Proposal of the

Italian Experimental Zooprophylactic Institutes

(*Istituti Zooprofilattici Sperimentali*)

EU-GMP for veterinary autogenous vaccines

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Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC defines 'high quality, safety and efficacy parameters for veterinary medicinal products in order to address common concerns regarding the protection of public health, animal health and the environment (recital 9). However, 'inactivated immunological veterinary medicinal products manufactured from pathogens and antigens obtained from an animal or animal in an epidemiological unit and used for the treatment of that animal or such animals in the same epidemiological unit or for the treatment of an animal or animal in a unit for which an epidemiological correlation has been confirmed' (Article 2(3)) 'should be manufactured in accordance with the principles of good manufacturing practice, detailed guidance on good manufacturing practice should be developed specifically for those products as they are manufactured differently from industrially prepared medicinal products. That would preserve their quality without hindering their manufacture and availability.' (recital 70).

Only articles 94, 105, 108, 117, 120, 123, and 134 of Regulation (EU) 2019/6 shall apply to autogenous vaccines.

To support the development of specific guidelines for the production of autogenous veterinary vaccines, complementing other documents already available such as document EMA/CMDv/452656/2016 REC-002-01: Recommendations for the manufacture, control, and use of inactivated autogenous veterinary vaccines within the EEA, and having regard to EMAV-Proposal: EU-GMP-Annex for Autogenous Vaccines_rev 01 — March 2021, the Experimental Zooprophylactic Institutes (II.ZZ.SS.) have developed a Position Paper aimed at defining rules that ensure a safe and high-quality product while preserving its peculiarities such as the need for rapid set-up times, the extemporaneity of production, the need for simultaneous processing of a high number of batches, set up also with a limited number of doses (even only 1 dose), the variability and specificity of antigenic formulation carried out on the basis of highly specialised diagnostic tests and the need to maintain low costs in products intended for small producers.

The Experimental Zooprophylactic Institutes

The Italian Experimental Zooprophylactic Institutes (II.ZZ.SS.) are bodies governed by public law that work together with the Ministry of Health. They are in close contact with the regional veterinary services and the ASL (Local Sanitary Authorities) and support the National Health Service with field activities and laboratory diagnostics, epidemiological surveillance, research and training in the areas of animal health and welfare, zoonoses, diseases transmitted from animals to humans and food safety, in compliance with the quality and prevention standards established by the European Union.

The IIZZSS on the national territory constitute a network of excellence that is able to provide health services both in the context of the planned activities and in emergency situations, also through the work of the National Reference Centres. They are an integrated health facility able to ensure a network of services to verify the health of food and the environment, for the protection of human health.

The Network of Institutes in Numbers:

- 10 Headquarters and 90 Peripheral Diagnostic Sections
- More than 2,500 employees, graduates in Veterinary Medicine, Biological Sciences, Chemistry, Computer Science, Statistics, Agricultural Sciences and Economics, and Humanities, Biomedical Laboratory Technicians, and Administrative Staff.

The Zooprophylactic Institutes are the only bodies authorized to produce veterinary autogenous vaccines in Italy, in accordance with Ministerial Decree 287/94 laying down rules on the production, use, and control of inactivated immunological veterinary medicinal products, having characteristics of autogenous vaccines, OJ General Series No.111 of 14-05-1994.

Premise

Vaccination is one of the most effective tools to prevent animal diseases and promote their health and well-being while improving the production of safe food to protect the consumer. The production of vaccines is one of the oldest and most important activities of IIZZSS. In fact, since their foundation the Institutes have focused their service in the field of public health, carrying out diagnostic and prevention activities with the preparation of specific vaccines for infectious diseases of income animals. In the period prior to the advent of antibiotics and the development of the pharmaceutical industry, autogenous immunological preparations were the only irreplaceable intervention tool for diffuse diseases, often zoonotic. Subsequently, autogenous vaccines were used only as an alternative or associative tool to antibiotic treatment, especially in “minor” animal species that affect a non-global market and in non-intensive farms, with a limited number of animals with family-type management. It follows that their use is carried out in contexts where the registered immunological medicinal products cannot be used or where they are not available. These vaccines are “highly specific” (including multivalent) vaccines obtained directly from microorganisms present in outbreaks or morbid forms of the herd or animal. The objective of the veterinary autogenous vaccines is to ensure adequate immunization prophylaxis in the absence of specific vaccines regularly authorized (with Marketing Authorisation) or in case of documented impossibility of use in the field for pharmacovigilance reasons. This case also includes the presence of outbreaks or morbid forms caused by specific scientifically recognized variants having little antigenic affinity with the strains present in the vaccines on the market. EU livestock agriculture is evolving towards systems more sensitive to health and the environment. Therefore, more and more farmers are adopting animal-friendly breeding or organic systems, including antibiotic-free breeding systems. The transition to modern farming requires attention to the economic impact of the new policy, including the costs for the production of autogenous vaccines. Moreover, the widespread phenomenon of antimicrobial resistance and the measures proposed at the European level to counteract it, have increased the use of these immunizing medicines in many EU countries.

Position Paper

General principles

This document defines the aspects of good manufacturing practices that can be applied to the manufacture of autogenous vaccines without compromising their quality and safety.

1. GENERAL REQUIREMENTS OF PRODUCERS

The manufacturer must ensure that the production is certified according to regulations and standards (e.g. EN ISO 9001:2015) aimed at guaranteeing the quality of the product. All stages of the production process must be certified. If not specified in this position paper, the principles set out in EN ISO 9001:2015 shall apply. In addition:

1.1. The manufacturer shall be authorized for the production of autogenous vaccines by the Competent Authority certifying by inspection that the requirements included in this document have been complied with.

1.2. All records must allow the traceability of each individual production phase, starting from the isolation and typing of the pathogen, up to the packaging, labelling, and distribution of the product.

1.3. All production phases must be reviewed regularly by the manufacturer and whenever the competent authority so requests.

1.4. For each individual production batch, a dossier must be available where documents relating to the isolation and classification of the pathogen used, the recording of all production phases, the results of the controls, and the Veterinary Medical Recipe are present.

1.5. Each batch of vaccine must be certified by a qualified person (paragraph 9), who attests its production according to certified procedures.

1.6. The producer must retain a rate of each batch for any quality control for at least 6 months after the expiry date.

1.7. The manufacturer must provide all product information (see below) and written instructions on its proper use and disposal.

1.8. The manufacturer must implement a system suitable to report to the Competent Authority any defect in the quality of the product or adverse effects that occurred during the use of the vaccine.

1.9. The autogenous vaccine may only be given for the treatment of the animal or animals in the same epidemiological unit from which the pathogen or antigens have been isolated or for the treatment of an animal or animals in a unit for which an epidemiological correlation has been confirmed.

2. GENERAL STRUCTURAL REQUIREMENTS

2.1. The facility, construction materials, and hygienic conditions of the premises must be suitable for the production of autogenous vaccines.

2.2. Production premises shall be designed and constructed in such a way as to follow the logical order of production and reduce the risk of cross-contamination.

2.3. Access to all premises shall be subject to specific control and only authorized personnel can access production and quality control premises.

2.4. The premises for production shall be separated from the premises where diagnostic tests and recreational activities are carried out, and from technical premises, warehouses, changing rooms, and toilets.

2.5. A detailed plan indicating the intended use of the premises and all the indications provided for in the Emergency Operational Plan, as well as a detailed flow of persons and materials, shall be available and displayed on site.
2.6. A clear separation between low and high-risk contamination areas must be provided, with a compensation zone in which to change clothes and wear specific Personal Protective Equipment (PPE).
2.7. Areas dedicated to the storage of materials, reagents, and finished products should be under appropriate controlled environmental conditions (temperature, humidity).
2.8. A clear physical or temporal separation between the different stages of production (initiation, fermentation/incubation, inactivation of broth, adjuvation, filling) must be ensured.
2.9. Production rooms must be equipped with smooth, impervious, non-damaged surfaces to minimize the accumulation of particulates and microorganisms and to facilitate cleaning and disinfection.
2.10. Airlocks must be provided to provide physical separation between environments and minimize bacterial and particulate contamination between different areas. They should be positioned for both staff and materials moving between different areas.
2.11. The movement of the material between different areas should be based on principles of Quality Risk Management (QRM) with cleaning and disinfection measures commensurate with the risk.
2.12. The most critical stages (preparation of broth, inactivation, washing, filling) must be carried out as described in the "production" chapter.

3. PRODUCTION

3.1. GENERAL REQUIREMENTS

3.1.1. On the basis of the specific characteristics of the pharmaceutical production of veterinary autogenous vaccines, there is a need to design and implement HVAC systems (Heating, Ventilation and Air Conditioning) according to a risk evaluation.
It is also known that these immunizing devices are characterized by high variability in the volume of product per batch (from a few hundred ml to several tens of litres of product) and a large number of batches are produced per year. These characteristics should be duly taken into account in order to guarantee that the duration of the production and release process is compatible with the needs of the therapies (prophylaxis vs metaphylaxis).

3.1.2. Production areas should be ventilated efficiently with respect to the risk analysis. Therefore, air coming from areas at higher risk of contamination should not be able to reach areas with a lower risk of contamination. If necessary, pressure gradients must be installed to avoid this eventuality. Air recirculation between areas can be allowed in case of passage between two exhaust HEPA or ULPA filters, regularly checked and with safeguard systems in case the system fails. The air circulation between the working area and the changing rooms must be separated. The air of the changing rooms must be equipped with a filtering system similar to that of the work area. The following shall be performed in class A/ISO 5 laminar flow hoods/modules:

- Open Product Handle
- Handling of components that will not undergo a sterilization process
- Handling materials in contact with sterile product
- Sterility controls

3.1.3. Given the low-risk profile, it is possible to work in the same room with more antigens in distinct laminar flow hoods/modules, avoiding cross-contamination.

3.1.4. Since production is limited to inactivated vaccines, it is considered that the risk of processing in a laminar flow hood inserted in a Grade 2 environment is, for the particular type of production described above, comparable to a grade 1 processing area (refer to 3.2.6 for grade 1 and 2).

3.1.5. Provided physically separated, multiple batches of vaccine can be stored in the same incubator.

3.1.6. All operators operating within the areas of grade 1 must wear disposable suits or specially dedicated workwear and specific PPE that will be worn in special changing rooms close to access via airlocks.

3.1. MONITORING AND CLASSIFICATION OF PRODUCTION ENVIRONMENTS

3.2.1 All materials in transit from grade 2 to grade 1 areas must be packed in a triple envelope (triple casing) in order to ensure the correct maintenance of microbiological parameters in the destination area.

3.2.2 Environmental monitoring shall be carried out on the basis of an accurate risk assessment.

3.2.3 The premises where vaccines are produced must be checked monthly for microbiological contaminations (bacteria and mycetes).

3.2.4 Planning of cleaning and disinfection of rooms and materials must be done.

3.2.5 The monitoring of the environments involves planned microbiological controls, proceeded and closely linked to the "risk assessment" study developed for the different production premises.

3.2.6 The production environments are classified according to the degree of controlled contamination into two types:

1. Grade 1: areas with high-level contamination control (e.g. production areas, production access areas).

Grade	air sample CFU/m^3	settle plates 90 mm CFU/1hour
1	15	10

2. Grade 2: rooms with low-level contamination control (e.g. materials/product storage, other accessory areas not directly communicating with the production areas).

Grade	air sample CFU/m^3	settle plates 90 mm CFU/1hour
2	250	200

3.2.7 The clear separation between Grade 1 and Grade 2 rooms will be guaranteed by the presence of airlocks for personnel and materials.

3.2.8 For Grade 1 areas, a schedule for periodic decontamination and microbiological monitoring is planned and implemented on the basis of a risk analysis. On the other hand, these operations are optional for Grade 2 premises and do not respond to a defined and precise schedule but rather to the needs that will be assessed from time to time by the head of the production laboratory.

3.2.9 Production units should be provided with separate locker rooms for staff operating in Grade 1 areas and for those engaged in Grade 2 areas. The changing rooms leading to grade 1 areas should be equipped with an appropriate HVAC system.

4. EQUIPMENT QUALIFICATION

4.1. All instruments and equipment used in the production processes of the different autogenous vaccines must be managed with quality criteria at least equivalent to the requirements of UNI EN ISO 9001:2015.

4.2. Equipment intended for volume measurements or weighing shall be subjected to calibration and in-service controls.

5. PROCESS VALIDATION

5.1. All processes related to the production of different types of autogenous vaccines must be described in detail in the Standard Operating Procedures validated by the Head of the Pharmaceutical Laboratory and by the Quality Manager. Each type of vaccine must correspond to a specific detailed production protocol. All the steps related to the production process must be recorded on specific documentation that can be paper or electronic or on both media. This documentation must allow, even retrospectively, to trace back to the operators involved and to the equipment used in each single production process of each type of autogenous vaccine (traceability). The documentation of each individual batch of autogenous vaccine must be kept for at least 5 years from the date of validity of the product. Retrospective validation of processes based on historical data is appropriate.

5.2. All critical equipment (bioreactors, biological hoods, incubators, refrigerators, freezers, balances, volumetric pumps, load cells, etc.) must be regularly maintained, calibrated, and monitored continuously (in particular incubators and freezers) keeping a paper or electronic copy of all the controls carried out.

5.3. Sterile filling processes shall be carried out exclusively by means of automated filling systems inside vertical laminar flow hoods within Grade 1 areas or, alternatively, within insulators (RABS) in Grade 1 or Grade 2 areas.

6. PROCEDURES FOR THE PRODUCTION OF AUTOGENOUS VACCINES

6.1. The materials used must ensure full compliance with current legislation to minimize the risk of TSE diseases and the potential biological material vector of TSE must be certified in accordance with the EMA guideline “Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products” as well as the standards of the official European Pharmacopoeia.

6.2. Control testing of residual levels of inactivating agents is tested according to European Pharmacopeia for substances regulated by Regulation 37/2010/EU. Each batch of material used for the preparation of the vaccines must be codified and identified in a unique way. Data on the origin, quality control, and safety must be recorded in a specific register.

6.3. Isolation and identification (biochemistry, serological, proteomics, or genetics) must be carried out by ISO 17025-accredited specialized laboratories.

6.4. All matrices used for the preparation of vaccines must be stored in appropriate containers marked with labels specifying the expiry date.

6.5. Viruses, bacteria, and cell lines must be manipulated with the seed-lot system and the origin. The date of isolation and number of passages must be recorded.

6.6. Genetically modified strains should not be used at all.

6.7. All material (reagents, culture media, adjuvants, or other excipients) should be certified and should comply with the indications of the European Pharmacopoeia, if applicable.

6.8. Strains used for the production of the vaccines shall be stored in such a way that they are available to the certifying body or competent authority in case of official controls

6.9. Bacterial strains used in vaccine production must be pure and any form of contamination with bacterial strains used for the production of other vaccine batches should be avoided.

6.10. Any form of contamination with environmental bacteria/mycetes should be avoided.

6.11. In the case of vaccines for animals intended for human consumption, the maximum residual MRL limits provided for in Regulation 37/2010/EU and the monograph 0062 of the European Pharmacopoeia as regards formaldehyde must be respected.

6.12. Other immunological medicinal products for veterinary or human use should not be manufactured in the same premises where autogenous vaccines are produced,

6.13. Each individual autogenous vaccine lot must be subjected to:
- chemical controls;
- physical controls (pH, turbidity, final appearance, total volume);
- sterility controls according to European Pharmacopoeia;
- absence of residues of the inactivating agent according to European Pharmacopoeia;
- test on the absence of residual pathogenicity according to European Pharmacopoeia (in vitro or biological tests on mouse or target species);
- if relevant, control of the maximum residual MRLs is provided for in Regulation 37/2010/EU and the monograph 0062 of the European Pharmacopoeia with regard to the inactivating agent.

6.14. The qualified person referred to in paragraph 11 shall record each batch of released vaccine. Such records shall be updated as the operations are carried out and shall remain available to the competent authority for one year after the expiry date of the lot or, if that period is less than five years after release, for at least five years.

6.15. Storage methods: if stored at refrigerated temperature, the vaccine may have an expiring date of 12 months from the time of filling.

7. WATER

7.1. Water is the most important excipient of a vaccine formulation and is used in many stages of vaccine production. On the basis of the intended use, different grades of quality are acceptable.

7.2. The table shows the minimum characteristics of water to be used as an excipient in the formulation of the vaccine:

Autogenous vaccines	Minimum acceptable quality of water
Parenteral vaccines	WFI
Vaccines for non-parenteral use	Purified Water

7.3. The characteristics of the water to be used for cleaning and rinsing phases are those described in the relevant EMA guideline on the quality of water for pharmaceutical use (EMA/CHMP/CVMP/QWP/496873/2018).

8. STEAM

8.1. The quality of the steam used for sterilization processes must be “clean” and of such quality as not to contaminate products and equipment.

8.2. Regular checks on steam parameters, such as:
a) presence of incondensable gases
b) overheating
c) dryness (contained moisture) of steam
d) conductivity
e) condensed vapor
f) presence of bacterial endotoxins (≤ 0.25 EU/ml)

9. STABILITY

9.1. There is no need for stability testing on the final product. Given the specific use of the product for non-routine emergency situations in the absence of a commercial product, storage under appropriate conditions for a period not exceeding 6 months is considered appropriate.

9.2. Filling volumes of the containers should be chosen in order to allow the use of the products within one working day.

10. PERSONNEL

10.1. The production must be entrusted to specialized and/or specifically trained and qualified personnel.

10.2. Staff must be subject to continuous education and specific training courses in microbiology, vaccine production, quality testing, and safety procedures (biosafety).

10.3. Prior to the start of production, a specific training course must be organized for staff involved in the production of autogenous vaccines.

10.4. All training and training activities must be documented.

10.5. Specific staff training registers must be drawn up and the structure's functional establishment plan must be available to the competent authority and regularly updated.

11. QUALIFIED PERSON RESPONSIBLE FOR THE MANUFACTURE AND RELEASE OF BATCHES

11.1. The holder of a manufacturing authorization shall permanently have the services of at least one qualified person who fulfils the following conditions:

11.1.1. he/she must hold a university degree in at least one of the following scientific disciplines: pharmacy, human medicine, veterinary medicine, chemistry, pharmaceutical chemistry, and technology, or biology.

11.1.2. he/she must have acquired the practice of at least two years in the activities of guaranteeing the quality of medicinal products, qualitative analysis of medicinal products, of quantitative analysis of active substances, and of the checks necessary to ensure the quality of veterinary medicinal products, on one or more holdings which have obtained manufacturing authorization. The duration of the required practical experience may be reduced by one year when the duration of the university course is at least five years and one and a half years when the duration of that university course is at least six years.

12. VETERINARY PRESCRIPTION

Veterinary autogenous vaccines shall be produced only following a veterinary prescription that contains at least the following elements:

a) identification of the animal or groups of animals to be treated;
b) name, surname, and contact details of the owner or keeper of the animal;
c) the date of the limitation period;
d) the name, surname, and contact details of the veterinarian, including, if available, the professional registration number;
e) the signature or equivalent form of electronic identification of the veterinarian;
f) the name of the prescribed medicinal product, indicating the active substances;
g) pharmaceutical form and dosage;
h) the quantity prescribed or the number of packages, indicating the size of the package;
i) the posology;
j) for food-producing animal species, the withdrawal period, even if equal to zero;

13. LABELLING

13.1 Labelling of the outer package

The outer package of an autogenous vaccine shall contain the following information and no other information than the following:

a) Name of the veterinary medicinal product and pharmaceutical form;
b) Statement of active substances
c) Package size
d) Target species

e) Route of administration
f) If relevant, the withdrawal period, even if is equal to zero
g) Expiry date, in the format: Exp. {mm/yyyy}
h) Special storage precautions
i) The words “Read the package leaflet before use”
j) The words “For animal treatment only”
k) The words “Keep out of the sight and reach of children”
l) Name or logo name of the manufacturer
m) Authorisation number, if applicable
n) Batch number preceded by the term “Lot”

13.2 Labelling of the immediate package

The immediate package of an autogenous vaccine shall contain the following information and no other information than the following:

a) Name of the veterinary medicinal product, followed by pharmaceutical form;
b) Statement of active substances
c) Target species
d) Route of administration
e) If relevant, the withdrawal period, even if is equal to zero
f) Expiry date, in the format: Exp. {mm/yyyy}
g) Special storage precautions
h) Name or logo name of the manufacturer
i) Batch number preceded by the term “Lot”

13.3 Labelling of small immediate packaging units

The small immediate packaging unit of an autogenous vaccine shall contain the following information and no other information than the following:

a) Name of the veterinary medicinal product
b) Quantitative particulars of the active substances
c) Batch number preceded by the term “Lot”
d) Expiry date, in the format: Exp. {mm/yyyy}

14. PACKAGE LEAFLET

The marketing authorization holder shall promptly make available a package leaflet for each autogenous vaccine. This package leaflet shall contain at least the following information:

a) Name of the veterinary medicinal product, followed by pharmaceutical form;
b) Composition
c) Target species
d) Indication of use
e) Contraindications
f) Special warnings
g) Adverse events
h) Dosage for each species, routes and method of administration
i) Advice on correct administration
j) If relevant, withdrawal period, even if is equal to zero
k) Special storage precautions
l) Special precautions for disposal
m) Authorisation number, if applicable
n) Date on which the package leaflet was last revised
o) Contacts details of the manufacturer, as appropriate, to report suspected adverse events