

This implementing act applies to the manufacture of active substances used as starting material in veterinary medicinal products. It applies to the manufacture of sterile active substances only up to the point immediately prior to the active substance being rendered sterile. The sterilisation and aseptic processing of sterile active substances are not covered in this part, but should be performed in accordance with the measures of GMP as laid down in the part dedicated on veterinary medicinal products of this Implementing Act and interpreted in guidelines published by the European Commission.

In the case of ectoparasiticides for veterinary use and parasiticides for veterinary use in bees, other standards than these guidelines, that ensure that the material is of appropriate quality, may be used.

This implementing act exclude, whole blood and plasma, as Directive 2002/98/EC and the technical requirements supporting that directive lay down the detailed requirements for the collection and testing of blood, however, it does include active substances that are produced using blood or plasma as raw materials.

Finally, this implementing act does not apply to bulk-packaged veterinary medicinal products and veterinary medicinal gases. It applies to all other active starting materials subject to any derogations described in the guidelines published by the European Commission where supplementary guidance for certain types of active substance may be found.

Section 17 gives guidance to parties who, among others, distribute or store an active substance or intermediate. This guidance is expanded in the Commission Implementing Regulation (EU) 2021/1280 of 2 August 2021 as regards measures on good distribution practice for active substances used as starting materials in veterinary medicinal products in accordance with Regulation (EU) 2019/6.

Section 19 contains guidance that only applies to the manufacture of active substances used in the production of investigational veterinary medicinal products specifically for clinical trials conducted according to VICH GL9 although it should be noted that its application in this case, although recommended, is not required by Community legislation.

An "Active Substance Starting Material" is a raw material, intermediate, or an active substance that is used in the production of an active substance and that is incorporated as a significant structural fragment into the structure of the active substance. An Active Substance Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. Active Substance Starting Materials normally have defined chemical properties and structure.

The manufacturer should designate and document the rationale for the point at which production of the active substance begins. For synthetic processes, this is known as the point at which "Active Substance Starting Materials" are entered into the process. For other processes (e.g. fermentation, extraction, purification, etc.), this rationale should be established on a case-by-case basis. Table 1 gives guidance on the point at which the Active Substance Starting Material is normally introduced into the process. From this point on, appropriate GMP as defined in this implementing act should be applied to these intermediate and/or active substance manufacturing steps. This would include the validation of critical process steps determined to impact the quality of the active substance. However, it should be noted that the fact that a manufacturer chooses to validate a process step does not necessarily define that step as critical. The requirements in this document would normally be applied to the steps shown in grey in Table 1. It does not imply that all steps shown should be completed. The stringency of GMP in active substance manufacturing should increase as the process proceeds from early steps to final steps, purification, and packaging. Physical processing of active substances, such as granulation, coating or physical manipulation of particle size (e.g. milling, micronising), should be conducted at least to the standards of this implementing act. This implementing act does not apply to steps prior to the first introduction of the defined "Active Substance Starting Material".

The glossary section should only be applied in the context of this implementing act. Some of the same terms are already defined in the implementing act on GMP for VMP and these therefore should only be applied in the context of that implementing act.

Application of this Guide to Active Substance Manufacturing

Type of Manufacturing	Application of this Guide to steps (shown in grey) used in this type of manufacturing				
Chemical Manufacturing	Production of the API Starting Material	Introduction of the API Starting Material into process	Production of Intermediate(s)	Isolation and purification	Physical processing, and packaging
Active Substance derived from animal sources	Collection of organ, fluid, or tissue	Cutting, mixing, and/or initial processing	Introduction of the API Starting Material into process	Isolation and purification	Physical processing, and packaging
Active Substance extracted from plant sources	Collection of plants	Cutting and initial extraction(s)	Introduction of the API Starting Material into process	Isolation and purification	Physical processing, and packaging
Herbal extracts used as API	Collection of plants	Cutting and initial extraction		Further extraction	Physical processing, and packaging
Active Substance consisting of comminuted or powdered herbs	Collection of plants and/or cultivation and harvesting	Cutting/ comminuting			Physical processing, and packaging
Biotechnology: fermentation/ cell culture	Establishment of master cell bank and working cell bank	Maintenance of working cell bank	Cell culture and/or fermentation	Isolation and purification	Physical processing, and packaging
"Classical" Fermentation to produce an API	Establishment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing, and packaging

2. Quality Management

2.1 Principles

2.10 Quality should be the responsibility of all persons involved in manufacturing.

2.11 Each manufacturer should establish, document, and implement an effective system for managing quality that involves the active participation of management and appropriate manufacturing personnel.

2.12 The system for managing quality should encompass the organisational structure, procedures, processes and resources, as well as activities necessary to ensure confidence that the active substance will meet its intended specifications for quality and purity. All quality related activities should be defined and documented.

2.13 There should be a quality unit(s) that is independent of production and that fulfills both quality assurance (QA) and quality control (QC) responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

2.14 The persons authorised to release intermediates and APIs should be specified.

2.15 All quality related activities should be recorded at the time they are performed.

2.16 Any deviation from established procedures should be documented and explained. Critical deviations should be investigated, and the investigation and its conclusions should be documented.

2.17 No materials should be released or used before the satisfactory completion of evaluation by the quality unit(s) unless there are appropriate systems in place to allow for such use (e.g. release under quarantine as described in Section 10.20 or the use of raw materials or intermediates pending completion of evaluation).

2.18 Procedures should exist for notifying responsible management in a timely manner of regulatory inspections, serious GMP deficiencies, product defects and related actions (e.g. quality related complaints, recalls, regulatory actions, etc.).

2.19 To achieve the quality objective reliably there must be a comprehensively designed and correctly implemented quality system incorporating Good Manufacturing Practice, Quality Control and Quality Risk Management.

2.2 Quality Risk Management

2.20 Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the active substance. It can be applied both proactively and retrospectively.

2.21 The quality risk management system should ensure that:

-the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the user, consumer and animal safety through communication with the user of the active substance

-the level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk

Examples of the processes and applications of quality risk management can be found, inter alia, in guidelines published by the EC.

2.3 Responsibilities of the Quality Unit(s)

2.30 The quality unit(s) should be involved in all quality-related matters.

2.31 The quality unit(s) should review and approve all appropriate quality-related documents.

2.32 The main responsibilities of the independent quality unit(s) should not be delegated. These responsibilities should be described in writing and should include but not necessarily be limited to:

1. Releasing or rejecting all APIs. Releasing or rejecting intermediates for use outside the control of the manufacturing company;

2. Establishing a system to release or reject raw materials, intermediates, packaging and labelling materials;

3. Reviewing completed batch production and laboratory control records of critical process steps before release of the active substance for distribution;

4. Making sure that critical deviations are investigated and resolved;

5. Approving all specifications and master production instructions;

6. Approving all procedures impacting the quality of intermediates or APIs;

7. Making sure that internal audits (self-inspections) are performed;

8. Approving intermediate and active substance contract manufacturers;

9. Approving changes that potentially impact intermediate or active substance quality;

10. Reviewing and approving validation protocols and reports;

11. Making sure that quality related complaints are investigated and resolved;

12. Making sure that effective systems are used for maintaining and calibrating critical equipment;

13. Making sure that materials are appropriately tested and the results are reported;

14. Making sure that there is stability data to support retest or expiry dates and storage conditions on APIs and/or intermediates where appropriate; and

15. Performing product quality reviews (as defined in Section 2.6)

2.4 Responsibility for Production Activities

The responsibility for production activities should be described in writing, and should include at least the following:

1. Preparing, reviewing, approving and distributing the instructions for the production of intermediates or APIs according to written procedures;

2. Producing APIs and, when appropriate, intermediates according to pre- approved instructions;

3. Reviewing all production batch records and ensuring that these are completed and signed;

4. Making sure that all production deviations are reported and evaluated and that critical deviations are investigated and the conclusions are recorded;

5. Making sure that production facilities are clean and when appropriate disinfected;

6. Making sure that the necessary calibrations are performed and records kept;

7. Making sure that the premises and equipment are maintained and records kept;

8.Making sure that validation protocols and reports are reviewed and approved;

9. Evaluating proposed changes in product, process or equipment; and

10. Making sure that new and, when appropriate, modified facilities and equipment are qualified.

2.5 Internal Audits (Self Inspection)

In order to verify compliance with the principles of GMP for APIs, regular internal audits should be performed in accordance with an approved schedule.

Audit findings and corrective actions should be documented and brought to the attention of responsible management of the firm. Agreed corrective actions should be completed in a timely and effective manner.

2.6 Product Quality Review

Regular quality reviews of APIs should be conducted with the objective of verifying the consistency of the process. Such reviews should normally be conducted and documented annually and should include at least:

- A review of critical in-process control and critical active substance test results;

- A review of all batches that failed to meet established specification(s);

- A review of all critical deviations or non-conformances and related investigations;

- A review of any changes carried out to the processes or analytical methods;

- A review of results of the stability monitoring program;

- A review of all quality-related returns, complaints and recalls; and

- A review of adequacy of corrective actions.

The results of this review should be evaluated and an assessment made of whether corrective action or any revalidation should be undertaken. Reasons for such corrective action should be documented. Agreed corrective actions should be completed in a timely and effective manner.

3. Personnel

3.1 Personnel Qualifications

3.10 There should be an adequate number of personnel qualified by appropriate education, training and/or experience to perform and supervise the manufacture of intermediates and APIs.

3.11 The responsibilities of all personnel engaged in the manufacture of intermediates and APIs should be specified in writing.

3.12 Training should be regularly conducted by qualified individuals and should cover, at a minimum, the particular operations that the employee performs and GMP as it relates to the employee's functions. Records of training should be maintained. Training should be periodically assessed.

3.2 Personnel Hygiene

3.20 Personnel should practice good sanitation and health habits.

3.21 Personnel should wear clean clothing suitable for the manufacturing activity with which they are involved and this clothing should be changed when appropriate. Additional protective apparel, such as head, face, hand, and arm coverings, should be worn when necessary, to protect intermediates and APIs from contamination.

3.22 Personnel should avoid direct contact with intermediates or APIs.

3.23 Smoking, eating, drinking, chewing and the storage of food should be restricted to certain designated areas separate from the manufacturing areas.

3.24 Personnel suffering from an infectious disease or having open lesions on the exposed surface of the body should not engage in activities that could result in compromising the quality of APIs. Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions should be excluded from activities where the health condition could adversely affect the quality of the APIs until the condition is corrected or qualified medical personnel determine that the person's inclusion would not jeopardize the safety or quality of the APIs.

3.3 Consultants

3.30 Consultants advising on the manufacture and control of intermediates or APIs should have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained.

3.31 Records should be maintained stating the name, address, qualifications, and type of service provided by these consultants.

4. Buildings and Facilities

4.1 Design and Construction

4.10 Buildings and facilities used in the manufacture of intermediates and APIs should be located, designed, and constructed to facilitate cleaning, maintenance, and operations as appropriate to the type and stage of manufacture. Facilities should also be designed to minimize potential contamination. Where microbiological specifications have been established for the intermediate or API, facilities should also be designed to limit exposure to objectionable microbiological contaminants as appropriate.

4.11 Buildings and facilities should have adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination.

4.12 Where the equipment itself (e.g., closed or contained systems) provides adequate protection of the material, such equipment can be located outdoors.

4.13 The flow of materials and personnel through the building or facilities should be designed to prevent mix-ups or contamination.

4.14 There should be defined areas or other control systems for the following activities:

-Receipt, identification, sampling, and quarantine of incoming materials, pending release or rejection;

-Quarantine before release or rejection of intermediates and APIs;

-Sampling of intermediates and APIs;

-Holding rejected materials before further disposition (e.g., return, reprocessing or destruction)

-Storage of released materials;

-Production operations;

-Packaging and labelling operations; and

-Laboratory operations.

4.15 Adequate, clean washing and toilet facilities should be provided for personnel. These washing facilities should be equipped with hot and cold water as appropriate, soap or detergent, air driers or single service towels. The washing and toilet facilities should be separate from, but easily accessible to, manufacturing areas. Adequate facilities for showering and/or changing clothes should be provided, when appropriate.

4.16 Laboratory areas/operations should normally be separated from production areas. Some laboratory areas, in particular those used for in-process controls, can be located in production areas, provided the operations of the production process do not adversely affect the accuracy of the laboratory measurements, and the laboratory and its operations do not adversely affect the production process or intermediate or API.

4.2 Utilities

4.20 All utilities that could impact on product quality (e.g. steam, gases, compressed air, and heating, ventilation and air conditioning) should be qualified and appropriately monitored and action should be taken when limits are exceeded. Drawings for these utility systems should be available.

4.21 Adequate ventilation, air filtration and exhaust systems should be provided, where appropriate. These systems should be designed and constructed to minimise risks of contamination and cross-contamination and should include equipment for control of air pressure, microorganisms (if appropriate), dust, humidity, and temperature, as appropriate to the stage of manufacture. Particular attention should be given to areas where APIs are exposed to the environment.

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

4.23 Permanently installed pipework should be appropriately identified. This can be accomplished by identifying individual lines, documentation, computer control systems, or alternative means. Pipework should be located to avoid risks of contamination of the intermediate or API.

4.24 Drains should be of adequate size and should be provided with an air break or a suitable device to prevent back-siphonage, when appropriate.

4.3 Water

4.30 Water used in the manufacture of APIs should be demonstrated to be suitable for its intended use.

4.31 Unless otherwise justified, process water should, at a minimum, meet World Health Organization (WHO) guidelines for drinking (potable) water quality.

4.32 If drinking (potable) water is insufficient to assure active substance quality, and tighter chemical and/or microbiological water quality specifications are called for, appropriate specifications for physical/chemical attributes, total microbial counts, objectionable organisms and/or endotoxins should be established.

4.33 Where water used in the process is treated by the manufacturer to achieve a defined quality, the treatment process should be validated and monitored with appropriate action limits.

4.34 Where the manufacturer of a non-sterile active substance either intends or claims that it is suitable for use in further processing to produce a sterile veterinary medicinal product, water used in the final isolation and purification steps should comply with requirements from relevant EMA Guidelines and EP monographs.

4.4 Containment

4.40 Dedicated production areas, which can include facilities, air handling equipment and/or process equipment, should be employed in the production of highly sensitizing materials, such as penicillins or cephalosporins, unless cleaning procedures are established, implemented and maintained to prevent cross-contamination.

4.41 Dedicated production areas should also be considered when material of an infectious nature or high pharmacological activity or toxicity is involved (e.g., certain steroids or cytotoxic anti-cancer agents) unless validated inactivation and/or cleaning procedures are established and maintained.

4.42 Appropriate measures should be established and implemented to prevent cross- contamination from personnel, materials, etc. moving from one dedicated area to another.

4.43 Any production activities (including weighing, milling, or packaging) of highly toxic non-pharmaceutical materials such as herbicides and pesticides should not be conducted using the buildings and/or equipment being used for the production of APIs. Handling and storage of these highly toxic non-pharmaceutical materials should be separate from APIs.

4.44 A comprehensive and effective quality system incorporating adequate quality controls and quality risk management should be used for determining the necessity for and the extent to which all production areas should be shared and to mitigate the associated risk of cross contamination.

4.5 Lighting

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

4.6 Sewage and Refuse

4.60 Sewage, refuse, and other waste (e.g., solids, liquids, or gaseous by-products from manufacturing) in and from buildings and the immediate surrounding area should be disposed of in a safe, timely, and sanitary manner. Containers and/or pipes for waste material should be clearly identified.

4.7 Sanitation and Maintenance

4.70 Buildings used in the manufacture of intermediates and APIs should be properly maintained and repaired and kept in a clean condition.

4.71 Written procedures should be established assigning responsibility for sanitation and describing the cleaning schedules, methods, equipment, and materials to be used in cleaning buildings and facilities.

4.72 When necessary, written procedures should also be established for the use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents to prevent the contamination of equipment, raw materials, packaging/labelling materials, intermediates, and APIs.

5. Process Equipment

5.1 Design and Construction

5.10 Equipment used in the manufacture of intermediates and APIs should be of appropriate design and adequate size, and suitably located for its intended use, cleaning, sanitization (where appropriate), and maintenance.

5.11 Equipment should be constructed so that surfaces that contact raw materials, intermediates, or APIs do not alter the quality of the intermediates and APIs beyond the official or other established specifications.

5.12 Production equipment should only be used within its qualified operating range.

5.13 Major equipment (e.g., reactors, storage containers) and permanently installed processing lines used during the production of an intermediate or active substance should be appropriately identified.

5.14 Any substances associated with the operation of equipment, such as lubricants, heating fluids or coolants, should not contact intermediates or APIs so as to alter their quality beyond the official or other established specifications. Any deviations from this should be evaluated to ensure that there are no detrimental effects upon the fitness for purpose of the material. Wherever possible, food grade lubricants and oils should be used.

5.15 Closed or contained equipment should be used whenever appropriate. Where open equipment is used, or equipment is opened, appropriate precautions should be taken to minimize the risk of contamination.

5.16 A set of current drawings should be maintained for equipment and critical installations (e.g., instrumentation and utility systems).

5.2 Equipment Maintenance and Cleaning

5.20 Schedules and procedures (including assignment of responsibility) should be established for the maintenance of equipment.

5.21 Written procedures should be established for cleaning of equipment and its subsequent release for use in the manufacture of intermediates and APIs. Cleaning procedures should contain sufficient details to enable operators to clean each type of equipment in a reproducible and effective manner. These procedures should include:

-Assignment of responsibility for cleaning of equipment;

-Cleaning schedules, including, where appropriate, sanitizing schedules;

-A complete description of the methods and materials, including dilution of cleaning agents used to clean equipment;

-When appropriate, instructions for disassembling and reassembling each article of equipment to ensure proper cleaning;

-Instructions for the removal or obliteration of previous batch identification;

-Instructions for the protection of clean equipment from contamination prior to use;

-Inspection of equipment for cleanliness immediately before use, if practical; and

-Establishing the maximum time that may elapse between the completion of processing and equipment cleaning, when appropriate.

5.22 Equipment and utensils should be cleaned, stored, and, where appropriate, sanitized or sterilized to prevent contamination or carry-over of a material that would alter the quality of the intermediate or active substance beyond the official or other established specifications.

5.23 Where equipment is assigned to continuous production or campaign production of successive batches of the same intermediate or API, equipment should be cleaned at appropriate intervals to prevent build-up and carry-over of contaminants (e.g. degradants or objectionable levels of micro-organisms).

5.24 Non-dedicated equipment should be cleaned between production of different materials to prevent cross-contamination.

5.25 Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents should be defined and justified.

5.26 Equipment should be identified as to its contents and its cleanliness status by appropriate means.

5.3 Calibration

5.30 Control, weighing, measuring, monitoring and test equipment that is critical for assuring the quality of intermediates or APIs should be calibrated according to written procedures and an established schedule.

5.31 Equipment calibrations should be performed using standards traceable to certified standards, if existing.

5.32 Records of these calibrations should be maintained.

5.33 The current calibration status of critical equipment should be known and verifiable.

5.34 Instruments that do not meet calibration criteria should not be used.

5.35 Deviations from approved standards of calibration on critical instruments should be investigated to determine if these could have had an impact on the quality of the intermediate(s) or API(s) manufactured using this equipment since the last successful calibration.

5.4 Computerized Systems

5.40 GMP related computerized systems should be validated. The depth and scope of validation depends on the diversity, complexity and criticality of the computerized application.

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

5.42 Commercially available software that has been qualified does not require the same level of testing. If an existing system was not validated at time of installation, a retrospective validation could be conducted if appropriate documentation is available.

5.43 Computerized systems should have sufficient controls to prevent unauthorized access or changes to data. There should be controls to prevent omissions in data (e.g. system turned off and data not captured). There should be a record of any data change made, the previous entry, who made the change, and when the change was made.

5.44 Written procedures should be available for the operation and maintenance of computerized systems.

5.45 Where critical data are being entered manually, there should be an additional check on the accuracy of the entry. This can be done by a second operator or by the system itself.

5.46 Incidents related to computerized systems that could affect the quality of intermediates or APIs or the reliability of records or test results should be recorded and investigated.

5.47 Changes to the computerized system should be made according to a change control system (as described in chapter 13) and should be formally authorized, documented and tested. Records should be kept of all changes, including modifications and enhancements made to the hardware, software and any other critical component of the system. These records should demonstrate that the system is maintained in a validated state.

5.48 If system breakdowns or failures would result in the permanent loss of records, a back-up system should be provided. A means of ensuring data protection should be established for all computerized systems.

5.49 Data can be recorded by a second means in addition to the computer system.

6. Documentation and Records

6.1 Documentation System and Specifications

6.10 All documents related to the manufacture of intermediates or APIs should be prepared, reviewed, approved and distributed according to written procedures. Such documents can be in paper or electronic form.

6.11 The issuance, revision, superseding and withdrawal of all documents should be controlled with maintenance of revision histories.

6.12 A procedure should be established for retaining all appropriate documents (e.g., development history reports, scale-up reports, technical transfer reports, process validation reports, training records, production records, control records, and distribution records). The retention periods for these documents should be specified.

6.13 All production, control, and distribution records should be retained for at least 1 year after the expiry date of the batch. For APIs with retest dates, records should be retained for at least 3 years after the batch is completely distributed.

6.14 When entries are made in records, these should be made indelibly in spaces provided for such entries, directly after performing the activities, and should identify the person making the entry. Corrections to entries should be dated and signed and leave the original entry still readable.

6.15 During the retention period, originals or copies of records should be readily available at the establishment where the activities described in such records occurred. Records that can be promptly retrieved from another location by electronic or other means are acceptable.

6.16 Specifications, instructions, procedures, and records can be retained either as originals or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records. Where reduction techniques such as microfilming or electronic records are used, suitable retrieval equipment and a means to produce a hard copy should be readily available.

6.17 Specifications should be established and documented for raw materials, intermediates where necessary, APIs, and labelling and packaging materials. In addition, specifications may be appropriate for certain other materials, such as process aids, gaskets, or other materials used during the production of intermediates or APIs that could critically impact on quality. Acceptance criteria should be established and documented for in-process controls.

6.18 If electronic signatures are used on documents, they should be authenticated and secure.

6.2 Equipment Cleaning and Use Record

6.20 Records of major equipment use, cleaning, sanitization and/or sterilization and maintenance should show the date, time (if appropriate), product, and batch number of each batch processed in the equipment, and the person who performed the cleaning and maintenance.

6.21 If equipment is dedicated to manufacturing one intermediate or API, then individual equipment records are not necessary if batches of the intermediate or active substance follow in traceable sequence.

In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use can be part of the batch record or maintained separately.

6.3 Records of Raw Materials, Intermediates, active substance Labelling and Packaging Materials

6.30 Records should be maintained including:

-The name of the manufacturer, identity and quantity of each shipment of each batch of raw materials, intermediates or labelling and packaging materials for API's; the name of the supplier; the supplier's control number(s), if known, or other identification number; the number allocated on receipt; and the date of receipt;

-The results of any test or examination performed and the conclusions derived from this;

-Records tracing the use of materials;

-Documentation of the examination and review of active substance labelling and packaging materials for conformity with established specifications; and

-The final decision regarding rejected raw materials, intermediates or active substance labeling and packaging materials.

6.31 Master (approved) labels should be maintained for comparison to issued labels.

6.4 Master Production Instructions (Master Production and Control Records)

6.40 To ensure uniformity from batch to batch, master production instructions for each intermediate and active substance should be prepared, dated, and signed by one person and independently checked, dated, and signed by a person in the quality unit(s).

6.41 Master production instructions should include:

-The name of the intermediate or active substance being manufactured and an identifying document reference code, if applicable;

-A complete list of raw materials and intermediates designated by names or codes sufficiently specific to identify any special quality characteristics;

-An accurate statement of the quantity or ratio of each raw material or intermediate to be used, including the unit of measure. Where the quantity is not fixed, the calculation for each batch size or rate of production should be included. Variations to quantities should be included where they are justified;

-The production location and major production equipment to be used;

-Detailed production instructions, including the:

-sequences to be followed,

-ranges of process parameters to be used,

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

-time limits for completion of individual processing steps and/or the total process, where appropriate; and

-expected yield ranges at appropriate phases of processing or time;

-Where appropriate, special notations and precautions to be followed, or cross references to these; and

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

6.5 Batch Production Records (Batch Production and Control Records)

6.50 Batch production records should be prepared for each intermediate and active substance and should include complete information relating to the production and control of each batch. The batch production record should be checked before issuance to assure that it is the correct version and a legible accurate reproduction of the appropriate master production instruction. If the batch production record is produced from a separate part of the master document, that document should include a reference to the current master production instruction being used.

6.51 These records should be numbered with a unique batch or identification number, dated and signed when issued. In continuous production, the product code together with the date and time can serve as the unique identifier until the final number is allocated.

6.52 Documentation of completion of each significant step in the batch production records (batch production and control records) should include:

-Dates and, when appropriate, times; -Identity of major equipment (e.g., reactors, driers, mills, etc.) used;

-Specific identification of each batch, including weights, measures, and batch numbers of raw materials, intermediates, or any reprocessed materials used during manufacturing;

-Actual results recorded for critical process parameters;

-Any sampling performed;

-Signatures of the persons performing and directly supervising or checking each critical step in the operation;

-In-process and laboratory test results;

-Actual yield at appropriate phases or times;

-Description of packaging and label for intermediate or API;

-Representative label of active substance or intermediate if made commercially available;

-Any deviation noted, its evaluation, investigation conducted (if appropriate) or reference to that investigation if stored separately; and

-Results of release testing.

6.53 Written procedures should be established and followed for investigating critical deviations or the failure of a batch of intermediate or active substance to meet specifications. The investigation should extend to other batches that may have been associated with the specific failure or deviation.

6.6 Laboratory Control Records

6.60 Laboratory control records should include complete data derived from all tests conducted to ensure compliance with established specifications and standards, including examinations and assays, as follows:

-A description of samples received for testing, including the material name or source, batch number or other distinctive code, date sample was taken, and, where appropriate, the quantity and date the sample was received for testing;

-A statement of or reference to each test method used;

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

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

-A record of all calculations performed in connection with the test, including, for example, units of measure, conversion factors, and equivalency factors;

-A statement of the test results and how they compare with established acceptance criteria;

-The signature of the person who performed each test and the date(s) the tests were performed; and

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

6.61 Complete records should also be maintained for:

-Any modifications to an established analytical method,

-Periodic calibration of laboratory instruments, apparatus, gauges, and recording devices;

-All stability testing performed on APIs; and

-Out of specification (OOS) investigations.

6.7 Batch Production Record Review

6.70 Written procedures should be established and followed for the review and approval of batch production and laboratory control records, including packaging and labelling, to determine compliance of the intermediate or active substance with established specifications before a batch is released or distributed.

6.71 Batch production and laboratory control records of critical process steps should be reviewed and approved by the quality unit(s) before an active substance batch is released or distributed. Production and laboratory control records of non-critical process steps can be reviewed by qualified production personnel or other units following procedures approved by the quality unit(s).

6.72 All deviation, investigation, and OOS reports should be reviewed as part of the batch record review before the batch is released.

6.73 The quality unit(s) can delegate to the production unit the responsibility and authority for release of intermediates, except for those shipped outside the control of the manufacturing company.

7. Materials Management

7.1 General Controls

7.10 There should be written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing, and approval or rejection of materials.

7.11 Manufacturers of intermediates and/or APIs should have a system for evaluating the suppliers of critical materials.

7.12 Materials should be purchased against an agreed specification, from a supplier or suppliers approved by the quality unit(s).

7.13 If the supplier of a critical material is not the manufacturer of that material, the name and address of that manufacturer should be known by the intermediate and/or active substance manufacturer.

7.14 Changing the source of supply of critical raw materials should be treated according to Section13, Change Control.

7.2 Receipt and Quarantine

7.20 Upon receipt and before acceptance, each container or grouping of containers of materials should be examined visually for correct labelling (including correlation between the name used by the supplier and the in-house name, if these are different), container damage, broken seals and evidence of tampering or contamination. Materials should be held under quarantine until they have been sampled, examined or tested as appropriate, and released for use.

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

7.22 If bulk deliveries are made in non-dedicated tankers, there should be assurance of no cross-contamination from the tanker. Means of providing this assurance could include one or more of the following:

-certificate of cleaning

-testing for trace impurities

-audit of the supplier.

7.23 Large storage containers, and their attendant manifolds, filling and discharge lines should be appropriately identified.

7.24 Each container or grouping of containers (batches) of materials should be assigned and identified with a distinctive code, batch, or receipt number. This number should be used in recording the disposition of each batch. A system should be in place to identify the status of each batch.

7.3 Sampling and Testing of Incoming Production Materials

7.30 At least one test to verify the identity of each batch of material should be conducted, with the exception of the materials described below in 7.32. A supplier's Certificate of Analysis can be used in place of performing other tests, provided that the manufacturer has a system in place to evaluate suppliers.

7.31 Supplier approval should include an evaluation that provides adequate evidence (e.g., past quality history) that the manufacturer can consistently provide material meeting specifications. Full analyses should be conducted on at least three batches before reducing in-house testing. However, as a minimum, a full analysis should be performed at appropriate intervals and compared with the Certificates of Analysis. Reliability of Certificates of Analysis should be checked at regular intervals.

7.32 Processing aids, hazardous or highly toxic raw materials, other special materials, or materials transferred to another unit within the company's control do not need to be tested if the manufacturer's Certificate of Analysis is obtained, showing that these raw materials conform to established specifications. Visual examination of containers, labels, and recording of batch numbers should help in establishing the identity of these materials. The lack of on-site testing for these materials should be justified and documented.

7.33 Samples should be representative of the batch of material from which they are taken. Sampling methods should specify the number of containers to be sampled, which part of the container to sample, and the amount of material to be taken from each container. The number of containers to sample and the sample size should be based upon a sampling plan that takes into consideration the criticality of the material, material variability, past quality history of the supplier, and the quantity needed for analysis.

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

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

7.4 Storage

7.40 Materials should be handled and stored in a manner to prevent degradation, contamination, and cross-contamination.

7.41 Materials stored in fiber drums, bags, or boxes should be stored off the floor and, when appropriate, suitably spaced to permit cleaning and inspection.

7.42 Materials should be stored under conditions and for a period that have no adverse effect on their quality, and should normally be controlled so that the oldest stock is used first.

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

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

7.5 Re evaluation

7.50 Materials should be re evaluated as appropriate to determine their suitability for use (e.g., after prolonged storage or exposure to heat or humidity).

8. Production and In-Process Controls

8.1 Production Operations

8.10 Raw materials for intermediate and active substance manufacturing should be weighed or measured under appropriate conditions that do not affect their suitability for use. Weighing and measuring devices should be of suitable accuracy for the intended use.

8.11 If a material is subdivided for later use in production operations, the container receiving the material should be suitable and should be so identified that the following information is available:

-Material name and/or item code;

-Receiving or control number;

-Weight or measure of material in the new container; and

-Re-evaluation or retest date if appropriate.

8.12 Critical weighing, measuring, or subdividing operations should be witnessed or subjected to an equivalent control. Prior to use, production personnel should verify that the materials are those specified in the batch record for the intended intermediate or API.

8.13 Other critical activities should be witnessed or subjected to an equivalent control.

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

8.15 Any deviation should be documented and explained. Any critical deviation should be investigated.

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

8.17 Materials to be reprocessed or reworked should be appropriately controlled to prevent unauthorized use.

8.2 Time Limits

8.20 If time limits are specified in the master production instruction (see 6.41), these time limits should be met to ensure the quality of intermediates and APIs. Deviations should be documented and evaluated. Time limits may be inappropriate when processing to a target value (e.g., pH adjustment, hydrogenation, drying to predetermined specification) because completion of reactions or processing steps are determined by in- process sampling and testing.

8.21 Intermediates held for further processing should be stored under appropriate conditions to ensure their suitability for use.

8.3 In-process Sampling and Controls

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

8.31 The acceptance criteria and type and extent of testing can depend on the nature of the intermediate or active substance being manufactured, the reaction or process step being conducted, and the degree to which the process introduces variability in the product's quality. Less stringent in-process controls may be appropriate in early processing steps, whereas tighter controls may be appropriate for later processing steps (e.g., isolation and purification steps).

8.32 Critical in-process controls (and critical process monitoring), including the control points and methods, should be stated in writing and approved by the quality unit(s).

8.33 In-process controls can be performed by qualified production department personnel and the process adjusted without prior quality unit(s) approval if the adjustments are made within pre-established limits approved by the quality unit(s). All tests and results should be fully documented as part of the batch record.

8.34 Written procedures should describe the sampling methods for in-process materials, intermediates, and APIs. Sampling plans and procedures should be based on scientifically sound sampling practices.

8.35 In-process sampling should be conducted using procedures designed to prevent contamination of the sampled material and other intermediates or APIs. Procedures should be established to ensure the integrity of samples after collection.

8.36 Out-of-specification (OOS) investigations are not normally needed for in-process tests that are performed for the purpose of monitoring and/or adjusting the process.

8.4 Blending Batches of Intermediates or APIs

8.40 For the purpose of this document, blending is defined as the process of combining materials within the same specification to produce a homogeneous intermediate or API. In-process mixing of fractions from single batches (e.g., collecting several centrifuge loads from a single crystallization batch) or combining fractions from several batches for further processing is considered to be part of the production process and is not considered to be blending.

8.41 Out-Of-Specification batches should not be blended with other batches for the purpose of meeting specifications. Each batch incorporated into the blend should have been manufactured using an established process and should have been individually tested and found to meet appropriate specifications prior to blending.

8.42 Acceptable blending operations include but are not limited to:

-Blending of small batches to increase batch size

-Blending of tailings (i.e., relatively small quantities of isolated material) from batches of the same intermediate or active substance to form a single batch.

8.43 Blending processes should be adequately controlled and documented and the blended batch should be tested for conformance to established specifications where appropriate.

8.44 The batch record of the blending process should allow traceability back to the individual batches that make up the blend.

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

8.46 If the blending could adversely affect stability, stability testing of the final blended batches should be performed.

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

8.5 Contamination Control

8.50 Residual materials can be carried over into successive batches of the same intermediate or active substance if there is adequate control. Examples include residue adhering to the wall of a micronizer, residual layer of damp crystals remaining in a centrifuge bowl after discharge, and incomplete discharge of fluids or crystals from a processing vessel upon transfer of the material to the next step in the process. Such carryover should not result in the carryover of degradants or microbial contamination that may adversely alter the established active substance impurity profile.

8.51 Production operations should be conducted in a manner that will prevent contamination of intermediates or APIs by other materials.

8.52 Precautions to avoid contamination should be taken when APIs are handled after purification.

9. Packaging and Identification Labelling of APIs and Intermediates

9.1 General

9.10 There should be written procedures describing the receipt, identification, quarantine, sampling, examination and/or testing and release, and handling of packaging and labelling materials.

9.11 Packaging and labelling materials should conform to established specifications. Those that do not comply with such specifications should be rejected to prevent their use in operations for which they are unsuitable.

9.12 Records should be maintained for each shipment of labels and packaging materials showing receipt, examination, or testing, and whether accepted or rejected.

9.2 Packaging Materials

9.20 Containers should provide adequate protection against deterioration or contamination of the intermediate or active substance that may occur during transportation and recommended storage.

9.21 Containers should be clean and, where indicated by the nature of the intermediate or API, sanitized to ensure that they are suitable for their intended use. These containers should not be reactive, additive, or absorptive so as to alter the quality of the intermediate or active substance beyond the specified limits.

9.22 If containers are re-used, they should be cleaned in accordance with documented procedures and all previous labels should be removed or defaced.

9.3 Label Issuance and Control

9.30 Access to the label storage areas should be limited to authorised personnel.

9.31 Procedures should be used to reconcile the quantities of labels issued, used, and returned and to evaluate discrepancies found between the number of containers labelled and the number of labels issued. Such discrepancies should be investigated, and the investigation should be approved by the quality unit(s).

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

9.33 Obsolete and out-dated labels should be destroyed.

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

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

9.36 A printed label representative of those used should be included in the batch production record.

9.4 Packaging and Labelling Operations

9.40 There should be documented procedures designed to ensure that correct packaging materials and labels are used.

9.41 Labelling operations should be designed to prevent mix-ups. There should be physical or spatial separation from operations involving other intermediates or APIs.

9.42 Labels used on containers of intermediates or APIs should indicate the name or identifying code, the batch number of the product, and storage conditions, when such information is critical to assure the quality of intermediate or API.

9.43 If the intermediate or active substance is intended to be transferred outside the control of the manufacturer's material management system, the name and address of the manufacturer, quantity of contents, and special transport conditions and any special legal requirements should also be included on the label. For intermediates or APIs with an expiry date, the expiry date should be indicated on the label and Certificate of Analysis. For intermediates or APIs with a retest date, the retest date should be indicated on the label and/or Certificate of Analysis.

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

9.45 Packaged and labelled intermediates or APIs should be examined to ensure that containers and packages in the batch have the correct label. This examination should be part of the packaging operation. Results of these examinations should be recorded in the batch production or control records.

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

10. Storage and Distribution

10.1 Warehousing Procedures

10.10 Facilities should be available for the storage of all materials under appropriate conditions (e.g. controlled temperature and humidity when necessary). Records should be maintained of these conditions if they are critical for the maintenance of material characteristics.

10.11 Unless there is an alternative system to prevent the unintentional or unauthorised use of quarantined, rejected, returned, or recalled materials, separate storage areas should be assigned for their temporary storage until the decision as to their future use has been taken.

10.2 Distribution Procedures

10.20 APIs and intermediates should only be released for distribution to third parties after they have been released by the quality unit(s). APIs and intermediates can be transferred under quarantine to another unit under the company's control when authorized by the quality unit(s) and if appropriate controls and documentation are in place.

10.21 APIs and intermediates should be transported in a manner that does not adversely affect their quality.

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

10.23 The manufacturer should ensure that the contract acceptor (contractor) for transportation of the active substance or intermediate knows and follows the appropriate transport and storage conditions.

10.24 A system should be in place by which the distribution of each batch of intermediate and/or active substance can be readily determined to permit its recall.

11. Laboratory Controls

11.1 General Controls

11.10 The independent quality unit(s) should have at its disposal adequate laboratory facilities.

11.11 There should be documented procedures describing sampling, testing, approval or rejection of materials, and recording and storage of laboratory data. Laboratory records should be maintained in accordance with Section 6.6.

11.12 All specifications, sampling plans, and test procedures should be scientifically sound and appropriate to ensure that raw materials, intermediates, APIs, and labels and packaging materials conform to established standards of quality and/or purity. Specifications and test procedures should be consistent with those included in the registration/filing. There can be specifications in addition to those in the registration/filing. Specifications, sampling plans, and test procedures, including changes to them, should be drafted by the appropriate organizational unit and reviewed and approved by the quality unit(s).

11.13 Appropriate specifications should be established for APIs in accordance with accepted standards and consistent with the manufacturing process. The specifications should include a control of the impurities (e.g. organic impurities, inorganic impurities, and residual solvents). If the active substance has a specification for microbiological purity, appropriate action limits for total microbial counts and objectionable organisms should be established and met. If the active substance has a specification for endotoxins, appropriate action limits should be established and met.

11.14 Laboratory controls should be followed and documented at the time of performance. Any deviation from the above described procedures should be documented and explained.

11.15 Any out-of-specification (OOS) result obtained should be investigated and documented according to a procedure. This procedure should require analysis of the data, assessment of whether a significant problem exists, allocation of the tasks for corrective actions, and conclusions. Any re-sampling and/or retesting after OOS results should be performed according to a documented procedure.

11.16 Reagents and standard solutions should be prepared and labelled following written procedures. "Use by" dates should be applied as appropriate for analytical reagents or standard solutions.

11.17 Primary reference standards should be obtained as appropriate for the manufacture of APIs. The source of each primary reference standard should be documented. Records should be maintained of each primary reference standard's storage and use in accordance with the supplier's recommendations. Primary reference standards obtained from an officially recognised source can be used without testing if stored under conditions consistent with the supplier's recommendations.

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

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

11.2 Testing of Intermediates and APIs

11.20 For each batch of intermediate and API, appropriate laboratory tests should be conducted to determine conformance to specifications.

11.21 An impurity profile describing the identified and unidentified impurities present in a typical batch produced by a specific controlled production process should be established for each API. The impurity profile should include the identity or some qualitative analytical designation (e.g. retention time), the range of each impurity observed, and classification of each identified impurity (e.g. inorganic, organic, solvent). The impurity profile is dependent upon the production process and origin of the API. Impurity profiles are not necessary for APIs from herbal or animal tissue origin. Biotechnology considerations are covered in VICH GL 40.

11.22 The impurity profile should be compared at appropriate intervals against the impurity profile in the regulatory submission or compared against historical data in order to detect changes to the active substance resulting from modifications in raw materials, equipment operating parameters, or the production process.

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

11.3 Validation of Analytical Procedures - see Section 12.

11.4 Certificates of Analysis

11.40 Authentic Certificates of Analysis should be issued for each batch of intermediate or active substance on request.

11.41 Information on the name of the intermediate or active substance including where appropriate its grade, the batch number, and the date of release should be provided on the Certificate of Analysis. For intermediates or APIs with an expiry date, the expiry date should be provided on the label and Certificate of Analysis. For intermediates or APIs with a retest date, the retest date should be indicated on the label and/or Certificate of Analysis.

11.42 The Certificate should list each test performed in accordance with compendial or customer requirements, including the acceptance limits, and the numerical results obtained (if test results are numerical).

11.43 Certificates should be dated and signed by authorised personnel of the quality unit(s) and should show the name, address and telephone number of the original manufacturer. Where the analysis has been carried out by a repacker or reprocessor, the Certificate of Analysis should show the name, address and telephone number of the repacker/ reprocessor and a reference to the name of the original manufacturer.

11.44 If new Certificates are issued by or on behalf of repackers/ reprocessors, agents or brokers, these Certificates should show the name, address and telephone number of the laboratory that performed the analysis. They should also contain a reference to the name and address of the original manufacturer and to the original batch Certificate, a copy of which should be attached.

11.5 Stability Monitoring of APIs

11.50 A documented, on-going testing program should be designed to monitor the stability characteristics of APIs, and the results should be used to confirm appropriate storage conditions and retest or expiry dates.

11.51 The test procedures used in stability testing should be validated and be stability indicating.

11.52 Stability samples should be stored in containers that simulate the market container. For example, if the active substance is marketed in bags within fiber drums, stability samples can be packaged in bags of the same material and in smaller-scale drums of similar or identical material composition to the market drums.

11.53 The first three commercial production batches should be placed on the stability monitoring program to confirm the retest or expiry date. However, where data from previous studies show that the active substance is expected to remain stable for at least two years, fewer than three batches can be used.

11.54 Thereafter, at least one batch per year of active substance manufactured (unless none is produced that year) should be added to the stability monitoring program and tested at least annually to confirm the stability.

11.55 For APIs with short shelf-lives, testing should be done more frequently. For example, for those biotechnological/biologic and other APIs with shelf-lives of one year or less, stability samples should be obtained and should be tested monthly for the first three months, and at three month intervals after that. When data exist that confirm that the stability of the active substance is not compromised, elimination of specific test intervals (e.g. 9 month testing) can be considered.

11.56 Where appropriate, the stability storage conditions should be consistent with the VICH guidelines on stability.

11.6 Expiry and Retest Dating

11.60 When an intermediate is intended to be transferred outside the control of the manufacturer's material management system and an expiry or retest date is assigned, supporting stability information should be available (e.g. published data, test results).

11.61 An active substance expiry or retest date should be based on an evaluation of data derived from stability studies.

11.62 Preliminary active substance expiry or retest dates can be based on pilot scale batches if

(1) the pilot batches employ a method of manufacture and procedure that simulates the final process to be used on a commercial manufacturing scale; and (2) the quality of the active substance represents the material to be made on a commercial scale.

11.63 A representative sample should be taken for the purpose of performing a retest.

11.7 Reference/Retention Samples

11.70 The packaging and holding of reference samples is for the purpose of potential future evaluation of the quality of batches of active substance and not for future stability testing purposes.

11.71 Appropriately identified reference samples of each active substance batch should be retained for one year after the expiry date of the batch assigned by the manufacturer, or for three years after distribution of the batch, whichever is the longer. For APIs with retest dates, similar reserve samples should be retained for three years after the batch is completely distributed by the manufacturer.

11.72 The reference sample should be stored in the same packaging system in which the active substance is stored or in one that is equivalent to or more protective than the marketed packaging

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

12. Validation

12.1 Validation Policy

12.10 The company's overall policy, intentions, and approach to validation, including the validation of production processes, cleaning procedures, analytical methods, in- process control test procedures, computerized systems, and persons responsible for design, review, approval and documentation of each validation phase, should be documented.

12.11 The critical parameters/attributes should normally be identified during the development stage or from historical data, and the ranges necessary for the reproducible operation should be defined. This should include:

-Defining the active substance in terms of its critical product attributes;

-Identifying process parameters that could affect the critical quality attributes of the API;

-Determining the range for each critical process parameter expected to be used during routine manufacturing and process control.

12.12 Validation should extend to those operations determined to be critical to the quality and purity of the API.

12.2 Validation Documentation

12.20 A written validation protocol should be established that specifies how validation of a particular process will be conducted. The protocol should be reviewed and approved by the quality unit(s) and other designated units.

12.21 The validation protocol should specify critical process steps and acceptance criteria as well as the type of validation to be conducted (e.g. retrospective, prospective, concurrent) and the number of process runs.

12.22 A validation report that cross-references the validation protocol should be prepared, summarising the results obtained, commenting on any deviations observed, and drawing the appropriate conclusions, including recommending changes to correct deficiencies.

12.23 Any variations from the validation protocol should be documented with appropriate justification.

12.3 Qualification

12.30 Before starting process validation activities, appropriate qualification of critical equipment and ancillary systems should be completed. Qualification is usually carried out by conducting the following activities, individually or combined:

-Design Qualification (DQ): documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose.

-Installation Qualification (IQ): documented verification that the equipment or systems, as installed or modified, comply with the approved design, the manufacturer’s recommendations and/or user requirements.

-Operational Qualification (OQ): documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges.

-Performance Qualification (PQ): documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications.

12.4 Approaches to Process Validation

12.40 Process Validation (PV) is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or active substance meeting its predetermined specifications and quality attributes.

12.41 There are three approaches to validation. Prospective validation is the preferred approach, but there are exceptions where the other approaches can be used. These approaches and their applicability are listed below.

12.42 Prospective validation should normally be performed for all active substance processes as defined in 12.12. Prospective validation performed on an active substance process should be completed before the commercial distribution of the final drug product manufactured from that API.

12.43 Concurrent validation can be conducted when data from replicate production runs are unavailable because only a limited number of active substance batches have been produced, active substance batches are produced infrequently, or active substance batches are produced by a validated process that has been modified. Prior to the completion of concurrent validation, batches can be released and used in final drug product for commercial distribution based on thorough monitoring and testing of the active substance batches.

12.44 An exception can be made for retrospective validation for well established processes that have been used without significant changes to active substance quality due to changes in raw materials, equipment, systems, facilities, or the production process. This validation approach may be used where:

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

(2) Appropriate in-process acceptance criteria and controls have been established;

(3) There have not been significant process/product failures attributable to causes other than operator error or equipment failures unrelated to equipment suitability; and,

(4) Impurity profiles have been established for the existing API.

12.45 Batches selected for retrospective validation should be representative of all batches made during the review period, including any batches that failed to meet specifications, and should be sufficient in number to demonstrate process consistency. Retained samples can be tested to obtain data to retrospectively validate the process.

12.5 Process Validation Program

12.50 The number of process runs for validation should depend on the complexity of the process or the magnitude of the process change being considered. For prospective and concurrent validation, three consecutive successful production batches should be used as a guide, but there may be situations where additional process runs are warranted to prove consistency of the process (e.g., complex active substance processes or active substance processes with prolonged completion times). For retrospective validation, generally data from ten to thirty consecutive batches should be examined to assess process consistency, but fewer batches can be examined if justified.

12.51 Critical process parameters should be controlled and monitored during process validation studies. Process parameters unrelated to quality, such as variables controlled to minimize energy consumption or equipment use, need not be included in the process validation.

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

12.6 Periodic Review of Validated Systems

12.60 Systems and processes should be periodically evaluated to verify that they are still operating in a valid manner. Where no significant changes have been made to the system or process, and a quality review confirms that the system or process is consistently producing material meeting its specifications, there is normally no need for revalidation.

12.7 Cleaning Validation

12.70 Cleaning procedures should normally be validated. In general, cleaning validation should be directed to situations or process steps where contamination or carryover of materials poses the greatest risk to active substance quality. For example, in early production it may be unnecessary to validate equipment cleaning procedures where residues are removed by subsequent purification steps.

12.71 Validation of cleaning procedures should reflect actual equipment usage patterns. If various APIs or intermediates are manufactured in the same equipment and the equipment is cleaned by the same process, a representative intermediate or active substance can be selected for cleaning validation. This selection should be based on the solubility and difficulty of cleaning and the calculation of residue limits based on potency, toxicity, and stability.

12.72 The cleaning validation protocol should describe the equipment to be cleaned, procedures, materials, acceptable cleaning levels, parameters to be monitored and controlled, and analytical methods. The protocol should also indicate the type of samples to be obtained and how they are collected and labelled.

12.73 Sampling should include swabbing, rinsing, or alternative methods (e.g., direct extraction), as appropriate, to detect both insoluble and soluble residues. The sampling methods used should be capable of quantitatively measuring levels of residues remaining on the equipment surfaces after cleaning. Swab sampling may be impractical when product contact surfaces are not easily accessible due to equipment design and/or process limitations (e.g., inner surfaces of hoses, transfer pipes, reactor tanks with small ports or handling toxic materials, and small intricate equipment such as micronizers and microfluidizers).

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

12.75 Equipment cleaning/sanitization studies should address microbiological and endotoxin contamination for those processes where there is a need to reduce total microbiological count or endotoxins in the API, or other processes where such contamination could be of concern (e.g., non-sterile APIs used to manufacture sterile products).

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

12.8 Validation of Analytical Methods

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

12.81 Methods should be validated to include consideration of characteristics included within the vICH guidelines on validation of analytical methods. The degree of analytical validation performed should reflect the purpose of the analysis and the stage of the active substance production process.

12.82 Appropriate qualification of analytical equipment should be considered before starting validation of analytical methods.

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

13. Change Control

13.10 A formal change control system should be established to evaluate all changes that may affect the production and control of the intermediate or API.

13.11 Written procedures should provide for the identification, documentation, appropriate review, and approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment (including computer hardware), processing steps, labelling and packaging materials, and computer software.

13.12 Any proposals for GMP relevant changes should be drafted, reviewed, and approved by the appropriate organisational units, and reviewed and approved by the quality unit(s).

13.13 The potential impact of the proposed change on the quality of the intermediate or active substance should be evaluated. A classification procedure may help in determining the level of testing, validation, and documentation needed to justify changes to a validated process. Changes can be classified (e.g. as minor or major) depending on the nature and extent of the changes, and the effects these changes may impart on the process. Scientific judgment should determine what additional testing and validation studies are appropriate to justify a change in a validated process.

13.14 When implementing approved changes, measures should be taken to ensure that all documents affected by the changes are revised.

13.15 After the change has been implemented, there should be an evaluation of the first batches produced or tested under the change.

13.16 The potential for critical changes to affect established retest or expiry dates should be evaluated. If necessary, samples of the intermediate or active substance produced by the modified process can be placed on an accelerated stability program and/or can be added to the stability monitoring program.

13.17 Current dosage form manufacturers should be notified of changes from established production and process control procedures that can impact the quality of the API.

14. Rejection and Re-Use of Materials

14.1 Rejection

14.10 Intermediates and APIs failing to meet established specifications should be identified as such and quarantined. These intermediates or APIs can be reprocessed or reworked as described below. The final disposition of rejected materials should be recorded.

14.2 Reprocessing

14.20 Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and reprocessing by repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography, milling) that are part of the established manufacturing process is generally considered acceptable. However, if such reprocessing is used for a majority of batches, such reprocessing should be included as part of the standard manufacturing process.

14.21 Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process. This is not considered to be reprocessing.

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

14.3 Reworking

14.30 Before a decision is taken to rework batches that do not conform to established standards or specifications, an investigation into the reason for non-conformance should be performed.

14.31 Batches that have been reworked should be subjected to appropriate evaluation, testing, stability testing if warranted, and documentation to show that the reworked product is of equivalent quality to that produced by the original process. Concurrent validation is often the appropriate validation approach for rework procedures. This allows a protocol to define the rework procedure, how it will be carried out, and the expected results. If there is only one batch to be reworked, then a report can be written and the batch released once it is found to be acceptable.

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

14.4 Recovery of Materials and Solvents

14.40 Recovery (e.g. from mother liquor or filtrates) of reactants, intermediates, or the active substance is considered acceptable, provided that approved procedures exist for the recovery and the recovered materials meet specifications suitable for their intended use.

14.41 Solvents can be recovered and reused in the same processes or in different processes, provided that the recovery procedures are controlled and monitored to ensure that solvents meet appropriate standards before reuse or co-mingling with other approved materials.

14.42 Fresh and recovered solvents and reagents can be combined if adequate testing has shown their suitability for all manufacturing processes in which they may be used.

14.43 The use of recovered solvents, mother liquors, and other recovered materials should be adequately documented.

14.5 Returns

14.50 Returned intermediates or APIs should be identified as such and quarantined.

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

14.52 Records of returned intermediates or APIs should be maintained. For each return, documentation should include:

-Name and address of the consignee

-Intermediate or API, batch number, and quantity returned

-Reason for return

-Use or disposal of the returned intermediate or API

15. Complaints and Recalls

15.10 All quality related complaints, whether received orally or in writing, should be recorded and investigated according to a written procedure.

15.11 Complaint records should include:

-Name and address of complainant;

-Name (and, where appropriate, title) and phone number of person submitting the complaint;

-Complaint nature (including name and batch number of the API);

-Date complaint is received;

-Action initially taken (including dates and identity of person taking the action);

-Any follow-up action taken;

-Response provided to the originator of complaint (including date response sent);and

-Final decision on intermediate or active substance batch or lot.

15.12 Records of complaints should be retained in order to evaluate trends, product- related frequencies, and severity with a view to taking additional, and if appropriate, immediate corrective action.

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

15.14 The recall procedure should designate who should be involved in evaluating the information, how a recall should be initiated, who should be informed about the recall, and how the recalled material should be treated.

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

16. Contract Manufacturers (including Laboratories)

16.10 All contract manufacturers (including laboratories) should comply with the GMP defined in this Guide. Special consideration should be given to the prevention of cross- contamination and to maintaining traceability.

16.11 Contract manufacturers (including laboratories) should be evaluated by the contract giver to ensure GMP compliance of the specific operations occurring at the contract sites.

16.12 There should be a written and approved contract or formal agreement between the contract giver and the contract acceptor that defines in detail the GMP responsibilities, including the quality measures, of each party.

16.13 The contract should permit the contract giver to audit the contract acceptor's facilities for compliance with GMP.

16.14 Where subcontracting is allowed, the contract acceptor should not pass to a third party any of the work entrusted to him under the contract without the contract giver's prior evaluation and approval of the arrangements.

16.15 Manufacturing and laboratory records should be kept at the site where the activity occurs and be readily available.

16.16 Changes in the process, equipment, test methods, specifications, or other contractual requirements should not be made unless the contract giver is informed and approves the changes.

17. Agents, Brokers, Traders, Distributors, Repackers, and Relabellers

17.1 Applicability

17.10 This section applies to any party other than the original manufacturer who may trade and/or take possession, repack, relabel, manipulate, distribute or store an active substance or intermediate.

17.11 All agents, brokers, traders, distributors, repackers, and relabellers should comply with GMP as defined in this Guide.

17.2 Traceability of Distributed APIs and Intermediates

17.20 Agents, brokers, traders, distributors, repackers, or relabellers should maintain complete traceability of APIs and intermediates that they distribute. Documents that should be retained and available include:

-Identity of original manufacturer

-Address of original manufacturer

-Purchase orders

-Bills of lading (transportation documentation)

-Receipt documents

-Name or designation of active substance or intermediate

-Manufacturer’s batch number

-Transportation and distribution records

-All authentic Certificates of Analysis, including those of the original manufacturer

-Retest or expiry date

17.3 Quality Management

17.30 Agents, brokers, traders, distributors, repackers, or relabellers should establish, document and implement an effective system of managing quality, as specified in Implementing Act on GDP for API, where relevant.

17.4 Repackaging, Relabelling and Holding of APIs and Intermediates

17.40 Repackaging, relabelling and holding of APIs and intermediates should be performed under appropriate GMP controls, as stipulated in this Guide, to avoid mix-ups and loss of active substance or intermediate identity or purity.

17.41 Repackaging should be conducted under appropriate environmental conditions to avoid contamination and cross-contamination.

17.5 Stability

17.50 Stability studies to justify assigned expiration or retest dates should be conducted if the active substance or intermediate is repackaged in a different type of container than that used by the active substance or intermediate manufacturer.

17.6 Transfer of Information

17.60 Agents, brokers, distributors, repackers, or relabellers should transfer all quality or regulatory information received from an active substance or intermediate manufacturer to the customer, and from the customer to the active substance or intermediate manufacturer.

17.61 The agent, broker, trader, distributor, repacker, or relabeller who supplies the active substance or intermediate to the customer should provide the name of the original active substance or intermediate manufacturer and the batch number(s) supplied.

17.62 The agent should also provide the identity of the original active substance or intermediate manufacturer to regulatory authorities upon request. The original manufacturer can respond to the regulatory authority directly or through its authorized agents, depending on the legal relationship between the authorized agents and the original active substance or intermediate manufacturer. (In this context "authorized" refers to authorized by the manufacturer.)

17.63 The specific guidance for Certificates of Analysis included in Section 11.4 should be met.

17.7 Handling of Complaints and Recalls

17.70 Agents, brokers, traders, distributors, repackers, or relabellers should maintain records of complaints and recalls, as specified in Section 15, or Implementing Act on GDP for API, where applicable, for all complaints and recalls that come to their attention.

17.71 If the situation warrants, the agents, brokers, traders, distributors, repackers, or relabellers should review the complaint with the original active substance or intermediate manufacturer in order to determine whether any further action, either with other customers who may have received this active substance or intermediate or with the regulatory authority, or both, should be initiated. The investigation into the cause for the complaint or recall should be conducted and documented by the appropriate party.

17.72 Where a complaint is referred to the original active substance or intermediate manufacturer, the record maintained by the agents, brokers, traders, distributors, repackers, or relabellers should include any response received from the original active substance or intermediate manufacturer (including date and information provided).

17.8 Handling of Returns

17.80 Returns should be handled as specified in Section 14.52, or Implementing Act on GDP for API, where applicable. The agents, brokers, traders, distributors, repackers, or relabellers should maintain documentation of returned APIs and intermediates.

18. Specific Requirements for APIs Manufactured by Cell Culture/Fermentation

18.1 General

18.10 Section 18 is intended to address specific controls for APIs or intermediates manufactured by cell culture or fermentation using natural or recombinant organisms and that have not been covered adequately in the previous sections. It is not intended to be a stand-alone Section. In general, the GMP principles in the other sections of this document apply. Note that the principles of fermentation for "classical" processes for production of small molecules and for processes using recombinant and non-recombinant organisms for production of proteins and/or polypeptides are the same, although the degree of control will differ. Where practical, this section will address these differences. In general, the degree of control for biotechnological processes used to produce proteins and polypeptides is greater than that for classical fermentation processes.

18.11 The term "biotechnological process" (biotech) refers to the use of cells or organisms that have been generated or modified by recombinant DNA, hybridoma or other technology to produce APIs. The APIs produced by biotechnological processes normally consist of high molecular weight substances, such as proteins and polypeptides, for which specific guidance is given in this Section. Certain APIs of low molecular weight, such as antibiotics, amino acids, vitamins, and carbohydrates, can also be produced by recombinant DNA technology. The level of control for these types of APIs is similar to that employed for classical fermentation.

18.12 The term "classical fermentation" refers to processes that use microorganisms existing in nature and/or modified by conventional methods (e.g. irradiation or chemical mutagenesis) to produce APIs. APIs produced by "classical fermentation" are normally low molecular weight products such as antibiotics, amino acids, vitamins, and carbohydrates.

18.13 Production of APIs or intermediates from cell culture or fermentation involves biological processes such as cultivation of cells or extraction and purification of material from living organisms. Note that there may be additional process steps, such as physicochemical modification, that are part of the manufacturing process. The raw materials used (media, buffer components) may provide the potential for growth of microbiological contaminants. Depending on the source, method of preparation, and the intended use of the active substance or intermediate, control of bioburden, viral contamination, and/or endotoxins during manufacturing and monitoring of the process at appropriate stages may be necessary.

18.14 Appropriate controls should be established at all stages of manufacturing to assure intermediate and/or active substance quality. While this Implementing Act starts at the cell culture/fermentation step, prior steps (e.g. cell banking) should be performed under appropriate process controls. This Implementing Act covers cell culture/fermentation from the point at which a vial of the cell bank is retrieved for use in manufacturing.

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

18.16 In general, process controls should take into account:

-Maintenance of the Working Cell Bank (where appropriate);

-Proper inoculation and expansion of the culture;

-Control of the critical operating parameters during fermentation/cell culture;

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

-Harvest and purification procedures that remove cells, cellular debris and media components while protecting the intermediate or active substance from contamination (particularly of a microbiological nature) and from loss of quality;

-Monitoring of bioburden and, where needed, endotoxin levels at appropriate stages of production; and

-Viral safety concerns as described in *ICH Guideline Q5A Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin*.

18.17 Where appropriate, the removal of media components, host cell proteins, other process-related impurities, product-related impurities and contaminants should be demonstrated.

18.2 Cell Bank Maintenance and Record Keeping

18.20 Access to cell banks should be limited to authorized personnel.

18.21 Cell banks should be maintained under storage conditions designed to maintain viability and prevent contamination.

18.22 Records of the use of the vials from the cell banks and storage conditions should be maintained.

18.23 Where appropriate, cell banks should be periodically monitored to determine suitability for use.

18.24 See *ICH Guideline Q5D Quality of Biotechnological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products for a more complete discussion of cell banking*.

18.3 Cell Culture/Fermentation

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

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

18.32 Personnel should be appropriately gowned and take special precautions handling the cultures.

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

18.34 Cell culture equipment should be cleaned and sterilized after use. As appropriate, fermentation equipment should be cleaned, and sanitized or sterilized.

18.35 Culture media should be sterilized before use when appropriate to protect the quality of the API.

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

18.37 Records of contamination events should be maintained.

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

18.4 Harvesting, Isolation and Purification

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

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

18.42 All equipment should be properly cleaned and, as appropriate, sanitized after use. Multiple successive batching without cleaning can be used if intermediate or active substance quality is not compromised.

18.43 If open systems are used, purification should be performed under environmental conditions appropriate for the preservation of product quality.

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

18.5 Viral Removal/Inactivation steps

18.50 See the *ICH Guideline Q5A Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin* for more specific information.

18.51 Viral removal and viral inactivation steps are critical processing steps for some processes and should be performed within their validated parameters.

18.52 Appropriate precautions should be taken to prevent potential viral contamination from pre-viral to post-viral removal/inactivation steps. Therefore, open processing should be performed in areas that are separate from other processing activities and have separate air handling units.

18.53 The same equipment is not normally used for different purification steps. However, if the same equipment is to be used, the equipment should be appropriately cleaned and sanitized before reuse.

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

19. APIs for Use in Clinical Trials – *not* applicable in the framework of the Advice

19.1 General

19.10 Not all the controls in the previous sections of this Guide are appropriate for the manufacture of a new active substance for investigational use during its development. Section 19 provides specific guidance unique to these circumstances.

19.11 The controls used in the manufacture of APIs for use in clinical trials should be consistent with the stage of development of the drug product incorporating the API. Process and test procedures should be flexible to provide for changes as knowledge of the process increases and clinical testing of a drug product progresses from pre-clinical stages through clinical stages. Once drug development reaches the stage where the active substance is produced for use in drug products intended for clinical trials, manufacturers should ensure that APIs are manufactured in suitable facilities using appropriate production and control procedures to ensure the quality of the API.

19.2 Quality

19.20 Appropriate GMP concepts should be applied in the production of APIs for use in clinical trials with a suitable mechanism of approval of each batch.

19.21 A quality unit(s) independent from production should be established for the approval or rejection of each batch of active substance for use in clinical trials.

19.22 Some of the testing functions commonly performed by the quality unit(s) can be performed within other organizational units.

19.23 Quality measures should include a system for testing of raw materials, packaging materials, intermediates, and APIs.

19.24 Process and quality problems should be evaluated.

19.25 Labelling for APIs intended for use in clinical trials should be appropriately controlled and should identify the material as being for investigational use.

19.3 Equipment and Facilities

19.30 During all phases of clinical development, including the use of small-scale facilities or laboratories to manufacture batches of APIs for use in clinical trials, procedures should be in place to ensure that equipment is calibrated, clean and suitable for its intended use.

19.31 Procedures for the use of facilities should ensure that materials are handled in a manner that minimizes the risk of contamination and cross-contamination.

19.4 Control of Raw Materials

19.40 Raw materials used in production of APIs for use in clinical trials should be evaluated by testing, or received with a supplier’s analysis and subjected to identity testing. When a material is considered hazardous, a supplier's analysis should suffice.

19.41 In some instances, the suitability of a raw material can be determined before use based on acceptability in small-scale reactions (i.e., use testing) rather than on analytical testing alone.

19.5 Production

19.50 The production of APIs for use in clinical trials should be documented in laboratory notebooks, batch records, or by other appropriate means. These documents should include information on the use of production materials, equipment, processing, and scientific observations.

19.51 Expected yields can be more variable and less defined than the expected yields used in commercial processes. Investigations into yield variations are not expected.

19.6 Validation

19.60 Process validation for the production of APIs for use in clinical trials is normally inappropriate, where a single active substance batch is produced or where process changes during active substance development make batch replication difficult or inexact. The combination of controls, calibration, and, where appropriate, equipment qualification assures active substance quality during this development phase.

19.61 Process validation should be conducted in accordance with Section 12 when batches are produced for commercial use, even when such batches are produced on a pilot or small scale.

19.7 Changes

19.70 Changes are expected during development, as knowledge is gained and the production is scaled up. Every change in the production, specifications, or test procedures should be adequately recorded.

19.8 Laboratory Controls

19.80 While analytical methods performed to evaluate a batch of active substance for clinical trials may not yet be validated, they should be scientifically sound.

19.81 A system for retaining reserve samples of all batches should be in place. This system should ensure that a sufficient quantity of each reserve sample is retained for an appropriate length of time after approval, termination, or discontinuation of an application.

19.82 Expiry and retest dating as defined in Section 11.6 applies to existing APIs used in clinical trials. For new APIs, Section 11.6 does not normally apply in early stages of clinical trials.

19.9 Documentation

19.90 A system should be in place to ensure that information gained during the development and the manufacture of APIs for use in clinical trials is documented and available.

19.91 The development and implementation of the analytical methods used to support the release of a batch of active substance for use in clinical trials should be appropriately documented.

19.92 A system for retaining production and control records and documents should be used. This system should ensure that records and documents are retained for an appropriate length of time after the approval, termination, or discontinuation of an application.

Definitions

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

"Acceptance Criteria" means numerical limits, ranges, or other suitable measures for acceptance of test results.

"Active Substance" – as defined in Art 4 (3) of Regulation (EU) 2019/6. The term Active Pharmaceutical Ingredient (API) should be considered interchangeable with the term "Active Substance".

"Active Substance Starting Material" means a raw material, intermediate, or an active substance that is used in the production of an active substance and that is incorporated as a significant structural fragment into the structure of the API. An active substance Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house.

"Batch" means a specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval.

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

"Bioburden" means the level and type (e.g. objectionable or not) of micro-organisms that can be present in raw materials, active substance starting materials, intermediates or APIs. Bioburden should not be considered contamination unless the levels have been exceeded or defined objectionable organisms have been detected.

"Calibration" means the demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements.

"Computer System" means a group of hardware components and associated software, designed and assembled to perform a specific function or group of functions.

"Computerized System" means a process or operation integrated with a computer system.

"Contamination" means the undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or active substance during production, sampling, packaging or repackaging, storage or transport.

"Contract Manufacturer" means a manufacturer performing some aspect of manufacturing on behalf of the original manufacturer.

"Critical" describes a process step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the active substance meets its specification.

"Cross-Contamination" means the contamination of a material or product with another material or product.

”Deviation” means the departure from an approved instruction or established standard.

“Documentation” means written procedures, instructions, contracts, records and data, in paper or in electronic form.

”Veterinary Medicinal Product” means the dosage form in the final immediate packaging intended for marketing. (Reference Q1A).

”Impurity” means any component present in the intermediate or active substance that is not the desired entity.

”Impurity Profile” means a description of the identified and unidentified impurities present in an active substance.

”In-Process Control (or Process Control)” means the checks performed during production in order to monitor and, if appropriate, to adjust the process and/or to ensure that the intermediate or active substance conforms to its specifications.

”Intermediate” means a material produced during steps of the processing of an active substance that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated. (Note: this Guide only addresses those intermediates produced after the point that the company has defined as the point at which the production of the active substance begins.)

”Manufacture” means all operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release, storage, and distribution of APIs and related controls.

”Material” means a general term used to denote raw materials (starting materials, reagents, solvents), process aids, intermediates, APIs and packaging and labelling materials.

”Mother Liquor” means the residual liquid which remains after the crystallization or isolation processes. A mother liquor may contain unreacted materials, intermediates, levels of the active substance and/or impurities. It may be used for further processing.

”Packaging Material” means any material intended to protect an intermediate or active substance during storage and transport.

”Procedure” means a documented description of the operations to be performed, the precautions to be taken and measures to be applied directly or indirectly related to the manufacture of an intermediate or API.

”Process Aids” means materials, excluding solvents, used as an aid in the manufacture of an intermediate or active substance that do not themselves participate in a chemical or biological reaction (e.g. filter aid, activated carbon, etc).

”Production” means all operations involved in the preparation of an active substance from receipt of materials through processing and packaging of the API.

”Qualification” means the action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.

”Quality Assurance (QA)” means the sum total of the organised arrangements made with the object of ensuring that all APIs are of the quality required for their intended use and that quality systems are maintained.

”Quality Control (QC)” means checking or testing that specifications are met.

”Quality Unit(s)” means an organizational unit independent of production which fulfills both Quality Assurance and Quality Control responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

”Quarantine” means the status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection.

”Raw Material” means a general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or APIs.

”Reference Standard, Primary” means a substance that has been shown by an extensive set of analytical tests to be authentic material that should be of high purity. This standard can be: (1) obtained from an officially recognised source, or (2) prepared by independent synthesis, or (3) obtained from existing production material of high purity, or (4) prepared by further purification of existing production material.

”Reference Standard, Secondary” means a substance of established quality and purity, as shown by comparison to a primary reference standard, used as a reference standard for routine laboratory analysis.

”Reprocessing” means introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography, milling) that are part of the established manufacturing process. Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process, and not reprocessing.

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

”Reworking” means subjecting an intermediate or active substance that does not conform to standards or specifications to one or more processing steps that are different from the established manufacturing process to obtain acceptable quality intermediate or active substance (e.g., recrystallizing with a different solvent).

”Signed (signature)” means the record of the individual who performed a particular action or review. This record can be initials, full handwritten signature, personal seal, or authenticated and secure electronic signature.

”Solvent” means an inorganic or organic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of an intermediate or API.

”Specification” means a list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the test described. It establishes the set of criteria to which a material should conform to be considered acceptable for its intended use. ”Conformance to specification” means that the material, when tested according to the listed analytical procedures, will meet the listed acceptance criteria.

”Validation” means a documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting pre-determined acceptance criteria.

”Validation Protocol” means a written plan stating how validation will be conducted and defining acceptance criteria. For example, the protocol for a manufacturing process identifies processing equipment, critical process parameters/operating ranges, product characteristics, sampling, test data to be collected, number of validation runs, and acceptable test results.

”Yield, Expected” means the quantity of material or the percentage of theoretical yield anticipated at any appropriate phase of production based on previous laboratory, pilot scale, or manufacturing data.

”Yield, Theoretical” means the quantity that would be produced at any appropriate phase of production, based upon the quantity of material to be used, in the absence of any loss or error in actual production.

Advice on the content of the implementing acts in what regards animal welfare

Animal welfare

General

A mandate was given for an expert group on implementing measures under Article 93(2) of Regulation (EU) 2019/6 as regards the good manufacturing practice for veterinary medicinal products and active substances used as starting materials to provide scientific recommendations on measures relating to GMP for active substances used as starting materials in veterinary medicinal products taking into account the Union and international standards of animal welfare when materials are prepared from animals and animals are used for the production or testing of veterinary medicinal products. Recital 68 of the NVR states that the good manufacturing practice should take into account the Union and international standards of animal welfare when active substances are prepared from animals.

Main aspects on use of animals in the manufacturing of medicinal products:

- Use of animal materials as starting materials including active substances and media components (blood, plasma, serum, antibodies, tissues, organs, primary cells, breeder eggs, fluids, proteins, hormones);

- Use of animals for testing (safety, potency).

Union Standards

The protection and welfare of animals is a priority for the EU. This includes wildlife, zoo animals, farm animals, animals in transport and animals used for scientific purposes. In recent decades, concern for animal welfare has been growing, the EU has developed and expanded the scope of legislation in this area to achieving the world´s highest animal welfare standards. Animal welfare is a value of the Union that is enshrined in Article 13 of the Treaty on the Functioning of the European Union (TFEU1).

Directive 98/58/EC lays down minimum standards for the protection of animals bred or kept for farming purposes. The horizontal directive lays down the standards for the protection of all farmed animals, specific acts cover the protection of pigs, calves, laying hens and chicken. There are also rules for welfare standards for the transport of animals and conditions at the time of their killing. Legislation has been put in place for wild animals in zoos.

Regarding animals in science, EU legislation is unique as it sets a final goal of full replacement of all animals used for scientific and educational purposes and is taking concrete action towards that goal. Studies that still need to be carried out on animals must be done in compliance with specific regulations that aim to improve the welfare of those animals.

The use of animals in scientific procedures including regulatory testing of veterinary medicinal products is strictly controlled within the EU, in accordance with Directive 2010/63/EU. Regulation (EU) 2019/1010 amending Directive 2010/63/EU introduced a new level of transparency to help progress towards eventually replacing animal use in science.

The Directive 2010/63/EU shall apply where animals are used or intended to be used in procedures, or bred specifically so that their organs or tissues may be used for scientific purposes. This Directive shall not apply for veterinary clinical trials required for the marketing authorization of a veterinary medicinal product.

This legislation expounds the principles of 3Rs (replacement, reduction and refinement), lays down strict conditions for the conduct of animal studies, and further articulates the ultimate goal to replace the use of all live animals for scientific and educational purposes as soon as it is possible to do so.

For animals used in scientific procedures to be used for the project purpose, various categories of project purposes are laid down in Commission Implementing Decision (EU) 2020/569 of 16 April 2020 establishing a common format and information content for the submission of the information to be reported by Member States pursuant to Directive 2010/63/EU of the European Parliament and of the Council on the protection of animals used for scientific purposes and repealing Commission Implementing Decision 2012/707/EU).

In addition to the requirements of Directive 2010/63/EU in relation to the welfare of animals in scientific procedures and the need to ensure appropriate implementation of the 3R principles, there is also a legal obligation to comply with the standards outlined in Annex III to Directive 2010/63/EU – Requirements for Establishments and for the Care and Accommodation of Animals, and an expectation of adherence to EC Recommendation 2007 – Guidelines for the accommodation and care of animals used for experimental and other scientific purposes.

If a substance is prepared from animals within the EU, the use of a live animal to harvest that substance does not fall under the scope of Directive 2010/63/EU on the protection of animals used for scientific purposes.

Art. 1 (2.) says: This Directive shall apply where animals are used or intended to be used in procedures, or bred specifically so that their organs or tissues may be used for scientific purposes.

According to Art. 3 (1) 'procedure' means any use, invasive or non-invasive of an animal for experimental or other scientific purposes, with known or unknown outcome, or educational purposes, which may cause the animal a level of pain, suffering, distress or lasting harm equivalent to, or higher than, that caused by the introduction of a needle in accordance with good veterinary practice.

According to Art. 5 procedures may be carried out for the following purposes only: (a) basic research; (b) translational or applied research with any of the following aims: (i) the avoidance, prevention, diagnosis or treatment of disease, ill-health or other abnormality or their effects in human beings, animals or plants. According to Art. 34 of Directive 2010/63/EU Member States shall ensure that the competent authorities carry out regular inspections of all breeders, suppliers and users, including their establishments, to verify compliance with the requirements of this Directive – competent bodies other than GMP inspectorates perform these inspections.

Directive 2010/63/EU is based on the harmonisation of the internal market. It regulates the use of animals in research and testing in the territory of the Union and cannot regulate activities outside the Union. Also, this Directive does not contain policy specific prohibitions, and does not describe when animals are required to be used. Additionally, the production of medicinal products is generally outside the scope of Directive 2010/63/EU. Only annex 5 of the current GMP guidelines refers to the general requirements for animal quarters, care and quarantine which are laid down in Directive 86/609/EEC which was replaced by 2010/63/EU.

Non-clinical health and environmental safety studies are planned, performed, monitored, recorded, reported and archived according to GLP Directive 2004/9/EC in which is determined the care, housing and containment of biological test systems.

As most EU animal welfare standards do not apply to imported products, concerns have been raised about the level of animal protection in partner countries. The lack of import standards could create

competitive disadvantages for EU manufacturers, who have to meet higher standards and associated costs. This situation must also be taken into account when, for example, active substances are prepared from animals in third countries, competitive disadvantages for EU manufacturers must be avoided.

According to EMA /CVMP/3Rs/506841/2017 Statement of the Committee for Medicinal Products for Veterinary Use, position on ethical use of animals in the testing, development and manufacture of veterinary medicines, the expectation should be that the animal studies needed to support the evaluation of a medicine intended for veterinary use will take into account EU requirements whether or not those animal studies are conducted within or outside the EU. The MAH should therefore consider EU ethical values and welfare standards relating to towards animals and requirements under EU legislation when developing medicines that are intended for marketing in the EU. In addition to applying the 3R principles to reduce, remove or replace the use of animals as outlined in the Directive 2010/63/EU, the use of animals for the manufacture or for any control tests for any veterinary medicine intended for supply in the EU is expected to conform to EU ethical principles and welfare standards. Animal studies or husbandry practices that would not be allowed in the EU should not be undertaken instead outside of the EU.

- Although, the Directive 2010/63/EU does not apply directly for animals used in manufacture of medicinal products, the 3R principles are an obligation laid down in the European Pharmacopeia when performing tests with animals: In accordance with the provisions of the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (European Treaty Series No 123), drawn up under the auspices of the Council of Europe, the Commission is committed to restricting the use of animals for pharmacopoeia trials whenever possible and encourages all who contribute to this work to look for alternative methods with it. A study with animals is included in a monograph only if it can be clearly shown that it is necessary to ensure a satisfactory study within the meaning of the pharmacopoeia.

- It is clearly said in chapter 1.1.2.2 3) that the European Pharmacopeia has a duty to follow the 3 R principles to reduce testing on animals: In accordance with the 3Rs (Replacement, Reduction, Refinement) principle of the European Convention for the Protection of Vertebrate Animals used for experimental and other scientific purposes, the European Pharmacopoeia has committed itself to phasing out the use of animals for testing purposes.

    - The safety test for every batch of vaccine has already been deleted in the recent past to reduce the use of animals but many third countries still demand this test.

GMP is, a priori, intended to control the manufacture of medicines in order to ensure their quality and patient/target animal safety, and in principle do not focus on animal welfare aspects. With reference to Directive 86/609/EEC, which was replaced by Directive 2010/63/EU, there are some GMP requirements connected to use of animals:

- condition used for animals intended for testing components, materials or products (Part I GMP Guide Chap. 6 item 6.25),

- frequency of testing where on-going stability monitoring would normally require testing using animals (Part I Chap. 6 item 6.32),

- isolation of animal houses from other areas (Part I Chap. 3 item 3.33.),

- requirements for premises for animals intended for production (Annex 5 points 18, 20),

- principles for breeding experimental animals, animal care, health (Annex 5 points 28-31)

- GMP inspectors can inspect the quality control procedures according to MA and Ph. Eu. requirements in order to ensure the principles of 3Rs are followed.
- GMP inspectors can inspect the compliance with the requirements in annex 5 for immunological veterinary medicinal products.

Part II of the GMP Guide doesn´t specify requirements for animal welfare. These guidelines exclude whole blood and plasma; however, it does include active substances that are produced using blood or plasma as raw materials. The manufacturer should designate and document the rationale for the point at which production of the active substance begins. Table 1 gives guidance on the point at which the Active Substance Starting Material is normally introduced into the process. From this point on, appropriate GMP, as defined in these guidelines, should apply to these intermediate and/or active substance manufacturing steps. In terms of active substances derived from animal sources, this GMP guide is applicable from the point of the introduction of active substance starting material into process. Collection of organ, fluid and tissue is not covered by this guideline.

Recently, animal welfare organizations have voiced concerns over the conditions and treatment of pregnant mares kept for ECG production in some countries. Equine Chorionic Gonadotropin is an important hormone produced by the placenta of pregnant mares and extracted from the blood of these mares. Animal welfare problems may arise if too much blood is collected at one time or during repeated collections or if the mares are not managed well. In some countries, mares are aborted after several months of pregnancy to permit them to become pregnant a second time in a year.

For this reason, for the production of Pregnant Mare Serum Gonadotropin (PMSG) the welfare standards for the treatment of mares should be equivalent whether or not the production facilities are based in the EU or third regions. It is also to be noted that there is currently a revision process ongoing of the Council Directive 98/58/EC of 20 July 1998 concerning the protection of animals kept for farming purposes. The Commission foresees to develop and propose additional provisions for the welfare of horses that could include empowerments to act based on future opinions of the European Food Safety Authority. Those general provisions and specific requirements might have an impact on the conditions of extraction of PMSG.

The group also highlights that other products which use animals during the manufacture should also be considered e. g. immunosera for human use and veterinary use - immunoglobulin fragments obtained from serum or plasma of immunized animals, collection of equine urine from pregnant mares to extract estrogen for treating menopausal symptoms in women, immunoglobulins collected from eggs of immunized poultry.

International Standards

The working group took into account also the draft of VICH guideline GOOD MANUFACTURING PRACTICE GUIDE FOR ACTIVE PHARMACEUTICAL INGREDIENTS used in Veterinary Medicinal Products. International, national, and regional standards implemented in the country/region where the active substance is manufactured, where it is used in the production of a veterinary medicinal product and where such a veterinary medicinal product is marketed must be observed but animal welfare is not specifically covered by this Guide.

International standards applied to animal welfare should also be taken into account. The World Organisation for Animal Health (WOAH, founded as OIE) Terrestrial and Aquatic Animal Health Codes provide standards for the improvement of animal health and welfare and veterinary public health worldwide, including through standards for safe international trade in terrestrial and aquatic animals and their products. The manuals provide a standardized approach to the diagnosis of the diseases listed in

the Terrestrial and Aquatic Codes. These standards should be used by Members to set up measures for the prevention, early detection, reporting and control of pathogenic agents in terrestrial animals (mammals, reptiles, birds and bees), including zoonotic agents. Implementation of the recommendations in the Terrestrial Code ensures the safety of international trade in animals and animal products, while avoiding unjustified sanitary barriers. 183 members countries are members of the OIE. China and India, the significant producers of active substances aren´t between the members. Terrestrial Animal Health Code (2022) in Volume I Section 7 address to Animal Welfare.

This code which sets out guiding principles for animal welfare, critical relationship between animal health and animal welfare, internationally recognised 'five freedoms' (hunger, thirst and malnutrition; fear and distress; physical and thermal discomfort; pain, injury and disease; normal patterns of behaviour), internationally recognised 'three Rs', the use of animals in agriculture, education and research, and for companionship, recreation and entertainment, makes a major contribution to the wellbeing of people.

Chapter 7.8. provides advice and assistance for Member Countries to follow when formulating regulatory requirements for the use of live animals in research and education. The term 'research' includes basic and applied research, testing and the production of biological materials. Animals to be used for production of biologicals and/or humanely killed for harvesting their cells, tissues and organs for scientific purposes are also covered. The system will, in practice, vary from country to country and in accordance with cultural, economic, religious and social factors. However, the OIE recommends that Member Countries address all the essential elements identified in this chapter in formulating a regulatory framework that is appropriate to their local conditions.

Another international standard which is also relevant is the CCAC guidelines on: antibody production. The Canadian Council on Animal Care (CCAC) is responsible for overseeing animal use in research, teaching and testing. It provides the only national oversight of animal-based scientific activities in Canada through a rigorous process of assessment and certification, and standards development and ensures that animals in science are used only when necessary, and that when they are, they receive optimal care according to high-quality, evidence-informed standards. In addition to the Guide to the Care and Use of Experimental Animals, Vol. 1, 2nd Edn., 1993 and Vol. 2, 1984, which lay down general principles for the care and use of animals, the CCAC also publishes guidelines on issues of current and emerging concerns. Compliance with these standards is a requirement to receive a CCAC Certificate of GAP – Good Animal Practice. The CCAC guidelines on antibody production has been developed by the CCAC ad hoc subcommittee on immunological procedures. The purpose of this document is to present guidelines for production of both polyclonal (pAb) and monoclonal antibodies (mAb) that assist investigators and research support personnel to achieve an acceptable immunological result with minimal discomfort for the animals involved.

In the US the Animal Welfare Act (AWA) requires that minimum standards of care and treatment be provided for certain animals bred for commercial sale, used in research, teaching, or testing, transported commercially or exhibited to the public. Animal Welfare Regulation - the Code of Federal Regulations at Animal Welfare 9 C.F.R. Parts 1, 2, and 3 provides detailed guidance and standards drafted and adopted by the USDA to implement and enforce the Animal Welfare Act. The AVMA - the nation's leading advocate for the veterinary profession,among others provides timely and relevant products and services that enhance AVMA members' opportunities for success and service, and support them in protecting the health and welfare of animals in their care. The AVMA offers the integrated principles for developing and evaluating animal welfare policies, resolutions, and actions.

In Asia, Several countries already have laws related to animal welfare but suffer from poor implementation or enforcement. Others are lacking in policies and regulations. In many countries the priorities, funding and personnel are lacking to ensure improved animal welfare.

In 2008, Australia spearheaded the development and formation of the Regional Animal Welfare Strategy for Asia, Far East and Oceania (RAWS) based on the Australian Animal Welfare Strategy to improve animal welfare. RAWS with membership from several countries like Malaysia, Bhutan, China, Indonesia, Republic of Korea and Thailand lead the changes and improvements on animal welfare. All these efforts are expected to increase the level of awareness on animal welfare through effective coordination, communication, education and training to ensure the coordinated regional approach on the implementation of the OIE animal welfare standards, achieve sustainable improvements in animal welfare and develop sustainable mechanism to coordinate and promote animal welfare programs and priorities.

Conclusions and recommendations

To complete this overview on animal welfare standards and problems relating to the introduction of animal welfare requirements in GMP, the expert group has listed below potential issues, short- or medium-term obstacles, limits and negative impacts that would be associated with the inclusion of these type of requirements in GMP for veterinary active substances and GMP for VMP:

- **Negative impact of unilateral implementation** of animal welfare requirements in veterinary GMP without corresponding requirements in human GMP;
- **Risk to availability of VMPs**: manufacturing in the EU would be disadvantaged;
- **The risk of discrepancy** between EU GMP and other international GMP **requirements;**
- **Negative impact on European GMP inspectorates**; no legal rights outside of the EU and lack of qualification to control explicitly animal welfare, GMP inspectors don´t have expertise in animal welfare or the capacity for this activity;
- **Lack of binding international standards** to follow, there is no recognised system of certification which could be used by the inspectorates as proof of good animal welfare standards.

After considering all the above factors the expert group recommends the following:

- **In a future revision of legislation for veterinary and human medicinal products, consideration should be given to develop provisions to place the responsibility on the MAH to declare, in the dossier, the AW conditions relevant to EU requirements, international standards or available certification of animal welfare where starting materials are produced from animals. Moreover, animal welfare and the existence of alternative production methods should be considered in the benefit-risk assessment of the medicinal product. (This would guarantee the consideration of animal welfare early enough and in the right context.)**
- **The group points out the importance of maintaining the same requirements for human and veterinary medicines and not to introduce more restrictive requirements for veterinary medicines than human side.**
- **Taking into account the current revision process for the Council Directive 98/58/EC of 20 July 1998 concerning the protection of animals kept for farming purposes and the impact that this revision might have on the conditions for the extraction of PMSG, the group advises to wait for the outcome of the ongoing revision of the Council Directive 98/58/EC.**

- **The group recommends to wait for the development and implementation of global harmonized guidance, after which a revision of GMP guidance can be considered, thus ensuring alignment between requirements applicable to veterinary and human medicinal products in all international regions.**
- **The group points that any discrepancy between EU GMP and other international GMP will have a negative impact on existing MRAs. Global, binding standards for animal welfare are urgently needed before establishing appropriate requirements within the EU.**

- **After the alignment of EU and international standards as well requirements for human and veterinary medicines it should be possible for GMP inspectors to verify animal welfare at least indirectly by way of a broad requirement for AW control in part I GMP Guide, point 5.27 Starting materials as proposed in the underlined text below:**

"5.27 The selection, qualification, approval and maintenance of suppliers of starting materials, together with their purchase and acceptance, should be documented as part of the pharmaceutical quality system. The level of supervision should be proportionate to the risks posed by the individual materials, taking account of their source, manufacturing process, supply chain complexity and the final use to which the material is put in the medicinal product. *When active substances of medicinal products are prepared from animals, EU and international animal welfare standards should be taken into account, during the approval of the supplier evaluation.* The supporting evidence for each supplier/material approval should be maintained. Staff involved in these activities should have a current knowledge of the suppliers, the supply chain and the associated risks involved. Where possible, starting materials should be purchased directly from the manufacturer of the starting material".

- **A broader requirement for AW control in part II GMP Guide, point 7.10 Material management – General controls – could also be included as proposed in the underlined text below:**

"7.10 Manufacturers of intermediates and/or APIs should have a system for evaluating the suppliers of critical materials. *When active substances are derived from animal sources, EU and international animal welfare standards should be taken into account during the approval of the supplier and the supporting evidence for such evaluations should be maintained.*"

Advice on the content of the implementing acts in what regards environmental measures

Environmental Aspect

General

While having undeniable benefits, pharmaceuticals for veterinary or human use, contain active substances that interact biologically at low concentrations with living systems when released in the environment. Residues of these pharmaceutical products may enter the environment during their manufacture, use and disposal. These pharmaceuticals in the environment, have been identified in various environmental locations, including sewage and surface water, groundwater, soil, air and non-target organisms. That environmental pollution caused by human and veterinary pharmaceuticals is considered as an emerging and global environmental problem. Not only does this have a negative impact on the environment itself, some waste and residues may have endocrine-disrupting potential and others may increase the risk of antimicrobial resistance (Source - OECD (2019), Pharmaceutical Residues in Freshwater: Hazards and Policy Responses, OECD Studies on Water, OECD Publishing, Paris,).

In order to not only reduce existing known environmental threats, but to also minimise potential hazards, an efficient abatement strategy requires to combine policy options at various stages of the pharmaceutical life cycle, using source-directed, use-orientated and end-of-pipe measures. A focus on preventive options early in the pharmaceutical life cycle, may deliver the most long-term, cost-effective and large-scale benefits.

In March 2019, the European Commission adopted the EU Strategic Approach to Pharmaceuticals in the Environment. The Approach which addresses pharmaceuticals for both human and veterinary use identifies six action areas concerning all stages of the pharmaceutical life cycle, where improvements can be made. Among them, proposed measures include source-directed approaches to promote greener manufacturing and to impose, incentivise or encourage measures in order to prevent the release of pharmaceuticals into terrestrial as well as the aquatic environment.

In line with this purpose, the Regulation 2019/6 introduces in recital 68, that the good manufacturing practice (GMP) should take into account measures to prevent or minimise discharge of active substances into the environment following an evaluation of the impact of such measures.

Although the largest source of pharmaceuticals entering the environment is their use, other less impactful sources have to be considered such as the discharge of effluent from manufacturing plants. Moreover, there is an asymmetric risk of discharge across the manufacturing supply chain: In the manufacturing supply chain of pharmaceuticals, the production phase of active substances such as that encountered in some of the countries (especially those outside the Union) that are major global producers of pharmaceuticals poses the highest risk of discharge than the production of finished products, because high production volumes lead to potentially high local concentrations in waste and wastewater and because the production of APIs typically takes place in liquid form which increases the risk of their transfer to the environment.

Besides that, other robust instruments to prevent the release of pharmaceutical residues to environment could complete GMP such as but not limited to:

- environment risk assessment & mitigation applied to the risk of discharge of manufacturing waste containing API,
- Environmental quality norms and water quality,

- standards emissions standards and limits/permits,
- substances ban,
- requirements of disclosure with regard to production chains (GMP and environmental audit),
- environmental criteria for green public procurement,
- Guidance documents that assist industrial operators with the design, operation, maintenance and decommission of manufacturing plants in compliance with environmental quality standards and discharge permit conditions.

These actions would concern primarily all pharmaceutical manufacturers engaging in synthesis and/ or production of active substances and, secondly, manufacturing sites for finished pharmaceutical products.

Pharmaceuticals used in veterinary and human sector recognised as potential environmental and food hazards are primarily medicinal products used in high volumes and pharmaceutical groups with special properties such as hormones, anticancer medicinal products, anti-inflammatory products, and antimicrobial medicinal products. Without any doubt, the development of antimicrobial resistance (AMR) is by far the largest risk for global public health of having pharmaceutical residues in the environment. AMR is a major European and global societal problem, involving many different sectors e.g. human medicine, veterinary medicine, animal husbandry, agriculture, environment and trade. It cannot be successfully tackled through isolated, sectoral efforts.

In 2019, the World Health Organization (WHO) declared antimicrobial resistance as one of the top 10 global public health threats facing humanity. In July 2022, the Commission, together with the Member States, identified AMR as one of the top three priority health threats.

On 26 April 2023, the European Commission adopted a proposal for a Council Recommendation on stepping up EU actions to combat antimicrobial resistance in a One Health approach. In this recommendation the council invite Commission and member states to support the WHO initiatives to prepare guidance on how good manufacturing practices should be implemented to waste and wastewater management in the context of the production of antimicrobials, following the WHO's Executive Board decision of 30 November 2018 on that matter.

It should be noted that, since the beginning, GMP have been, a priori, intended to control the manufacture of medicines in order to ensure their quality and patient/target animal safety, and in principle do not focus on the environmental aspects of these. However, through its successive versions, GMP have included many aspects that can impact the protection of the environment and workers. By the way, there is some set of GMP clauses fully reproduced in this advice (e.g. cross contamination strategy in Part I Chap. 3 item 3.6, Chap. 5 5.17 to 5.22, and Part II Chap 4.4. containment, Chap 4.6 Sewage and Refuse) that, if fully implemented, should therefore prevent many different types of waste from contaminating the environment.

To complete this overview on proposal for environmental measures in GMP, the expert group has listed below already identified potential setbacks, short- or medium-term obstacles, limits and negative impacts that could be associated to the inclusion of these type of requirements in GMP for veterinary active substances and GMP for VMP:

- Impact of an unilateral implementation of environmental measure to vet sector:

    - **Risk on availability**: Vet sector is a small market (4-5%) comparing to the human market. Introducing environmental measures in IA on GMP for VMP and GMP for veterinary active substances would introduce more restrictive requirements for vet side than human side. This could lead to at best to an increase in the investment and financial

burden for vet sector only and, at worst to a dissuade in the supply of raw materials by APIs manufacturers, particularly in third countries, to vet sector, becoming less commercially attractive and more restrictive than human side. These consequences would go against the Reg 2019/6 objectives of reducing the administrative and financial burden, enhancing the internal market and increasing the availability of veterinary medicinal products.

- **Risk on traceability and circumvention**: the fact that the same active substance is often produced for use in both veterinary medicinal products and medicinal products for human use and that such active substances are produced on the same manufacturing sites would encourage the active substance manufacturers in third countries to continue to produce on the less restrictive requirements (i.e. human), to export them to Europe labelled as human active substances and then once in Europe, nothing would prevent any broker or distributor to feed vet sector with these API.

- Impact in relation to applicability for 3rd countries:

  - **The risk of discrepancy** between EU GMP and other international GMP thus impacting MRA and other reliance concepts, as well as EU manufacturers' competitiveness. The process of incorporating environmental criteria into GMP would need to be carefully managed to ensure buy-in and prevent withdrawal of GMP agreements by countries.

  - **Risk for evaluation**: There is a number of impacted sites located in third countries that are not specifically inspected currently (only audited by QP of the MIA holder in EU – MS have not sufficient human resources to inspect all);

  - **Risk for implementation**: There could be differences between the interests of consumer states (EU) and producer states (3rd countries) in implementing environmental measures during manufacturing, as long as there is no international harmonised approach. Action on pharmaceuticals in the environment is much more likely to be extended and sustained if it is mainstreamed into broader health, agricultural and environmental projects (e.g. WHO One Health approach provides such a framework).

  - **Risk for availability**: Implementing such criteria would take time and put the whole GMP framework at risk if not adopted internationally, which potentially could result in trade and patient/animal/user access related issue in case of non-compliance on this area.

- Impact on EU GMP inspectorate:

  - **Lack of qualifications and accreditation**: EU GMP inspectors have no background (training, experience and legal rights) on environmental aspect;
  - **Risk of discrepancy and competency**: the verification of environmental standards within the EU is usually performed by specific inspection bodies authorised by dedicated regulations other than GMP inspectorate;
  - **Lack of human resources**: The shift of the burden on the EU GMP inspectorate's shoulders without any additional resources, while in the meantime resources are already

very limited and focused on the quality of the product, especially for the inspection of sites within third countries;

- Impact in relation with EU/international standards and threshold:

    - **Lack of standards and limits**: Difficulties without the determination of international / European specific discharge thresholds or health based targets for all active substances in relevant environmental compartments;

    - **Lack of means for concrete applicability**: There are many interrogations on practicality relating to the verifications and the compliance management process (e.g., determination of antibiotic limits for the effluents, etc.) especially in third countries.

According to the European and international context and taking in account the current high uncertainty of benefits for implementing unilaterally such environmental measures in GMP to vet sector only, the expert group recommend:

1. for the time being, to adopt some form of pause,

2. to support WHO initiatives to prepare guidance on how good manufacturing practices should be implemented to waste and wastewater management in the context of the production of antimicrobials and;

3. to assess then, when published, the opportunity for updating the IA on GMP for VMP and GMP for vAPI, together with the human side which is currently involved in the Reform of the EU pharmaceutical legislation.