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SC II Inactivated Autogenous Veterinary Vaccines

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 when a disease affects a specific group of animals and (1) where no authorised vaccines suitable for the target animal species are available or (2) 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 medicinal products are not considered effective in controlling the disease outbreak. In these circumstances a veterinarian can use an Inactivated Autogenous Veterinary Vaccines prepared from pathogens obtained from an animal or animals on a farm or unit and use it for the treatment of that animal or animals in the same farm or unit.

It may be possible to use Inactivated Autogenous Veterinary Vaccines in farms or units that are geographically distinct but part of the same integrated breeding, rearing and / or production chain. In this case animals may need to be vaccinated before transferred to the unit where the pathogen is present. It is recognised that in aquaculture pathogens move freely in water and therefore may infect separate aquaculture units. Any epidemiological link to justify the extent of use of an Inactivated Autogenous Veterinary Vaccine is to be defined and documented by the prescribing veterinarian and documentation made available for review by the competent authority, if required.

Inactivated Autogenous Veterinary Vaccines prepared for use in an individual country should only be prepared from pathogens isolated in that country.

Inactivated Autogenous Veterinary Vaccines are an important additional prophylactic tool to assist in the management of diseases which would normally require antibiotic treatment and thereby reduce the risk of antimicrobial resistance.

2. LEGAL PROVISIONS AND CONDITIONS FOR USE

Inactivated Autogenous Veterinary Vaccines are intended to be used as a response on a limited scale and for 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. Inactivated 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 2013, as amended (VMR)[1] and Inactivated Autogenous Veterinary Vaccines manufacturers can apply for an authorisation to allow them to manufacture a specific Inactivated Autogenous Veterinary Vaccine, providing a veterinary surgeon has confirmed a need and fully justified the use of an Inactivated Autogenous Veterinary Vaccine in place of 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

Collection of samples and identification of the pathogen

A proper diagnosis of the infectious disease on the farm or unit must 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 Veterinary 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 Veterinary Vaccine or diagnostic laboratory.

Traceability of the samples taken to obtain the pathogen used to manufacture the vaccine 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 Inactivated Autogenous Veterinary Vaccine manufacturer. General guidance is included in *Supplementary Chapter V F. Aseptic Preparation of Unlicensed Medicines*.

For viral Inactivated Autogenous Veterinary Vaccines, isolation and purification should be done in accordance with the requirements of the monograph for Veterinary Vaccines.

Organisms used for the Inactivated Autogenous Veterinary Vaccines production must 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.

Use of the isolate as starting material

Viruses and bacteria used in the manufacture of Inactivated Autogenous Veterinary Vaccines are handled in a seed-lot system. A record of the origin, date of isolation and passage history (including purification and characterisation procedures) should be maintained for each seed lot.

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

Viral seed material should be shown to be free of extraneous agents according to Appendix XV J (Vet) 2. Management of Extraneous Agents in Immunological Veterinary Medicinal Products. 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 encephalopathies (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 & HealthCare (EDQM) may be suitable. The requirements of the monograph for Veterinary Vaccines apply.

All starting materials used in the preparation of Inactivated Autogenous Veterinary Vaccines should comply with relevant pharmacopoeial standards (including the monographs for Substances for Pharmaceutical Use and Pharmaceutical Preparations).

For starting materials that do not 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 appropriately according to the requirements of the competent authority.

Adequate measures should be in place to avoid contamination with other seeds or antigens not intended to be formulated with the Inactivated Autogenous Veterinary Vaccines.

Re-use 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 Inactivated Autogenous Veterinary 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, specifications for all types of Inactivated Autogenous Veterinary 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 Veterinary Vaccines prescription for the selected strains and their justification of use of the vaccine. Records should allow tracing back all manufacturing operations and isolation history.

The holder of the authorisation to manufacture Inactivated Autogenous Veterinary Vaccines (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 Veterinary Vaccine and the name of the veterinarian 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 competent 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 the Inactivated Autogenous Veterinary 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 Inactivated Autogenous Veterinary Vaccines to the competent authority. In case of serious quality defects or serious adverse reactions the Inactivated Autogenous Veterinary Vaccines manufacturer or attending veterinarian shall report as soon as possible to the competent authority.

2. Starting materials (excluding isolate / antigen)

Starting materials include all components which are used in the manufacture of the Inactivated Autogenous Veterinary Vaccines (including seed materials, cells used for the production of viral vaccine, culture medium, adjuvants, excipients and primary packaging). In this part of the chapter starting materials, except seed materials, are addressed. Seed materials are addressed above.

A seed lot system should be in place for cells used in the production of viral vaccines. The seed lot should be stored as long as required by the competent authority. Cell cultures used for the production of Inactivated Autogenous Veterinary 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 Veterinary Vaccines. 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 for human use by the World Health Organisation should not be used during the production of Inactivated Autogenous Veterinary Vaccines.

The MRL for pharmacologically active substances defined by food regulations, such as thiomersal and formaldehyde, shall be met for Inactivated Autogenous Veterinary Vaccines intended for food-producing species.

If preservatives are used, the efficacy should be tested as required by the general monographs for Substances for Pharmaceutical Use and Pharmaceutical Preparations.

Inactivation Products should be inactivated by the addition of an appropriate 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 throughout the whole inactivation process.

A validated inactivation process and test for complete inactivation is critical for ensuring the safety of an Inactivated Autogenous Veterinary 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 of being inactivated by the selected method of inactivation is established based on the inactivation kinetics data. Extrapolation of inactivation kinetics results to higher pre-inactivation titres than 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 Veterinary Vaccines 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. Appropriate validation of the test must be conducted. Test for Sterility should be performed on samples representative of the bulk / finished product, matrix, and excipients. In case of small batches, samples for sterility testing can be taken from the bulk during filling. Validation of the test should be provided.

Free formaldehyde A test for free formaldehyde is required where formaldehyde is used as the inactivation agent.

Preservative The preservative content should be determined, if applicable and the limits set according to the requirements for Substances for Pharmaceutical Use and Pharmaceutical Preparations.

On-farm safety test An on-farm safety test is a requirement and satisfactory results must to be obtained before use of the Inactivated Autogenous Veterinary 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 Inactivated Autogenous Veterinary 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

Bacterial endotoxins The endotoxin content should be tested as using the Appendix XIV C. Test for Bacterial Endotoxins. Where Gram-negative pathogens or other microorganisms producing endotoxins are used, the requirements should be agreed by the competent authority.

Viral vaccines

Absence of extraneous agents The absence of extraneous agents should be ensured according to the requirements of Appendix XV J (Vet) 2. Management of Extraneous Agents in Immunological Veterinary Medicinal Products. A risk assessment approach can be taken. This takes into account the list of pathogens relevant to the target species and species of origin of any biological starting material, as well as the health status of the animals from which the isolate originated, other isolates handled at the sites of isolation and manufacture, control measures used during production, including fully validated inactivation kinetics. 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 potential viral extraneous agents which are relevant to the species. Validation of any test used for extraneous agents testing should be provided.

5. STABILITY

Finished products should be protected from light, and stored and transported at a temperature of 2° to 8°, unless appropriate supporting data or justification is provided. Tests on the stability of the finished product are not expected for Inactivated Autogenous Veterinary 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.

Due to a lack of in-use stability studies for Inactivated Autogenous Veterinary Vaccines, the filling volume must be chosen so that the complete content of one container can be used within one working day (8 hours).

6. LABELLING

The small scale individual nature of autogenous vaccines means that there is a particular need for a standard approach to labelling to ensure that suppliers and users are aware of the composition, production and legal status of the product which allows them to make an informed risk assessment of the intended use. Critical items of information are name, strength, route of administration, dosage and warnings. These should be located together on the pack and appear in the same field of view.

The labelling requirements should be provided on the immediate packaging and, if present, on the outer packaging and the package leaflet, subject to the agreement of the competent authority. The label states:

— Name and address of the manufacturer.

— Batch number.

— Expiry date.

— Composition: Inactivated microorganism(s) or antigen(s) and adjuvant(s); and, where applicable, any antimicrobial preservative added to the Inactivated Autogenous Veterinary Vaccine.

— Name and address of the veterinarian.

— Dosing and method of administration.

— Target species and subcategory of animals for which the Inactivated Autogenous Veterinary Vaccines is intended.

— Details of the farm or unit where the Inactivated Autogenous Veterinary Vaccines is to be used.

— Storage conditions.

— The words “For animal treatment only”.

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

— Precaution regarding handling of the unconsumed or unused Inactivated Autogenous Veterinary Vaccines.

— Withdrawal period, if relevant.

1 The Veterinary Medicines Regulations is available on Legislation.gov.uk.