Co-ordination Group for Mutual Recognition and Decentralised Procedures – Veterinary

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Recommendations for the manufacture, control and use of inactivated autogenous veterinary vaccines within the EEA

1. Introduction

Autogenous vaccines are currently covered by national legislation in Member States (MS). In a world where animals and their pathogens circulate freely, it is important to ensure a harmonisation at the Economic European Area (EEA) level with regard to this kind of immunological veterinary medicinal products (IVMP), covering the manufacture and the use of inactivated autogenous vaccines to safeguard European food-production and consumer protection and to respond adequately to disease and animal welfare threats. Inactivated autogenous vaccines are a useful addition to licensed[1] vaccines in animal disease control and in maintaining animal health. The use of vaccines including inactivated autogenous vaccines can be an additional prophylactic tool to avoid occurrence of diseases which require antibiotic treatment. The wide use of inactivated autogenous vaccines and cross-border move of vaccinated animals is currently common practice within the EEA. Therefore the need for harmonized requirements for the production and control of inactivated autogenous vaccines is obvious even if the legal competence is on national basis. All MS of the EEA accept inactivated bacterial autogenous vaccines. However inactivated viral autogenous vaccines are accepted only in certain MS, see Annex 1 for a detailed list. This guidance describes the scope and the recommendations for the use of inactivated autogenous vaccines as well as the prerequisites for manufacturing and testing. Those should ensure a similar level of "obligations of means" throughout EEA. However additional national requirements may apply, and anyone planning to manufacture or use autogenous vaccines should check the relevant requirements with the responsible authority.

It would be desirable to take forward these recommendations and include within the current legislative review, however in the interim these principles should be followed.

2. Scope

These recommendations give scientific advice for the production, control, use and the monitoring (pharmacovigilance), of inactivated autogenous vaccines.

[1] Licensed vaccines means in conformity with the European Commission – Directive 2001/82/as amended or Regulation 726/2004

They define a minimal level of manufacturing process and control practices to ensure the quality of these products. Safety of these products is mostly ensured through the recommendations regarding production and control but neither clinical safety nor clinical efficacy of inactivated autogenous vaccines are assessed and regulated.

The recommendations do not include the various technical and administrative obligations which need to be respected by manufacturers and veterinarians in the different EEA MS. It is up to each MS to decide about the processes allowing the manufacture and the use of inactivated autogenous vaccines. National law on autogenous vaccines should be respected.

It should be highlighted that the use of live autogenous vaccines is not allowed in most of the EEA MS and should be currently discouraged within the EEA. In absence of requirements regarding the properties of the live strain (as actually regulated for the vaccines granting a marketing authorisation), the dissemination hazard linked to the use of live autogenous vaccines is not under control. Live autogenous vaccines are outside the scope of this document.

Even if these minimum requirements for production and control aim to facilitate the free cross border use of inactivated autogenous vaccines, requirements with respect to import of inactivated autogenous vaccines have to be set by responsible authority.

3. Definition

Directive 2001/82/EU Article 3 (1) b) excludes the following products from the scope of the Directive: "*Inactivated immunological veterinary medicinal products which are manufactured from pathogens and antigens obtained from an animal or animals from a holding and used for the treatment of that animal or the animals of the holding in the same locality.*"

The wording of the directive does not reflect the recent situation of integrated concepts of breeding/ rearing/production of animals within the EEA. Therefore a concept of an epidemiological link is proposed to fit with the current practices throughout Europe. Indeed sometimes 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. In those exceptional cases, animals destined to be moved to another farm or their parental lines should be prior administered with an inactivated autogenous vaccine in order to confer immunity to the animals before they encounter the pathogen in the farm they are transferred to. It is especially applicable for poultry and pigs when there are integrated production chains. For the special situation of the aquaculture, it should be highlighted that pathogens can move freely into the environment. Animals can therefore be in contact with pathogens without being moved between sites.

To reflect the current situation in husbandry within the EEA the current regulation is interpreted as follows:

<u>Same locality:</u>
-"Same locality" as stated in the definition of inactivated autogenous vaccines should be understood as "*same and single rearing site and/or same farm where the pathogen(s) is/are*

present or multiple rearing sites and/or farms having an epidemiological link." The terms "same locality" cover the concept of an epidemiological unit in which animals share the same epidemiological status i.e. the same pathogen (identical isolate).

Same rearing site/same farm:
- "Same rearing site and/or same farm" means "*a place where several rearing building(s) are located with only short distance between them. On these places animals are regularly raised."*

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 locality. It is mainly applicable for poultry or pigs when considering parental lines raised in production chain systems. For aquatic animals, 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 aquatic species."*

Exception with respect to the ruminant target species:
Those definitions do not apply for inactivated autogenous vaccines intended for ruminants due to Transmissible Spongiform Encephalopathy (TSE) risk. The use of inactivated autogenous vaccines intended for ruminants should be restrained to farm/site where the pathogen has been collected without being extended to other groups of animals and rearing sites/farms. In particular, the use of inactivated autogenous vaccines for ruminants should be considered nationally according to the TSE situation of the country. And use of viral autogenous vaccines in ruminants may be banned in some countries (see annex 1).

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

The use of inactivated autogenous vaccines should only be considered to solve an exceptional epidemiological situation in the respective establishment in the relevant locality 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.

If no suitable licensed IVMP is available in the EEA, the responsible veterinarian is obliged to provide professionally sound justification to the responsible authority regarding the need to solve the health situation with the use of inactivated autogenous vaccines.

The use of inactivated autogenous vaccines should be considered if there is no other IVMP suitable to be used under the cascade prescriptions (articles 10 and 11 of Directive 2001/82/EC) for the same species.

Conditions to use an autogenous vaccine:

1. 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 in the EEA.

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

2. The specific pathogen was isolated from the concerned/same locality/animal during an outbreak of the disease.

NB: As soon as a suitable vaccine is granted a marketing authorisation in the EEA, the authorisation to use/manufacturing an inactivated autogenous vaccine should be withdrawn.

Documents supporting the above mentioned prerequisites must be submitted by the veterinarian according to the national requirements to the responsible authorities. And the manufacturer for autogenous vaccines must have a manufacturing authorisation for autogenous vaccines.

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.

Inactivated autogenous vaccines must be manufactured solely from the pathogens or antigens which were obtained in the concerned locality; and they are only allowed to be used in this same locality. It is generally not acceptable to add any other pathogens or antigens or licensed IVMPs to the inactivated autogenous vaccines.

To renew the manufacturing authorisation if required, it should be proven that pathogens or antigens obtained in the previous sampling are still relevant with respect of the epidemiological situation present in the locality concerned. Reuse of isolates may be authorized if it has been verified that they are still relevant for the locality.

5. Obligations of the responsible veterinarian depending on national provisions

The veterinarian who has made the initial diagnosis (together with the diagnostic laboratory) of the involved infectious agent and ordered the prescription 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 under his responsibility and only in the locality were the pathogen was isolated.

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 administer the vaccine first in a small number of animals in the concerned locality. The appropriate methodology of the test should be agreed in concertation with the responsible authority. If severe adverse events occur, the inactivated autogenous vaccines must not be used in additional animals.

The responsible veterinarian and/or the owner should report to the responsible authority and to the inactivated autogenous vaccine manufacturer within a time frame required by the responsible authority after observation of any suspected quality defects and any suspected adverse reactions related to the use of the inactivated autogenous vaccine.

6. Requirements for manufacturers:

6.1. General

The manufacturing authorisation will be issued based on the national provisions. The following points are regarded as essential :

- The manufacturer must hold a specific manufacturing authorisation for inactivated autogenous vaccines specifying the antigens and based on the relevant national provisions.

- The manufacturing authorisation is granted to a manufacturer based on the documents provided. The compliance of the manufacturing with the recommendations is checked by inspection means.

- The manufacture of inactivated autogenous vaccines should be performed in accordance with the conditions provided in the manufacturing authorisation.

- A manufacturer should have a designated person ensuring the quality of each individual batch of inactivated autogenous vaccine and the compliance with legislation. Requirements for the qualification apply as laid down in Art. 53 of Dir. 2001/82/EC as amended. Deviations need to be justified and may be accepted by the responsible authority.

- The manufacturer should follow the principles and guidelines of Good Manufacturing Practices (GMP) or at least the requirements of production and product testing conditions as described in these recommendations. Other aspects and obligations regarding the manufacture of inactivated autogenous vaccines can be governed by national legislation.

- The manufacturer should be able to provide: the name of the veterinarian who issued the prescription for the inactivated autogenous vaccine and the veterinarians responsible for the animals belonging to the same locality, a list of antigen/adjuvants intended to be used for the production if requested by the responsible authority and a manufacturing documentation as described below.
- The manufacturer should confirm the compliance with regulation 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).

- The manufacturer must have in place appropriate documentation (Standard Operating Procedures (SOPs), manufacturing and quality control instructions, specifications…) for any type of inactivated autogenous vaccines (according to the type of purification steps if any, adjuvant, pathogens, packaging materials etc.).

- Manufacturing records (including the inactivated autogenous vaccine veterinary prescription) must be kept in accordance with the principles and guidelines of GMP or at least the requirements of production and product control conditions as described in these recommendations. Records should allow tracing back all manufacturing operations and isolation history. A Product Quality Review on the production of the vaccines may be performed regularly, if required by the responsible authority or by national legislation.

- Any batch of an inactivated autogenous vaccine must be certified by a designated person to ensure that the batch has been manufactured and checked in accordance with the principles and guidelines of GMP or at least the requirements of production and product control conditions as described in this these recommendations and any other relevant legal requirements before it is used.

- The manufacturer should keep enough of reference samples of all starting materials and the finished product of every manufactured batch of an inactivated autogenous vaccine under the established storage conditions and in compliance with national regulation to perform controls as required by responsible authority.

- Inactivated autogenous vaccines must only be supplied to the veterinarian(s) responsible of the animals belonging to the same locality, in agreement with the veterinarian(s) who issued the prescription for the inactivated autogenous vaccine and in accordance with national regulations for distribution of inactivated autogenous vaccines.

- The manufacturer shall provide the end-user (veterinarian) with all the information in writing necessary to let him make the benefit-risk balance of the use of this inactivated autogenous vaccines.

- The manufacturer shall report to the responsible authority in the MS where the inactivated autogenous vaccine has been used any suspected quality defects in the time limits provided by the responsible authority or the national legislation (to end-users as well) and any suspected adverse reactions related to the use of the inactivated autogenous vaccines which are 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

Compliance with chapter 3, annex 1 and 5 of the GMP Guideline (GL) is required. If not possible, at least the below requirements should be met :

- Construction and hygienic conditions of the rooms need to be adequate to produce autogenous vaccines.

- Unauthorised access to the production and quality control rooms is not accepted.

- Rooms for production are separated from rooms dedicated to testing and other rooms, e.g. for diagnostic tests, research, recreation, and workshops, warehouses, toilettes and technical rooms.

- A blueprint should be available allocating the main characteristics and features of the relevant rooms.

- The rooms dedicated to production and testing should have airlocks for personnel and materials if appropriate.

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

- The rooms should be monitored concerning hygienic and environmental conditions in area of controlled air.

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

- The different steps of production should be performed separately (separation by time or space) in particular inactivation procedures have to be separated from living microorganisms management.

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

- Main equipment such as fermenters, incubators, laminar flow hoods, autoclaves or ovens should be appropriately qualified and/or validated.

- Incubators, freezers and refrigerators should be monitored. The monitoring schedule should be checked, documented and evaluated. Temperature and pressure controlled equipment should be adequately calibrated. Waste and drain water should be disinfected on an established basis.

6.3 Personnel

Compliance with chapter 2 of the GMP Guideline is required. If not possible, at least the below requirements should be met :

- The manufacturer has permanently and continuously at his disposal the services of at least one qualified person in line with the definitions in Art. 53 and 55 of Dir. 2001/82/EU as amended. Deviations are subject to the decision of the responsible authority.

- An organisation chart indicating the duties and responsibilities of all personnel should be laid down in writing. Also a qualified person should be designated as responsible for release of inactivated autogenous vaccine batches. The tasks, duties and responsibilities of head of quality control, head of production and qualified person have to be documented.

- 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 regular basis.

- A training program for all personnel should be established and should cover the principles and the guidelines of the GMP or at least the requirements of production and control conditions as described in these recommendations. 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.

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

- Production has to be performed under aseptic 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

- A proper diagnosis of the infectious disease in an animal / in the locality shall be performed, including differential diagnosis.

- Samples should always be taken in the respective locality or the epidemiological link where the inactivated autogenous vaccine should be used. Antibiotic pre-treatments shall be considered before taking samples.

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

- Active substances used for the inactivated autogenous vaccines production should not be come out of notifiable diseases agents in EEA and the isolates must not have been biotechnologically modified from the isolation onwards.

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

7.2 Isolation and identification

- Isolation and identification of the antigen shall be conducted by a competent authorised contract site according to validated method and SOP (e.g. a diagnostic laboratory or a licensed manufacturer).

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

- A time span for the use of the isolates for the production of an autogenous vaccine may be required by responsible authority

8. Procedure for manufacture and formulation of inactivated autogenous vaccines

The general principles as mentioned under 6.1 apply where appropriate. In particular the principles and guidelines of GMP or at least the requirements of production and product control conditions as described in these recommendations shall apply.

8.1 Starting materials

- Starting materials include all components which are used in the manufacture of the inactivated autogenous vaccine (including active substances/seed materials, culture medium, adjuvants and other excipients).

- Starting materials (except active substances/seed materials) for inactivated autogenous vaccines should comply with the provisions laid down in the Ph. Eur. or pharmacopoeias of the EEA Member States.

- In case starting materials of animal origin are used (including cells 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.

- It must been ensured that seed material, cell cultures, serum batches and other 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” as well as with the provisions of the relevant Ph.Eur. monographs by submitting the pertinent documents. Certificates of suitability which are issued by the European Directorate for the Quality of Medicines (EDQM) for the relevant Ph. Eur. monographs may be suitable.

- A system of seed lot should be in place in compliance with annex 5 of the GMP GL. Seed lot should be kept stored as long as required by the responsible authority.

- 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

- Seed material must be pure, i.e. it shall only contain the isolated pathogen but no mixed cultures of other antigens. Minimum requirements are testing for purity including extraneous agents and identity testing. The requirements of the Ph. Eur., taking into account the relevant pathogen species should be considered.

- Starting materials must be sterile according to Ph. Eur. 2.6.1.

- Immediate packages should fulfil the requirements of Ph. Eur.

8.2 Production

- In ideal cases production and control are performed under GMP conditions complying with Dir. 91/412/EU and the relevant guidelines and at least should be performed in line with GMP principles.

- 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 in order to avoid cross-contamination.

- Production should be done on a batch basis only.

- The manufacturing process should not include genetic manipulation of the isolate used to produce the vaccine.

- The whole manufacturing process must be conducted under conditions ensuring the required quality of the product.

- Antibiotics should not be added during the production of an inactivated autogenous vaccine. If the use of antibiotics cannot be avoided, they have to comply with MRL Regulation 37/2010/EU, and the use should be justified.

- Antibiotics shall not be used as preservatives.

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

- Live virus titre/number of viable bacteria of the bulk must be determined before inactivation and maximum pre-inactivation titre/count established.
- Critical manufacturing operations shall be validated.

- Filling may be required to be in compliance with the requirements for manufacture of sterile medicinal products in accordance with the Guidelines to Good Manufacturing Practice, Part I, Annex 1.

- 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.

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

8.3 Inactivation

- Products should be inactivated by the addition of an inactivation agent accompanied by sufficient agitation. 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.

- 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.

- For viral autogenous vaccines, inactivation process and validation of the inactivation process should be addressed to the responsible authority for approval. Requirements for inactivation validation set in European guidelines regarding viral vaccines should be met.

8.4 Controls on the finished product

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

Sterility: The sterility should be tested according to the Ph. Eur. monograph 2.6.1. In case of small batches, samples for sterility testing can be taken from the bulk during filling.

Complete inactivation: Inactivation should be tested with at least two passages in the production medium. The test for inactivation must be validated and the detection limits must be defined. Control testing of residual levels of inactivating agents is required. The provisions for testing and limits laid down in Ph. Eur. apply.

Bacterial vaccines:

- *Endotoxin content* (in case of use of gram-negative pathogens or other microorganisms producing endotoxins - to be determined by responsible authority). The endotoxin content should be tested as required by Ph. Eur.

Viral vaccines:

- *Absence of extraneous agents*: Absence of extraneous agents should be ensured according to requirements of the Ph. Eur. and European guidelines regarding extraneous agents in viral vaccines. Validation of any test used for extraneous agents testing should be provided.

9. Stability

Tests on the stability of the finished product are not expected for inactivated autogenous vaccines. Storage in appropriate conditions for 6-12 months starting from final filling is considered acceptable.

As no studies on in-use-stability in general are available for these vaccines, the filling size 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 filling size.

10. Labelling

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

The following 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)
- Name and address of the responsible veterinarian
- Dosing and method of administration
- Target species and subcategory of animals for which the inactivated autogenous vaccine is intended
- Locality where the antigens or pathogens used for manufacture of the inactivated autogenous vaccine were sampled
- 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
- Withdrawal period if relevant

ANNEX 1

Member States within EEA in which the production and the use of viral inactivated autogenous vaccines **are authorised**:

BE, CZ, DE, HU, IT, LV, PL, UK

Member States within EEA in which the production and the use of viral autogenous vaccines **are not authorised**:

DK, ES, FI, FR, HR, IS, NO, PT; SE, SK

For those MS not mentioned, no information is available.

ANNEX 2

List of abbreviations:

EDQM: European Directorate for the Quality of Medicines

EEA: Economic European Area

GL: Guideline

GMO: Genetically Modified Organism

GMP: Good Manufacturing Practices

IVMP: Immunological veterinary medicinal product

MRL: Minimum Residue Limit

MS: Member State

Ph. Eur.: European Pharmacopoeia

SOP: Standard Operating Procedure

TSE: Transmissible Spongiform Encephalopathy