EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

The Director-General

Brussels
SANTE.DDG2.E.5/LG/ci (2022)5880615

Sent by e-mail only

Dear Ms Cooke,

Subject: 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

On 28 January 2022, the Regulation on veterinary medicinal products ('VMP Regulation') became applicable.

According to Article 93(2) of the VMP Regulation, the Commission is to adopt, by means of implementing acts, measures on Good Manufacturing Practise ('GMP') for veterinary medicinal products and active substances used as starting materials.

The GMP requirements set out in the VMP Regulation apply to veterinary medicinal products authorised in accordance with Article 5, to homeopathic veterinary medicinal products registered in accordance with Article 86, to veterinary medicinal products allowed to be used in a Member State in accordance with Article 5(6), to inactivated immunological veterinary medicinal products which are manufactured from pathogens and antigens obtained from an animal or animals in an epidemiological unit and used for the treatment of that animal or those animals in the same epidemiological unit or for the treatment of an animal or animals in a unit having a confirmed epidemiological link (also known as 'inactivated autogenous vaccines'), as well as to the active substances used therein.

Article 153(4) requires the Commission to adopt the necessary implementing acts at the latest by 29 January 2025. In light of the strict timeline set for the adoption of the required implementing acts, I would like to request the Agency to provide scientific advice to inform the adoption of the measures.

For the requirements on GMP for active substances used as starting materials in veterinary medicinal products, please take into account the following:

Ms Emer Cooke
Executive Director
European Medicines Agency
Domenico Scarlattilaan 6
NL-1083 HS Amsterdam
E-mail: emer.cooke@ema.europa.eu

- the policy reasoning and purpose of GMP to ensure a quality warranty system on the manufacturing of active substances used as starting materials in 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 published in *EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines*;

- the ongoing work on the revision of Annex 4 and 5 to *EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines*;

- the ongoing work on a GMP guide for Active Pharmaceutical Ingredients used in veterinary medicinal products developed through the Veterinary International Conference on Harmonisation (VICH);

- existing international standards and guidelines on GMP of active substances, e.g. ICH Q7 *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients* and the PIC/S GMP Guide (*Part II: Basic Requirements for Active Pharmaceutical Ingredients*), PE 009-16 (Part II), WHO *Good Manufacturing Practices for Active Pharmaceutical Ingredients (Bulk Drug Substances)*, Annex 2, WHO Technical Report Series 957, 2010 and international 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 active substances used as starting materials in medicinal products for human use and in veterinary medicinal products;

- the fact that the same active substance is often produced for use in both veterinary medicinal products and medicinal products for human use, that such active substances are 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 active substances used in novel therapy veterinary medicinal products as defined in Article 4(43) considering the specific nature of those products;

- if the GMP requirements need to be adapted for the manufacturing of active substances used in homeopathic veterinary medicinal products registered in accordance with Article 86 considering the specific nature of those products;

- 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.

For the requirements on GMP for veterinary medicinal products, please take into account the following:

- 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.

When elaborating on the above, the objectives of Regulation (EU) 2019/6, namely 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*' should be considered.

Relevant excerpts from the VMP Regulation are included in Annex I for your convenience.

We would kindly ask for your contribution by the end of December 2023. We would also ask that the Agency update our services on the main progress of its work quarterly.

We would like to thank you for your collaboration.

Yours sincerely,

[e-signed]
Sandra GALLINA

Encl.: Annex I

c.c.: Mr I. Claassen (EMA)
Mr K. Berend, Ms E. Zamora Escribano, Mr L. Goranov,
Mr D. Minne (SANTE)

Annex I

EXCERPTS FROM THE VMP REGULATION CONTAINING REFERENCES TO GOOD MANUFACTURING PRACTICE FOR ACTIVE SUBSTANCES/VMPs/AUTOGENOUS VACCINES

Recital 66

In order to facilitate the movement of veterinary medicinal products and to prevent checks carried out in one Member State being repeated in others, minimum requirements should be applied to veterinary medicinal products manufactured in, or imported from, third countries.

Recital 67

The quality of veterinary medicinal products manufactured within the Union should be guaranteed by requiring compliance with the principles of good manufacturing practice for medicinal products irrespective of their final destination.

Recital 68

The good manufacturing practice for the purpose of this Regulation should take into account 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 should be also taken into account. Any such measures should only be adopted following an evaluation of their impact.

Recital 69

In order to ensure the uniform application of principles of good manufacturing practice and good distribution practice, the compilation of Union procedures for inspections and exchange of information should serve as a basis for competent authorities when performing controls on manufacturers and wholesale distributors.

Recital 70

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

Article 2

Scope

[…]

2. In addition to the products referred to in paragraph 1 of this Article, Articles 94 and 95 shall also apply to active substances used as starting materials in veterinary medicinal products.

3. In addition to the products referred to in paragraph 1 of this Article, Articles 94, 105, 108, 117, 120, 123 and 134 shall also apply to inactivated immunological veterinary medicinal products which are manufactured from pathogens and antigens obtained from an animal or animals in an epidemiological unit and used for the treatment of that animal or those animals in the same epidemiological unit or for the treatment of an animal or animals in a unit having a confirmed epidemiological link.

4. By way of derogation from paragraphs 1 and 2 of this Article, only Articles 55, 56, 94, 117, 119, 123, 134 and Section 5 of Chapter IV shall apply to veterinary medicinal products authorised in accordance with Article 5(6).

5. By way of derogation from paragraph 1 of this Article, Articles 5 to 15, 17 to 33, 35 to 54, 57 to 72, 82 to 84, 95, 98, 106, 107, 110, 112 to 116, 128, 130 and 136 shall not apply to homeopathic veterinary medicinal products which are registered in accordance with Article 86.

Article 87

Application and procedure for registration of homeopathic veterinary medicinal products

1. The following documents shall be included in the application for a registration of a homeopathic veterinary medicinal product:

[…]

(d) the manufacturing authorisation for the homeopathic veterinary medicinal products concerned;

Article 93

Obligations of the holder of a manufacturing authorisation

1. The holder of a manufacturing authorisation shall:

[…]

(j) comply with good manufacturing practice for veterinary medicinal products and use as starting materials only active substances which have been manufactured in accordance with good manufacturing practice for active substances and distributed in accordance with good distribution practice for active substances;

Article 94

Certificates of good manufacturing practice

1. Within 90 days of an inspection, the competent authority shall issue a certificate of good manufacturing practice of the manufacturer for the manufacturing site concerned if the inspection establishes that the manufacturer in question is in compliance with the requirements laid down in this Regulation and with the implementing act referred to in Article 93(2).

2. If the outcome of the inspection referred to in paragraph 1 of this Article is that the manufacturer does not comply with good manufacturing practice, such information shall be entered into the manufacturing and wholesale distribution database referred to in Article 91.

3. The conclusions reached following an inspection of a manufacturer shall be valid throughout the Union.

4. A competent authority, the Commission or the Agency may require a manufacturer established in a third country to undergo an inspection as referred to in paragraph 1, without prejudice to any arrangements which may have been concluded between the Union and a third country.

5. Importers of veterinary medicinal products shall ensure, before those products are supplied to the Union, that the manufacturer established in a third country is in possession of a certificate of good manufacturing practice issued by a competent authority or, where the third country is party to an arrangement concluded between the Union and the third country, there is an equivalent confirmation.

Article 95

Importers, manufacturers and distributors of active substances established in the Union

1. Importers, manufacturers and distributors of active substances used as starting materials in veterinary medicinal products, that are established in the Union, shall register their activity with the competent authority of the Member State in which they are established and shall comply with good manufacturing practice or good distribution practice, as applicable;

Article 97

Qualified person responsible for manufacturing and batch release

[…]

6. The qualified person referred to in paragraph 1 shall ensure that each batch of the veterinary medicinal products is manufactured in compliance with good manufacturing practice, and tested in compliance with the terms of the marketing authorisation. That qualified person shall draw up a control report to that effect. Such control reports shall be valid throughout the Union.

7. Where veterinary medicinal products are imported, the qualified person referred to in paragraph 1 shall ensure that each imported production batch has undergone in the Union a full qualitative and a quantitative analysis of at least all the active substances, and all the other tests necessary to ensure the quality of the veterinary medicinal products in accordance with the requirements of the marketing authorisation and that the batch manufactured is in compliance with good manufacturing practice.

Article 153

Transitional provisions regarding delegated and implementing acts

[…]

4. Without prejudice to the date of application of this Regulation, the Commission shall adopt the delegated acts referred to in Article 109(1) and the implementing acts referred to in Articles 17(2) and (3), 93(2), 109(2) and 115(5) at the latest by 29 January 2025. Such delegated and implementing acts shall apply at the earliest on 28 January 2022.

Article 159

Transitional provisions regarding certain certificates of good manufacturing practice

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).