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SC XI Supplementary Chapter XI: Inactivated Autogenous Vaccines for Veterinary Use

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This chapter gives guidance on the minimum quality standards required for the preparation, manufacture, and control of inactivated veterinary autogenous vaccines and their use and monitoring.

1. INTRODUCTION

Inactivated autogenous veterinary vaccines are custom made for use in exceptional circumstances in response to a specific and immediate local need. This is usually when a disease affects a specific group of animals and where no authorised vaccines suitable for the target animal species are available, or where an attending veterinarian has made an evaluation that the available authorised vaccine(s) lack the required efficacy or are inappropriate for use in the affected animals, and where other authorised veterinary medicinal products are not considered effective in controlling the disease outbreak. In these circumstances a veterinarian can have an inactivated autogenous vaccine prepared from pathogens obtained from an animal or animals on a farm or unit and used for the treatment of that animal or animals in the same farm or unit.

It may be possible to use autogenous vaccines in production farms or units that are geographically distinct but part of the same integrated breeding, rearing and / or production chain where animals may need to be vaccinated before moving onto the unit where they encounter the pathogen, or in the example of aquaculture where it is recognised that pathogens may move freely into the environment and therefore may infect separate aquaculture units. Any epidemiological link to justify the extent of use of an autogenous vaccine is to be defined and documented by the prescribing veterinarian and documentation available for review by the competent authority if required.

Inactivated autogenous vaccines prepared for use in an individual country should only be prepared from pathogens isolated in that country to reduce the risk of the introduction of exotic pathogens.

Autogenous veterinary vaccines are an important additional prophylactic tool to assist in the management of diseases which may require antibiotic treatment and thereby reduce the risk of antimicrobial resistance.

2. LEGAL PROVISIONS / CONDITIONS FOR USE

Autogenous vaccines are intended as a response on a limited scale and to an immediate need. They are manufactured to a level of quality assessed by the competent authority to assure safety at their scale of use. Most autogenous vaccines are inactivated bacterial products because they are simpler to manufacture and carry lower risk. Viral vaccines are more complex to manufacture due to the nature of viral growth which requires a cell substrate as well as specific growth and inactivation conditions. This makes them inherently higher-risk products and therefore subject to more stringent quality standards to ensure the vaccines are safe and free from extraneous viruses. Autogenous veterinary vaccines are prepared, manufactured and used according to relevant national or regional legislation.

In the UK autogenous vaccines are legislated by the Veterinary Medicines Regulations (VMR)[1] and autogenous vaccine manufacturers can apply for an authorisation to allow them to manufacture a specific autogenous vaccine, providing a veterinary surgeon has confirmed a need and fully justified the use of an autogenous vaccine in preference to a fully authorised vaccine. The manufacturing premises, method of production and control processes are assessed by the competent authority to ensure that the production process will result in a consistently safe product. If these are all satisfactory an authorisation to manufacture is granted which in the UK is known as an Autogenous Vaccine Authorisation (AVA).

3. PREPARATION AND MANUFACTURE

Isolation of the pathogen and use as a starting material for vaccine production

1. Collection of samples, tissues of the infected animal's isolation and identification of the pathogen

A proper diagnosis of the infectious disease on the farm or unit shall be performed, including consideration of potential differential diagnosis.

Samples should always be taken from an animal or animals on the respective farm or unit where the inactivated autogenous vaccine is to be used.

Sampling shall be conducted by the responsible veterinarian, and where necessary with the cooperation with the manufacturer of the inactivated autogenous vaccines / diagnostic laboratory.

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

Isolation and identification of the pathogen shall be conducted by a competent authorised contract site, such as a diagnostic laboratory and / or a licensed veterinary autogenous vaccine manufacturer, according to validated methods and Standard Operating Procedures.

For viral inactivated autogenous vaccines, isolation and purification should be done in accordance with the principles of the European Pharmacopeia.

Active substances used for the inactivated autogenous vaccine production should not be from pathogens of official notifiable diseases relevant to the country or region.

The isolates must not be subject to biotechnological modification at any stage, from isolation through to the finished vaccine

2. Use of the isolate as starting material

Viruses and bacteria 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 seed lot.

Virus and bacterial seed lots must be tested for identity and purity, i.e. they shall only contain the isolated pathogen but no mixed cultures of other contaminating microorganisms.

Viral Seed material should be shown to be free of extraneous agents according to the pharmacopoeia. The requirements of the pharmacopoeia with respect to the relevant pathogen species should be considered; for extraneous agents testing, the list of agents to be tested is limited to those that cannot be excluded through a risk assessment. Testing methods for the detection of extraneous agents must be validated.

It must be ensured that starting materials originating from animals which might spread transmissible spongiform encephalopathy (TSE) comply with the relevant provisions of the TSE regulation of the region, by submitting the pertinent documents. Certificates of suitability which are issued by the European Directorate for the Quality of Medicines (EDQM) may be suitable. The requirements of the monograph for Veterinary Vaccines apply.

Where such a monograph is available, the starting materials, must comply with the specific monograph requirements of the pharmacopoeia. A copy of a representative certificate of analysis for each starting material demonstrating compliance with the pharmacopoeia should be provided.

For starting materials that don't have a monograph, the name of each starting material (including trade name, scientific synonyms), description, function, material specifications and purity should be provided.

Seed lots should be stored as long as required by the competent authority.

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

Reuse of bacterial or viral seeds for the production of further batches of autogenous vaccines for use on a farm or unit where the pathogen was originally isolated may be authorised in agreement with the competent authority and where it is demonstrated or justified that the seeds are still relevant to the pathogens in the field and for managing disease outbreaks on the farm or unit.

Manufacture

1. Manufacturing standard

The manufacture or preparation of autogenous vaccines should be in accordance with the principles of Good Manufacturing Practice (GMP) using facilities, personnel, premises, documentation and equipment appropriate for the scale of manufacture and particular class of vaccines in accordance with a quality management system. The manufacturer must have appropriate documentation in place, such as but not limited to Standard Operating Procedures (SOPs), manufacturing and quality control instructions, and specifications for all types of inactivated autogenous vaccines proposed to be manufactured from the isolation, diagnosis and storage of the microorganisms, the manufacture, inactivation and purification (if required), through to the filling into the final containers and quality control tests on the vaccine.

Manufacturing records should include the inactivated autogenous vaccine veterinary prescription for the selected strains and their justification of use of the autogenous vaccine. Records should allow tracing back all manufacturing operations and isolation history.

The holder of the authorisation to manufacture autogenous vaccine (which may be the veterinarian or the manufacturer depending upon national legislation) 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, the veterinary justification for use,

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 shall provide the end-user (veterinarian) with the necessary information in writing to let them make the benefit-risk assessment of the use of this inactivated autogenous vaccine.

The manufacturer and / or attending veterinarian shall report any suspected quality defects and any suspected adverse reactions / events related to the use of the autogenous veterinary vaccines to the competent authority. In case of serious quality defects or serious adverse reactions the autogenous vaccine manufacturer or attending shall report immediately (within 15 days) to the responsible authority.

2. Starting materials (excluding isolate/antigen)

Starting materials include all components which are used in the manufacture of the autogenous vaccine (including active substances/seed materials, cells used for the production of viral vaccine, culture medium, adjuvants, excipients and primary packaging). In this part starting materials except active substances/seed materials are addressed. Active substances/seed materials are addressed above.

For cells used in the production of viral vaccines a system of seed lot should be in place. Seed lot should be stored as long as required by the responsible authority. Cell cultures used for the production of autogenous vaccines shall comply with Appendix XV J (Vet) 1. Cell Cultures for the Production of Vaccines for Veterinary Use; for extraneous agents testing, the list of agents to be tested is limited to those that cannot be excluded through a risk assessment. Testing methods for the detection of extraneous agents must be validated.

3. Production

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 by a validated method before inactivation and a maximum pre-inactivation titre / count established.

Antibiotics should not be added during the production of an inactivated autogenous vaccine. If the use of antibiotics during manufacture cannot be avoided, they must comply with Maximum Residue Limits (MRL) Regulations of the region and the use should be justified. Antibiotics that are classified as critically important should not be used during production.

The MRLs for pharmacologically active substances defined by food regulations shall be met for autogenous vaccines intended for food-producing species: MRLs pursuant to the regulations of the relevant region and Veterinary Vaccines concerning thiomersal and formaldehyde.

If preservatives are used, the efficacy should be tested as required by the pharmacopoeia.

3.1. 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. A suitable temperature must be maintained through the whole inactivation process.

A validated inactivation process and test for complete inactivation is critical for ensuring the safety of an autogenous vaccine and a robust data package will be required at the time of submission or fulfilled as part of the condition of authorising the manufacture of the vaccine.

The validation of the inactivation can be carried out exemplarily on a strain of one group of pathogens (strain X of YYYY spp.) and justification of the relevance / representativeness of the selected exemplar strain to the other strains of the group of pathogens must be provided.

The maximum titre of the vaccine microorganism capable to be inactivated by the selected method of inactivation is established based on the inactivation kinetics data. Extrapolation of inactivation kinetics results to higher pre-inactivation tires than that those used in the corresponding validation studies is not acceptable. It is permitted to concentrate a representative culture to demonstrate kinetics at the highest titre that may be achieved during routine manufacture with justification that this represents a worst-case situation.

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 requirements of the monograph for Veterinary Vaccines apply.

4. CONTROLS ON THE FINISHED PRODUCT

Before the finished inactivated autogenous vaccine is supplied to the veterinarian for administration to the animal, it must be subject to the following tests as a minimum:

Sterility The sterility should be tested according to Appendix XVI A. Test for Sterility. In case of small batches, samples for sterility testing can be taken from the bulk during filling. Validation of the test should be provided according to Appendix XVIII Methods of Sterilisation. Test for Sterility and should be performed on samples representative of the bulk / finished product, matrix, and excipients.

Free formaldehyde Where formaldehyde is the inactivation agent.

Preservative The preservative content should be determined, if applicable and the limits set according to the pharmacopoeia.

On-farm safety test An on-farm safety test is a requirement and satisfactory results obtained before use of the vaccine batch is extended to the entire group of animals to be vaccinated. In general, the test is conducted in at least two animals of the target species on the site of use of the vaccine and monitored for an appropriate period of time. The competent authority should be consulted on the requirements for dosage and monitoring periods and the exact method must be agreed before the test is conducted.

Bacterial vaccines

Endotoxin content The endotoxin content should be tested as required by the SC IC Guidelines for using the Test for Bacterial Endotoxins (in case of use of Gram-negative pathogens or other microorganisms producing endotoxins - to be determined by the competent authority).

Viral vaccines

Absence of extraneous agents Absence of extraneous agents should be ensured according to requirements of Appendix XV J (Vet) 2. Management of Extraneous Agents in Immunological Veterinary Medicinal Products. A risk assessment approach can be conducted considering the health status of the animals from which the isolate originated, other isolates handled at the sites of isolation and manufacture, the starting materials and control measures during production including the inactivation kinetics validation, the list of pathogenic viral extraneous agents relevant to the species. When a risk assessment ensures freedom of relevant viral extraneous agents at the final product stage, no additional tests for viral extraneous agents are performed on the final product. Otherwise, the final

product is tested for relevant potential viral extraneous agents as identified relevant to the species. Validation of any test used for extraneous agents testing should be provided.

5. STABILITY

Finished product should be stored and transported at 2-8°C and protected from light unless appropriate supporting data or justification is provided. Tests on the stability of the finished product are not expected for inactivated autogenous vaccines. Storage in appropriate conditions for 12 months starting from the date of final filling is considered acceptable. A longer shelf life may be granted if appropriate supporting data or justification are provided or as agreed with the competent authority.

As no studies on in-use stability in general are available for these vaccines, the filling size must be chosen in such a way that the content of one container can be used up within one working day (8 hours).

6. LABELLING

In principle the labelling should comply as far as possible with the provisions laid down in the pharmacopoeia.

The following considerations 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:

— Name and address of the manufacturer.

— Batch number.

— Expiry date.

— Composition: Inactivated microorganism(s) / antigen(s) and adjuvant(s); and where applicable any antimicrobial preservative added to the vaccine.

— Name and address of the veterinarian.

— Dosing and method of administration.

— Target species and subcategory of animals for which the inactivated autogenous vaccine is intended.

— Details of the farm/unit where the vaccine is to be used.

— Storage conditions.

— The words “For animal treatment only”.

— Any further precautions given in the prescription issued by the veterinarian.

— Precaution regarding handling of the unconsumed or unused inactivated autogenous vaccine.

— Withdrawal period if relevant.

1 The VMR is available on Legislation.gov.uk.