EMAV European Manufacturers of Autogenous Vaccines & Sera

EMAV Proposal: EU-GMP-Annex for Autogenous vaccines

Autogenous vaccines and sera are an important and well-established tool of veterinary medicine to fill the gaps left by licensed vaccines and sera in all categories of animals, contributing to the survival and well-being of livestock, pets, zoo- and exotoc animals by protecting against life-threatening infectious, especially rare infectious diseases.
Autogenous vaccines are also key to the reduction of use of antimicrobial substances and the need for pharmaceutical treatments in general, for the improvement of animal welfare by science-based prophylactic measures and to the protection of the environment at the same time.

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 general conditions for the standardisation and harmonisation of the manufacturing and use of Autogenous vaccines in future.

It defines in 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."

To support the development of a specific GMP guidance for Autogenous vaccines European manufacturers have compiled common positions for future standards for the manufacturing of autogenous vaccines. This position paper is an invitation of EMAV to competent authorities, users and other stakeholders to define a new standard for manufacturing and for a secured availability of Autogenous vaccines.

About EMAV

EMAV –European Manufacturers of Autogenous Vaccines and Sera - is representing recognised manufacturers of Autogenous vaccines and antisera for animals in Europe.
EMAV combines the interests of manufacturers of specific vaccines and sera for livestock, pets and exotic animals, to promote the European harmonization process.

EMAV e.V. is a registered Association by German law. European Manufacturers of Autogenous Vaccines & Sera's is listed at the EC Transparency Register with the ID nb. 224469535841-56.
The association does not operate as a commercial business.

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1. Introduction and definition

1.1. On January 7, 2019, the Official Journal of the European Union published REGULATION (EU) 2019/6 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 11 December 2018 on veterinary medicinal products.
For the first time in the EU, autogenous vaccines are subject to European regulation. In the repealed Directive 2001/82/EG autogenous vaccines were excluded.
In the new Regulation (EU) 2019/6 recital #70 and the Articles 2(3),4 (44), 94, 105, 106(5), 108, 117, 120, 123, 134 and 159 shall apply to autogenous vaccines (for a complete view on all European legal texts mentioning autogenous vaccines, please refer to the end of this annex).

1.2. The immunological veterinary medicinal products as defined in Article 2(3) will be referred to as autogenous vaccine(s) (AVs)in the different documents and paragraphs. They are defined as 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 or expected epidemiological link.

1.3. The aforementioned definition of autogenous vaccines includes their use for both individual animals and groups of animals and particularly emphasizes the non-industrial manufacturing process as a defining feature of these products. The GMP criteria to be newly developed for these products in accordance with Regulation (EU) 2019/6 are therefore to be applied to autogenous vaccines for all types of animals, to pets and domestic animals, zoo and wild birds as well as to farm animals.The product definition and the GMP rules to be applied to it are independent of the quantity of vaccine manufactured; they apply equally to any batch size.

1.4. Autogenous vaccines are generally accepted as a useful tool in the control of infectious diseases in animals by filling prophylactic gaps left by licensed vaccines. Especially in light of the One Health approach (antimicrobial resistance, food safety, zoonoses) in food producing animals, autogenous vaccines are a useful alternative to antibiotic treatment, hence an important contribution to human and animal welfare. Viral vaccines are also included as viral infections cause primary disease triggering secondary bacterial infections, again subject to treatment with antibiotics.

1.5. In contrast to licensed vaccines, and according to Article 106(5) of the new Regulation, autogenous vaccines 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. It is to note that there are restricted conditions under which it is possible to use an autogenous vaccine, even when a licensed vaccine is registered for the same indications.

1.6. Autogenous vaccines are custom-made and non-industrial products. Due to the large number of animal species and related pathogenic agents, the variety of autogenous products manufactured is very wide. Each method of manufacture is specifically adapted to the large number of different viral and bacterial isolates, serotypes, toxins and combinations thereof. This underlines the importance of good knowledge about the isolated microorganism, application of the optimal manufacturing method as well as a day by day flexibility required in the manufacture of these low volume products. The number of animals to be treated can be extremely small (even down to one individual). Manufacturers of autogenous vaccines, must have the ability to produce batches of variable antigen composition and size in a non-industrial scale. Therefore detailed guidelines of good manufacturing practice should be specifically prepared for those products as they are manufactured in a way that differs from industrially prepared products. That preserves their quality without hindering their manufacture and availability.

1.7. As mentioned in the autogenous vaccine definition of Regulation 2019/6, there are significant further legal limitations put on autogenous vaccines i.e. they are always inactivated and they are used only in an epidemiological unit or localities with an epidemiological link.

1.8. The concept of an epidemiological link reflects the recent situation of integrated concepts of breeding/rearing/production of animals within the EEA. It is defined to fit with the current practices throughout Europe. It may be useful to use inactivated autogenous vaccines in production units that are geographically distinct (and sometimes far away from each other) but being part of the same breeding/rearing/production chain and linked by the movements of animals. This is standard practice for poultry and pigs in integrated production chains. As pathogens can spread freely into the environment, animals can be exposed to pathogens without being moved between sites. Therefore an epidemiological link is to be defined and documented by the responsible veterinarian.

1.9. The wide use of autogenous vaccines and cross-border movement of vaccinated animals is currently common practise within the EEA. Therefore harmonised requirements for the production and control of autogenous vaccines are needed to safeguard European food-production and consumer protection and to respond adequately to disease and animal welfare threats.

2. Scope

2.1. This Annex deals with products which are manufactured from pathogens and antigens obtained from an animal or animals in an epidemiological unit as defined in Regulation 2019/6/EC 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 as defined in Regulation 2019/6/EC. For practical reasons the immunological veterinary medicinal product will be referred to as autogenous vaccine(s) in the different paragraphs. Detailed guidelines of good manufacturing practice should be specifically prepared for those products since they are manufactured in a way that is different from

industrially prepared products. Live autogenous vaccines are outside the scope of this document. The scope of the Annex is to give the detailed and specific guidelines for the manufacturing of inactivated autogenous vaccines.

3. Principles of this annex

3.1. This annex details all aspects of GMP that are specific for autogenous vaccines. It is a stand alone document. Any other GMP-rules not laid out in this annex do not apply to manufacturing of AVs.

4. Principles/Definitions/Preconditions applicable for manufacture and use of veterinary autogenous vaccines

4.1. The use of inactivated autogenous vaccines should be considered to solve an exceptional epidemiological situation provided that there is no licensed IVMP available in the respective MS and/or in EEA to solve this exceptional situation, or if it was shown that licensed veterinary medicinal products have not been efficacious on the concerned establishment.

4.2. The need for using autogenous vaccines is documented by the responsible veterinarian under his responsibility. This documentation is available for inspection by the competent authorities.
The use of inactivated autogenous vaccines should be considered if there is no other IVMP suitable to be used for the same species.

4.3. Conditions to use an autogenous vaccine:

a) No appropriate vaccine is licensed in the EEA or lack of efficacy of licenced vaccines on the farm/site in question has been experienced and reported to the responsible authority.

That means:
No licenced vaccine related to the pathogen and target species is available.

or

Lack of efficacy of the licenced vaccine for the indication and relevant farm/site has been reported to the Pharmacovigilance system by the responsible veterinarian.

or

The licenced vaccines do not contain the same antigens type - e.g. serotype/serovar, capsular antigen type, fimbria type, etc. or the authorised conditions of use of the vaccine does not fit with the field situation. If needed, the antigenic characterisation of the isolates, justifying the exceptional use may be required to ensure the appropriateness of the autogenous vaccine with respect to the farm-specific pathogen.

and

b) The specific pathogen was isolated from the concerned epidemiological unit/link.

4.4. As soon as a suitable vaccine is granted a marketing authorisation and is available in the EEA, it is mandatory for the prescribing veterinarian to use the licensed vaccine, unless as stated above a lack of efficacy of the licensed vaccine is reported.

4.5. Documents supporting the above mentioned prerequisites and motivation of use of the autogenous vaccine must be available for inspection with the prescribing veterinarian.

4.6. Means for an appropriate consideration are for instance the list of licensed vaccines issued by the MS as well as Pharmacovigilance notifications on lack of efficacy that have been received and confirmed.

4.7. Inactivated autogenous vaccines must be manufactured solely from the pathogens or antigens which were obtained within the concerned epidemiological unit/link; and they are only allowed to be used in this same epidemiological unit.

4.8. To extend the use of a given vaccine is in the responsibility of the prescribing veterinarian with respect to the changing epidemiological situation present in the locality/epidemiological unit concerned.

5. Obligations of the responsible veterinarian depending on national provisions

5.1. The veterinarian who has prescribed the autogenous vaccine is responsible for the administration of the inactivated autogenous vaccine in the field. Precaution must be taken that the vaccine is only used by the responsible veterinarian who issued the inactivated autogenous vaccine prescription or by staff under his responsibility and only within the epidemiological unit / link were the pathogen was isolated.

5.2. Before the inactivated autogenous vaccine is used in a large number of animals in the clinical practice, it may be recommended to the responsible veterinarian to first administer the vaccine to a small number of animals in the concerned locality. The appropriate test method should be agreed with the responsible authority. If severe adverse events occur, the inactivated autogenous vaccines must not be used in further animals.

5.3. In case that suspected quality defects or suspected adverse reactions related to the use of the autogenous vaccine are observed, the responsible veterinarian and/or the owner should report immediatly to the responsible authority and to the manufacturer of the inactivated autogenous vaccine.

6. Requirements for manufacturers

6.1. General

6.1.1. The manufacturing authorisation will be issued based on the provisions as specified in this annex. The following points are regarded as essential:

a) The manufacturer must hold a specific manufacturing authorisation for inactivated autogenous vaccines specifying the list of antigens that can be handled on site.
b) The manufacturing authorisation is granted to a manufacturer based on the documents provided. The compliance of the manufacturing with this annex is verified by means of inspections.
c) The manufacture of autogenous vaccines should be performed in accordance with the conditions detailed in the manufacturing authorisation.
d) Every batch of an inactivated autogenous vaccine must be released by a designated person to ensure that the batch has been manufactured and tested in accordance with the principles and guideline described in this annex.
e) The manufacturer should be able to provide: the name of the veterinarian who issued the prescription for the inactivated autogenous vaccine and the name of the veterinarians responsible for the animals of the epidemiological unit(s) concerned, a list of antigens/adjuvants intended to be used for production.
f) The manufacturer should confirm compliance with regulations concerning TSE (Note for guidance on minimising the risk of TSE agents via human and veterinary medicinal products) and Maximum Residue Limit (MRL) (Regulation 37/2010/EU).
g) Manufacturing records must be kept and should allow to trace all manufacturing operations and isolation history in accordance with the principles and guideline described in this annex.
h) Autogenous vaccines must be supplied only to the veterinarian(s) responsible for the animals belonging to the concerned epidemiological unit(s), in agreement with the veterinarian(s) who issued the

prescription for the inactivated autogenous vaccine and in accordance with relevant regulations for distribution of inactivated autogenous vaccines.

i) The manufacturer shall provide the end-user (veterinarian) with all information in writing, necessary to allow a benefit-risk analysis for the use of such inactivated autogenous vaccines.

j) The manufacturer shall report to the responsible authority in the MS where the autogenous vaccine has been used: any suspected quality defects within the period of time set by the responsible authority or the relevant legislation (to end-users as well) as well as any suspected adverse reactions related to the use of the autogenous vaccines which were made known to the manufacturer. In case of serious quality defects or serious adverse reactions, the inactivated autogenous vaccines manufacturer shall report immediately to the responsible authority.

6.2. Facilities

6.2.1. PREMISES

6.2.1.1. General

a) Unauthorised access to the production and quality control rooms is prohibited.

b) The manufacture of autogenous vaccines should be carried out in clean areas, accessible only through airlocks for personnel and/or for equipment and materials. Clean areas should be maintained to an appropriate cleanliness standard and supplied with air which has passed through filters of an appropriate efficiency.

c) Premises should preferably be laid out to allow production to take place in areas which follow in a logical order and correspond to the sequence of the operations and to the required cleanliness levels.

d) The adequacy of the working and in-process storage space should permit 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 false application of any of the manufacturing- or control steps.

e) The measures taken to prevent cross-contamination should be commensurate with the risks. Quality Risk Management principles should be used to assess and control the risks. If applicable, suitable technical or organisational measures like separation in time or space, should be taken to prevent cross-contamination.

f) Separate units should exist for production, quality testing, storage, diagnostics, recreation, and workshops, warehouses, toilettes and technical rooms.

g) Suitable storage rooms should be available to ensure suitable storage conditions (e.g. temperature, humidity…).

h) Formulation and Filling is required to be in compliance with the requirements for manufacture of autogenous vaccines as described in 6.2.1.2.m.

i) Construction, construction materials and hygienic conditions of the rooms need to be adequate to produce autogenous vaccines.

j) In clean areas, all exposed surfaces should be smooth, impervious and unbroken in order to minimize the shedding or accumulation of particles or micro-organisms and to permit the repeated application of cleaning agents and disinfectants where applicable.

k) To reduce the accumulation of dust and to facilitate cleaning there should be no inaccessible recesses and a minimum of projecting ledges, shelves, cupboards and equipment. Doors should be designed to avoid recesses that cannot be cleaned.

l) Airlocks should be designed and used to provide physical separation and to minimize microbial and particulate contamination of the different areas, if applicable. They should be in place for material and personnel moving from different grades. Typically airlocks used for personnel movement are separate to those used for material movement and include counter-locking mechanisms.

m) The movement of material from clean not classified (CNC) to grade C should be based on QRM principles, with cleaning and disinfection commensurate with the risk.

n) A cleaning and disinfection management for rooms, materials and personnel should be established.

o) Documentation relating to the premises should be readily available in a plant master file. The manufacturing site and buildings should be described in sufficient detail (by means of plans and written explanations) to clearly identify the designation and conditions of use for all the rooms as well as the biological agents which are handled in them. The flow of people and product should also be clearly marked.

6.2.1.2. Production

a) The whole manufacturing process must be conducted under conditions ensuring the required quality of the product.
b) Live biological agents should be handled in adequately controlled areas.
c) Based on risk management, production areas should be efficiently 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.
d) Air from lower cleanroom-wise classes must be prevented from reaching the area of higher cleanroom classes. Furthermore, pathogenous air from clean areas must be prevented from reaching adjacent areas. If necessary, suitable pressure stages must be installed to prevent this eventuality (pressure cascades are monitored by pressure indicators).
e) Air should be extracted through HEPA or ULPA filters and not re-circulated except into the same area, and provided further HEPA/ULPA filtration is used (normally this condition would be met by routing the re-circulated air through the normal supply HEPAs/ULPAs for that area).
f) Recycling of air between areas may be permissible under condition that it passes through two exhaust HEPAs/ULPAs, which are monitored and checked on a regular basis for integrity, and provided there are adequate measures for safe venting of exhaust air should this filter fail;
g) Changing rooms should be supplied with air filtered to the same standard as that for the work area, and equipped with air extraction facilities to produce an adequate air circulation independent of that of the work area. Material locks should normally be ventilated in the same way, but unventilated locks, or those equipped with supply air only, may also be acceptable.

h) Manufacture of autogenous vaccines in a multi-product facility is acceptable when appropriate risk mitigation measures commensurate with the risks are implemented to prevent mix-ups and cross-contamination.

i) Production operations such as cell maintenance and media preparation should be separated. Inactivation procedures have to be separated from handling of living microorganisms.

j) The possibility of using more than one biosafety cabinet in the same room is acceptable if effective technical and organisational measures are implemented to separate the activities.

k) Given their lower risk profile, concurrent production of antigens in separate laminar flow hoods placed in the same room may be acceptable if appropriate measures are implemented to avoid mix-ups and cross contamination.

l) The simultaneous incubation/storage of different batches within the same incubator is acceptable if they are physically separated.

m) The following clean room grades can be attributed for the manufacture of autogenous vaccines, examples of operations to be carried out in the various environmental grades are given below:

Grade A*
Blending and Filling of final product
Handling of open product
Handling of product components that are not subsequently sterilised
Handling of sterile product-contacting materials
Sterility control of final product

Grade C*
Background environment for Grade A* areas in viral antigen production and blending and filling of final product

Grade D*
Background environment for Grade A* areas in bacterial antigen production
Handling of equipment or materials and media dedicated to sterilization or filtration

n) Equipment should be designed and constructed to meet the particular requirements for the manufacture of each product. Before being put into operation the critical equipment (e.g. fermenters, incubators, laminar flow hoods, autoclaves or ovens) should be qualified and subsequently maintained regularly.

o) Equipment monitoring requirements should be determined during qualification.

6.2.2. Environmental MONITORING

6.2.2.1. Premises should be suitable for the intended operations and they should be adequately controlled to ensure an appropriate environment.

6.2.2.2. An appropriate environmental monitoring programme is an important tool to assess the effectiveness of contamination control measures and identify specific threats to the purity of the products.

6.2.2.3. In order to establish a robust environmental monitoring programme, i.e. locations, frequency of monitoring and incubation conditions (e.g. time, temperature(s) and aerobic and/or anaerobic conditions), appropriate risk assessments should be conducted based on detailed knowledge of the process inputs, the facility, equipment, specific processes, operations involved and knowledge of the typical microbial flora found. These risk assessments should be re-evaluated at defined intervals in order to confirm the effectiveness of the site's environmental monitoring programme, and they should be considered in the overall context of the trend analysis and the contamination control strategy for the site.

6.2.2.4. For classification, the airborne particles equal to or greater than 0.5 µm should be measured. This measurement should be performed both, at rest and in operation.

6.2.2.5. Environmental monitoring programmes should address the following parameters, if applicable for the particular site:

a) The clean room grades (A*, C*, D*) are defined exclusively by their limits for monitoring as given below. Room grades are determined by particle monitoring; in areas where additional monitoring is required (e.g. settle plates in filling areas) these values are also taken into account. The recommended maximum limits for each grade are also specified in the following tables:

Environmental monitoring for airborne particles

Non-viable Monitoring, recommended limits for airborne particle concentration in monitoring for each grade: (table 1)

Grade	**Recommended maximum limits for particles ≥ 0.5 µm/ m³**		**Recommended maximum limits for particles ≥ 5 µm/ m³**	
	in operation	**at rest**	**in operation**	**at rest**
A*	3 520	3 520	20	20
C*	3 520 000	352 000	29 000	2 900
D*	Set a limit on risk assessment	3 520 000	Set a limit on risk assessment	29 000

Monitoring parameters such as the frequency, locations, duration and sample size for monitoring / sampling have to be determined based on risk assessments (scheduled monitoring, non-continuous).

b) Microbiological monitoring:
Based on a risk assessment, environmental monitoring via settle plates is required during formulation and filling operations where the product is exposed to the environment.
Based on a risk assessment, additional microbiological monitoring measures (e.g. air sampling, contact plates, glove prints) can be carried out as appropriate. The following action limits are recommended:
Microbiological Monitoring, recommended action limits in monitoring for each grade: (table 2)

Grade	**Air sample** cfu/ m^3	**Settle Plates** (diam. 90 mm) cfu/4 hours	**Contact plates** (diam. 55 mm) cfu/plate	**Glove print 5 fingers** on both hands cfu/glove
A*	1	1	1	1
C*	100	50	25	-
D*	200	100	50	-

Settle plates: Individual settle plates may be exposed for less than 4 hours. Where settle plates are exposed for less than 4 hours the limits in the table should still be used. Settle plates should be exposed for the duration of critical operations and changed as required after 4 hours.

c) Specific device parameters, (e.g. time, temperature, differences in air pressure, relative humidity, flow rates)

6.2.2.6. Sampling methods should not pose a risk of contamination to the manufacturing operations.

6.2.2.7. The frequency and locations for sampling have to be determined based on risk assessments. Appropriate measures have to be defined should the results exceed the action limit.

6.2.2.8. Whenever intermediates or the final product can come in contact with air, the rooms need to have suitable monitoring, while the product itself should be handled under laminar flow.

6.2.2.9. The definition of "at rest" is the room complete with all HVAC systems, utilities functioning and with manufacturing equipment installed as specified but without personnel in the facility and the manufacturing equipment being static.

6.2.2.10. The "in operation" state is the condition where the installation is functioning in the defined operating mode with the specified number of personnel working.

6.2.2.11. For grade A* monitoring, it is important that sampling should be performed at locations posing the highest risk of contamination to the sterile equipment surfaces, container-closures and product in order to evaluate maintenance of sterile conditions during critical operations.

6.2.2.12. Appropriate alert and action limits should be set for the results of particulate and microbiological monitoring.

6.2.2.13. Appropriate alert and actions limits should be defined. With a view to identify potential changes that may be detrimental to the process, the alert limits for grades C* to D* should be lower than those specified as action limits and should be based on the area performance.

6.2.2.14. If action limits are exceeded the event is to be rapidly identified. Operating procedures should stipulate an investigation followed by corrective and preventive action.
These should be documented.

6.2.2.15. If microorganisms are detected in a grade A* zone, they should be identified to species level and the impact of such microorganisms on product quality (for each batch concerned) and state of control should be evaluated.

6.3. QUALIFICATION

6.3.1. Premises and critical equipment and HVAC installations used in the manufacture of autogenous vaccines should be qualified. Through the qualification of premises and critical equipment (e.g. fermenters, incubators, laminar flow hoods, autoclaves or ovens), it is established that premises and equipment are suitable for the intended operations.

6.3.2. Decisions on the scope and extent of the qualification should be based on a risk assessment, which should be documented.

6.3.3. Qualification stages for equipment, facilities, utilities and systems:
Qualification activities can consider all stages from initial development of the user requirements specification through to the end of use of the critical equipment and premises. The main stages and some suggested criteria (although this depends on individual project circumstances and may be different) which could be included in each stage are indicated below:

6.3.4. User requirements specification (URS)
The specification for critical equipment and premises should be defined in a URS and/or a functional specification. The URS should be a point of reference throughout the validation life cycle.

6.3.5. Design qualification (DQ)
The next element in the qualification of critical equipment and premises is DQ where the compliance of the design with autogenous vaccine-GMP should be demonstrated and documented. The requirements of the user requirements specification should be verified during the design qualification.

6.3.6. Installation qualification (IQ)

IQ should be performed on critical equipment and premises in an extent proportionate to the relevance of the equipment.

IQ can include the following:

Verification of the correct installation of components, instrumentation, equipment, pipe work and services against the engineering drawings and specifications;

Verification of the correct installation against predefined criteria;

Collection and collation of supplier operating and working instructions and maintenance requirements;

Calibration of instruments;

Verification of construction materials.

6.3.7. Operational qualification (OQ)

OQ normally follows IQ but depending on the complexity of the equipment, it may be performed as a combined Installation/Operation Qualification (IOQ).

OQ should include representative tests that have been developed from the knowledge of processes, systems and equipment to ensure the system is operating as designed.

6.3.8. Performance qualification (PQ)

PQ should normally follow the successful completion of IQ and OQ. However, it may in some cases be appropriate to perform it in conjunction with OQ or Process Validation.

PQ can include the following:

Tests, using production materials, qualified substitutes or simulated product proven to have equivalent behaviour under normal operating conditions with representative products. The frequency of sampling used to confirm process control should be justified.

6.3.9. Re-Qualification

Clean rooms should be requalified periodically and after significant changes to equipment, facility or processes based on the principles of QRM.

6.3.10. Qualification of utilities

The quality of clean steam, water for injection, compressed air, other gases etc. should be confirmed following installation using the qualification steps described above.

The period and extent of qualification should reflect any seasonal variations, if applicable, and the intended use of the utility.

A risk assessment should be carried out where there may be direct contact with the product, e.g. heating, ventilation and air-conditioning (HVAC) systems, or indirect contact such as through heat exchangers to mitigate any risks of failure.

Current drawings should be available that identify critical system attributes such as: pipeline flow, pipeline slopes, pipeline diameter and length, tanks, valves, filters, drains and sampling points.

6.4. Personnel

6.4.1. The manufacturer has at his disposal the services of at least one qualified person in line with the definitions in Art. 97 of Regulation 2019/6. Deviations are subject to the decision of the responsible authority. Presence in smaller production units is not permanently required.

6.4.2. Any batch of an inactivated autogenous vaccine must be released by a designated person to ensure that the batch has been manufactured and checked in accordance with the requirements of production and product control conditions as described in this Annex and any other relevant legal requirements before it is used.

6.4.3. An organisation chart indicating the duties and responsibilities of all personnel should be laid down in writing. The tasks, duties and responsibilities of head of quality control, head of production and qualified person have to be documented.

6.4.4. The key personnel should attend trainings focusing on hygiene, microbiology vaccine production and testing. The trainings should be documented and/or recorded and repeated on a regular basis.

6.4.5. A training program for all personnel should be established and should cover the requirements of production and control conditions as described in this Annex. Beside this basic training, new personnel should receive training appropriate to the duties assigned to them. Training prior and during work should be performed and documented and/or recorded. Training effectiveness has to be checked.

6.4.6. Hygienic management should be established, documented and trained annually. The training sessions should be documented and/or recorded.

6.4.7. Production has to be performed under special conditions where necessary (e.g. antigen production, filling). Relevant requirements for protective clothes should be defined and justified based on risk.

7. Isolation of the antigen used thereafter as starting material

7.1. Collection of samples, tissues of the infected animals

7.1.1. A proper diagnosis of the infectious disease in an animal / in the concerned epidemiological unit(s) shall be performed, including differential diagnosis.

7.1.2. Samples should always be taken in the respective epidemiological unit where the inactivated autogenous vaccine will be used, or in the locality having an epidemiological link with this unit. Antibiotic pre-treatments shall be considered before taking samples.

7.1.3. Sampling shall be conducted by a veterinarian, possibly in co-operation with the manufacturer of the inactivated autogenous vaccines/diagnostic laboratory.

7.1.4. Active substances used for the inactivated autogenous vaccines production should not originate from or contain agents which are notifiable diseases in EEA.

7.1.5. Traceability of the samples taken to obtain the microorganisms used to manufacture the active substances should be ensured.

7.2. Isolation and identification

7.2.1. Isolation and identification of the antigen shall be conducted by a competent authorised contract site according to Standard Operating Procedures (e.g. a diagnostic laboratory or a licensed manufacturer).

7.2.2. For viral autogenous vaccines, isolation and purification should be done in accordance with the principles laid down in European Pharmacopoeia (Ph. Eur.).

8. Procedure for manufacture and formulation of inactivated autogenous vaccines

The general principles as mentioned under 6.1 apply where appropriate. In particular the requirements of production and product control conditions as described in this section shall apply.

8.1. Starting materials

8.1.1. The autogenous vaccine manufacturer should establish quality requirements for the starting materials (specifications) which should cover aspects of the production, testing and control, storage, and other aspects of handling and distribution as appropriate. For non-monographed starting materials the specification of the supplier of the starting material should be sufficient, if the vaccine quality fulfils the specified requirements.

8.1.2. Manufacturer or supplier of excipients, adjuvants and primary packaging materials should be qualified before they can be approved as supplier to ensure the required quality of the materials.

8.1.3. Starting materials include all components which are used in the manufacture of the autogenous vaccine (including active substances/seed materials, culture medium, adjuvants, excipients and primary packaging). In this part starting materials except active substances/seed materials are addressed. Starting materials for autogenous vaccines should comply with the provisions laid down in the Ph. Eur. or pharmacopoeias of the EEA Member States.

8.1.4. In case starting materials of animal origin are used (including cells and virus for production of viral vaccines), they shall comply with the relevant monographs as well as with the general monographs and chapters of the Ph. Eur; for extraneous agent testing, as prescribed, the list of agents to be tested is limited to those that cannot be excluded throughout a risk assessment.

8.1.5. It must be ensured that materials originating from animals which might transmit TSE comply with the provisions of the "Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products".

8.1.6. Specifications for starting and primary or printed packaging materials should be established by the autogenous vaccine manufacturer and include or provide reference to, if applicable:

a) A description of the materials, including:
b) The designated name and the internal code reference;
c) The reference, if any, to a pharmacopoeial monograph;
d) The approved suppliers and, if reasonable, the original producer of the material;
e) Qualitative and quantitative requirements with acceptance limits;
f) Geographical origin, in case of material of animal origin;
g) Animal species from which the material are derived, if applicable;
h) Storage conditions and precautions.

8.1.7. There should be written procedures and records for the receipt and release of starting materials, primary, secondary and printed packaging materials:

a) 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. The incoming goods control/inspection on each delivery should be documented.
b) For the release, the control of the compliance of the suppliers certificate and the specification of the autogenous vaccine manufacturer is essential.
c) If one material delivery is made up of different batches, each batch must be considered seperately for release.

8.1.8. The results of tests on starting materials must comply with the specifications. Where the tests take a long time (e.g. eggs from SPF flocks) it may be necessary to process starting materials before the results of analytical controls are available. In such cases, the release of a finished product is conditional

upon satisfactory results of the tests on starting materials. In case of lack of specified tests by the supplier additional testing lies in the responsibility of the manufacturer.

8.1.9. The level of supervision and further testing by the autogenous vaccine manufacturer should be proportionate to the risks posed by the individual materials.

8.1.10. Starting materials in the storage area should be appropriately labelled. Labels should bear at least the following information:

a) the designated name of the product and the internal code reference (if applicable);
b) a batch number;
c) storage conditions;
d) the status of the contents (e.g. in quarantine, on test, released, rejected);
e) an expiry date or a date beyond which retesting is necessary.

8.1.11. Where fully computerised storage systems are in place, the use of automated systems (e.g. use of barcodes) is permitted, and replaces the in information 8.1.10 a) to e) in writing on the label.

8.1.12. Reference sample:

a) A reference sample is a sample of a batch of starting material or packaging material which is stored for the purpose of being analysed should the need arise during the shelf life of the batch concerned.
b) The need for taking reference samples is limited to excipients, adjuvants, primary packaging material.
c) The reference samples serve as a record of the starting material and can be assessed in the event of, for example, a dosage form quality complaint, a labelling/packaging query or a pharmacovigilance report.
d) Records of traceability of samples should be maintained and be available for review by competent authorities.

8.1.13. Samples of starting materials are taken by approved personnel and methods.

8.1.14. Samples should be stored in appropriate containers with distinctive labelling under the established storage conditions for at least three months beyond the expiry date of the finished product concerned.

8.2. Seed lot, animal derived antigen bulks and cell bank system

8.2.1. Viruses, bacteria and cell lines used in the manufacture of autogenous vaccines are handled in a seed-lot system. A record of the origin, date of isolation and passage history (including purification and characterisation procedures) is maintained for each master seed lot.
For animal derived antigen bulks that are not propagated for production, the origin of the active substance, date of isolation, purification and characterisation must be documented.

8.2.2. Seed material, animal derived antigen bulks and cell banks must be ensured to be free of extraneous agents acc. to Ph.Eur. based on testing and risk analysis. Seed material must be tested for the identity, i.e. it shall only contain the isolated pathogen but no mixed cultures of other antigens.

8.2.3. Testing methods for the detection of extraneous agents must be validated.

8.2.4. Adequate measures should be in place to avoid mix-up and/or contamination with other antigens not intended to be in the inactivated autogenous vaccine as active substances.

8.3. Water

8.3.1. The quality of steam, water, air, other gases etc. should be confirmed and appropriately qualified following installation.

8.3.2. Water treatment plants and distribution systems should be designed, constructed and maintained to minimize the risk of microbial contamination and proliferation so as to ensure a reliable source of water of an appropriate quality. Water produced should comply with the current monograph of the relevant Pharmacopeia.

8.3.3. Potable Water is not covered by a pharmacopoeial monograph but must comply with the regulations on water intended for human consumption of a quality equivalent to that defined in Directive 98/83/EC, or laid down by the competent authority. Testing should be carried out at the manufacturing site to confirm the quality of the water. Potable water may be used in chemical synthesis and in the early stages of cleaning pharmaceutical manufacturing equipment unless there are specific technical or quality requirements for higher grades of water.

8.3.4. Water for injections (WFI) should be produced from purified water, stored and distributed in a manner which prevents microbial growth. Where the WFI is produced by methods other than distillation further techniques post Reverse osmosis (RO) membrane should be considered such as nanofiltration and ultrafiltration.

8.3.5. Water systems should be validated to maintain the appropriate levels of physical, chemical and microbial control, taking seasonal variation into account.

8.3.6. Water flow should remain turbulent through the pipes to prevent microbial adhesion.

8.3.7. To prevent the formation of biofilms, sterilization or disinfection or regeneration of water systems should be carried out according to a predetermined schedule and also when microbial counts exceed action and alert limits. Disinfection of a water system with chemicals should be followed by a validated rinsing procedure. Water should be analyzed after disinfection/regeneration; results should be approved before the start of use of the water system.

8.3.8. A suitable sampling schedule should be in place to ensure that representative water samples are obtained for analysis on a regular basis.

8.3.9. Regular ongoing chemical and microbial monitoring of water systems should be performed with alert limits based on the qualification that will identify an adverse trend in the performance of the systems. Sampling should include all outlets and user points at a specified interval. A sample from the worst case sample point, e.g. the end of the distribution loop return, should be included each time the water is used for manufacturing and manufacturing processes. A breach of an alert limit should trigger review and follow-up, which might include investigation and corrective action. Any breach of an action limit should lead to a root cause investigation and risk assessment.

8.3.10. WFI systems should include continuous monitoring systems such as Total Organic Carbon (TOC) and conductivity.

8.3.11. Water is the most commonly used excipient in medicinal products: the minimum quality of water selected depends on the intended use of the product, according to a risk based approach to be applied as part of an overall control strategy.

a) Table 3 summarises the acceptable quality of water as an excipient in the final formulation:

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

* WFI is recommended in order to ensure the vaccines' safety and product quality (avoid introduction of undesirable microorganisms in the finished product formulation) unless otherwise justified (i.e. for some non-sterile veterinary vaccines for non-parenteral use, purified water might be accepted)

In general, the same quality of water should be used for the final rinse of equipment, containers/closures as is used for the final stage of manufacture of the active substance or used as an excipient in a medicinal product.

b) Table 4 summarises the acceptable quality of water used for cleaning/rinsing of equipment,

Cleaning/Rinsing of Equipment	PRODUCT TYPE	Minimum Acceptable quality of water
Initial rinse	Intermediates and AS	Potable Water
Initial rinse including CIP of equipment, containers and closures, if applicable.	Medicinal products – non sterile	Potable Water
Final rinse including CIP of equipment, containers and closures, steam in sterilization processes of these materials, if applicable.		Purified Water or use same quality of water as used in manufacture of medicinal product, if higher quality than Purified Water
Initial rinse including CIP of equipment, containers and closures, if applicable.	Sterile products	Purified Water
Final rinse including CIP of equipment, containers and closures, steam in sterilization processes of these materials, if applicable.	Sterile non-parenteral products	Purified Water or use same quality of water as used in manufacture of medicinal product, if higher quality than Purified Water
	Sterile parenteral products	WFI

8.3.12. Steam used for sterilization

a) Purified water, with a low level of endotoxin, should be used as the minimum quality feed water for the pure steam generator.

b) Steam used for sterilization processes should be of suitable quality and should not contain additives at a level which could cause contamination of product or equipment. The quality of steam used for sterilization of porous loads and for Steam-In-Place (SIP) should be assessed periodically against validated parameters. These parameters should include consideration of the following examples: non-condensable gases, dryness value (dryness fraction), superheat and steam condensate quality.

8.4. Production

8.4.1. Production and control are performed under conditions as described in this annex.

8.4.2. The production of autogenous vaccines involves added complexity in comparison to registered products with respect to antigen combinations and hence manufacturing routines. Procedures based on a risk assessment should be in place justifying the production of multiple batches in the same room on the same day.

8.4.3. Adequate measures should be in place to avoid mix-up and/or contamination with other antigens not intended to be in the inactivated autogenous vaccine as active substances. Separation of live and inactivated antigen should be ensured.

8.4.4. Before any manufacturing operation starts, 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.

8.4.5. Adequate measures should be in place preventing cross contamination and mix-up of materials while working with different antigens at the same time in the same room.

8.4.6. Production of inactivated autogenous vaccines shall not be performed in the same facilities and with the same equipment used for the production of licensed IVMPs unless validated and approved measures have been taken to avoid cross-contamination or mix-up.

8.4.7. Antibiotics shall not be used as preservatives.

8.4.8. The production method should be described and documented in detail (including culture, pathogen replication, inactivation, concentration and blending of the final product).

8.4.9. Antigenic mass determination, like virus titre/number of viable bacteria of the antigen bulk (can be correlated with methods e.g. OD measurement) must be determined by any validated method before inactivation. A maximum pre-inactivation titre/count has to be established.

8.4.10. Production has to be performed under conditions that prevent the contamination of the final product where necessary (e.g. antigen production, filling). Relevant requirements for protective clothes should be defined and justified based on risk.

8.4.11. The maximum residue limits for ingredients defined by food regulations shall be met for autogenous vaccines intended for food-producing species : MRLs pursuant to Regulation 37/2010/EU and Ph. Eur. monograph 0062 concerning thiomersal and formaldehyde.

8.4.12. If preservatives are used, the efficacy should be tested as required by Ph. Eur.

8.4.13. Cleaning & Disinfection

a) A cleaning and disinfection management for rooms, materials and personnel should be established.

b) More than one type of disinfecting agent should be employed, and should include the periodic use of a sporicidal agent, if applicable. Disinfectants should be shown certified to be effective for the application (e.g. by the supplier or scientific literature).

c) Monitoring of the effectiveness of the cleaning and disinfection management should be undertaken regularly in order to show the effectiveness of the disinfection programme and to detect the development of resistant and/or spore forming strains.

8.5. Inactivation

8.5.1. Products should be inactivated by the addition of an inactivation agent accompanied by sufficient agitation or other validated methods. The mixture should then be transferred to a second sterile vessel, unless the container is of such a size and shape as to be easily inverted and shaken to wet all internal surfaces with the final culture/inactivation mixture. Suitable temperature has to be maintained through the whole inactivation process.

8.5.2. Complete inactivation: Inactivation should be tested with at least two passages in the production medium or other validated methods. The test for inactivation must be validated and the detection limits must be defined. Control testing of residual levels of inactivating agents is required for substances regulated by Regulation 37/2010/EU. The provisions for testing and limits laid down in Ph. Eur. apply.

8.5.3. Data on inactivation must be collected and inactivation should be validated. The validation of the inactivation including all test systems can be carried out exemplarily on a strain of one group of pathogens (strain x of YYYY spp.). Inactivation validation shall be performed in line with Ph. Eur. requirements.

8.5.4. As part of the approval to allow the manufacturing of viral autogenous vaccines, the method of inactivation and the results of the validation of the inactivation process should be addressed to the responsible

authority. Requirements for inactivation validation set in European guidelines regarding viral vaccines should be met.

8.6. Validation

8.6.1. Critical manufacturing steps need to be validated. 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. The validation may be carried out together for several antigens when they are prepared in the same way. The extend to which a process is considered validated based on existing data of related organisms shall be based on sound justification.

8.6.2. Bracketing could be justified for validation of products based on extensive process knowledge in conjunction with an appropriate ongoing verification programme.

8.6.3. Process validation of products can be realized as a prospective validation, a concurrent validation or as a retrospective validation where this is justified.

8.6.4. Equipment, facilities, utilities and systems used for process validation should be qualified. Test methods used in qualification, validation, clean exercises or qualification control should be validated for their intended use.

8.7. Quality Controls on the finished product

8.7.1. Before the finished autogenous vaccine is supplied to the veterinarian for administration to the animal, it has to be subject to the following tests at minimum:

8.7.2. Sterility: The sterility should be tested according to the method described in Ph. Eur. monograph 2.6.1. with the following adaptations to autogenous vaccines:

a) In case of small batches, samples for sterility testing can be taken from the bulk during filling. e.g. batches of less than 100 vials/bottles, samples for sterility testing can be taken from the bulk during filling, using 10 % of the bulk or 1 ml, whichever is less. Altered sampling sizes and frequencies need to be representative and justified.

b) Sterility should be tested under laminar flow. The environment should be monitored via settlement plates.

c) The validation of the sterility test using the control strains as defined in Ph. Eur. 2.6.1 has to be performed when performing process validation. Process validation should follow a risk based approach focussing on excipients added to the final formulation. Revalidation in case of changes in the product should be matrix-based.

8.7.3. Controls which are crucial for the quality but which cannot be carried out on the finished product, should be performed at an appropriate stage of production.

8.7.4. Retention sample: One bottle of retention sample from each batch of finished product should be retained for at least 6 months after the expiry date. The sample should be contained in its finished primary packaging or in packaging composed of the same material as the primary container in which the product is marketed.

9. Stability

9.1. Tests on the stability of the finished product are not expected for inactivated autogenous vaccines. Storage in appropriate conditions for 12 months starting from final filling is considered acceptable.

9.2. As no studies on in-use-stability in general are available for these vaccines, the vial or bottle size and filling volume has to be chosen in such a way that the content of one container can be used up within one working day (8 hours). It is up to the responsible veterinarian to order the correct vial or bottle size.

10. Labelling

10.1. In principle the labelling should comply as far as possible with the provisions laid down in Ph. Eur. and may be subject to harmonised requirements.

10.2. The following harmonised particulars should be provided on the immediate packages and, if present, on the outer packages and in the package leaflet subject to agreement of the responsible authority:

- Manufacturer
- Batch number
- Expiry date
- Composition: Inactivated antigen(s) and adjuvant/(s)
- Dosing and method of administration
- Target species and subcategory of animals for which the inactivated autogenous vaccine is intended
- Storage conditions
- The words "For animal treatment only"
- Any further precautions given in the prescription issued by the responsible veterinarian
- Precaution regarding handling of the unconsumed or unused inactivated autogenous vaccine (if required)
- Withdrawal period if relevant

11. Glossary

Epidemiological link:
"Groups of animals have an epidemiological link when one of them is to be put in contact with pathogens it has never met before, but which are present in the other group of animals raised in another rearing site/farm. The movement of animals between rearing sites/farms should be considered when establishing the epidemiological link. As a consequence, animals raised on rearing sites/farms geographically distinct, that have an epidemiological link, are belonging to the same unit. It is mainly applicable for poultry or pigs when considering parental lines raised in production chain systems. An epidemiological link also exists between different farms/sites within one geographic area; where an identical pathogen is circulating and spread e.g. by wild species. Therefore the epidemiological unit is defined under the responsibility of the prescribing veterinarian."

Critical equipment
Critical equipment is equipment used in production or quality control that has significant influence on the outcome of a production process or on the quality of the final product (e.g. fermenters, incubators, laminar flow hoods, autoclaves or ovens).