REGISTRATION DOSSIER STRUCTURE

FOR AN IMMUNOLOGICAL VETERINARY PRODUCT

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Contents

STRUCTURE OF A REGISTRATION DOSSIER FOR VETERINARY IMMUNOLOGICAL PRODUCTS

PART 1: PRODUCT INFORMATION

1. A Administrative Information

This section should include the completed and signed Mutual Recognition Application Form, including the name and brief description of the product, name and address of the applicant, the name and address of the manufacturer, list of countries where the immunological veterinary product is already registered, list of countries participating in this MR procedure.

1. B Summary of Product Characteristics, Primary container label, secondary container text (carton) and Packaging leaflet

1. B.1 Summary of Product Characteristics
1. B.2 Primary container label, secondary container text (carton)
1. B.3 Package leaflet

PART 2: QUALITY, MANUFACTURE AND CONTROL

2. A Quantitative and Qualitative Particulars

2. A.1 Table of qualitative and quantitative composition

Provide a table showing the qualitative and quantitative composition of the product, per dose, in terms of

Active ingredient(s)
The constituents of the adjuvant(s) where applicable
The constituents of the excipients including preservatives, stabilisers, emulsifiers, colourants, etc.

2. A.2 Containers

Provide detailed descriptions of the containers including their composition, the volume contained, and the closures, overage, if any, with justification.
Indicate how the containers are sterilised and if the method is appropriate.

2. B Method of Manufacture

2. B.1 Flow chart

Provide a flow chart showing the various stages of manufacture including antigen manufacture, any purification or concentration procedures, blending and filling. Show the stages where sampling is taken for Quality Control tests, naming the tests performed at each stage.

2. B.2 Detailed description of manufacture

Describe the key stages of manufacture detailing the precautions taken to ensure that the method produces a final product of consistent quality.
Include quantitative descriptions of all the substances used during manufacture and indicate the steps at which they are added.

Indicate the stages at which samples are taken for quality control testing during production. Descriptions of the tests performed will be included in sections 2D and 2E.

2. C Control of Starting Materials

Starting materials means all components used in the production of the veterinary immunological product. The OIE Manual, Ph. Eur., BP, USP or 9CFR requirements, where appropriate monographs exist, must apply to all substances in the product. References to other compendial standards will be considered on their merits.
Suppliers' certificates of analysis and suppliers' or applicant's raw material specifications must be provided in an Annex to this part of the application dossier.

2. C.1 Starting materials listed in pharmacopoeias

2. C.2 Starting materials not listed in one of these pharmacopoeias

2. C.2.1 Starting materials of non-biological origin

2. C.2.2 Starting materials of biological origin

Whenever possible, immunological production should be based on a seed lot system and on established cell banks. Each master seed lot must be assigned a specific coded description for identification purposes.
For production of antisera and other biologicals where production is carried out in animals, the origin, general health and immune status of the producing animals must be verified. Defined pools of source materials must be used.
The origin, source and history of starting materials shall be described and documented.

2. C.2.2.1 Cell seed materials

Details shall be provided including the source, history, seed lot system, designation/identification of master cell seed, processing to ensure freedom from extraneous agents, methods and results of testing for freedom from extraneous agents, and evidence that master cell seed tests comply with the OIE Manual, Ph. Eur, BP, USP or 9CFR (where applicable).
When cell seeds are used, the cell characteristics shall be shown to have remained unchanged up to the highest passage level used for production.

2. C.2.2.2 Seed materials

2. C.2.2.2.1 Master seed

Provide a record of the origin (i.e. country and species), date of isolation, storage conditions and passage history of all seed materials (eg virus, bacteria, fungi, protozoa and rickettsias), including purification and characterisation procedures and substrates used.
Provide the results of tests to demonstrate that the master seed lot is pure and free from extraneous agents must be performed as per OIE Manual, Ph. Eur., BP, USP or 9CFR, where monographs exist. For live attenuated immunological products, proof of the genetic and phenotypic stability of the attenuation characteristics of the seed must be provided.
A release specification of the master seed organism must be provided.

2. C.2.2.2.2 Working seed
The method of preparation and description of the working seed lot must be provided. The description must include the range of passage levels to be used for production, controls applied; tests carried out on working seed lot and storage conditions.
A release specification for the working seed organism must be provided.

2. C.3 Minimising the risk of TSE: Other substances of animal origin
The applicant should provide details of the source including the animal species. The extent to which this is adequately described and specified should be mentioned. The sterilisation processes and the controls applied to these substances should be described, especially with regard to extraneous agents. The validation data of the methods used should be provided.

2. C.4 Media preparation
The qualitative composition of media used for seed culture preparation and for production must be provided. The grade of each named ingredient must be specified. Where media or ingredients are claimed as proprietary, this should be indicated and an appropriate description provided. Ingredients that are derived from animals shall be specified as to the source species and country of origin, and must comply to compendial specifications where relevant.

2. D In-process control tests

2. D.1 Test methods and limits of acceptance
All critical analytical test procedures must be described in sufficient detail to enable the procedures to be assessed. Procedures must be validated where appropriate and the results of validation studies on all key procedures as identified by the manufacturer must be provided.
Applicants must provide information on critical tests performed for each control stage, as follows:

- title and test reference
- timing and frequency
- function of test
- a brief description of the test (a more detailed description should be given as the Annexe to Part 2 with details and results of the validation studies as appropriate).

The assay methodology for detoxified or inactivated immunological active substances must be provided in detail and the limit of detection specified.
Kinetics of inactivation or detoxification must be provided. If the inactivant is neutralised, the test for complete inactivation must be carried out immediately after neutralisation.

2. D.2 Antigen stability
Provide results to demonstrate the shelf life of the antigen(s) when stored prior to formulation into Finished Product.

2. E Control Tests on the Finished Product
Detailed information on final product tests performed on each batch, including the batch release specification, must be provided. This should include, as appropriate:

1. Appearance
2. Identification of the active (immunogenic) ingredient(s)

3. Sterility and purity including testing for *Mycoplasma*
4. Safety
5. Batch titre or batch potency
6. pH
7. Adjuvant (where applicable)
8. Preservative (where applicable)
9. Residual humidity (where applicable)
10. Viscosity (where applicable)
11. Emulsion (where applicable)
12. Inactivation and residual inactivant (where applicable).

For each test, applicants must provide information on:

- title and test reference (specify monographs where appropriate)
- timing and frequency
- function of the test
- brief description of the test. (A detailed description should be given as an Annexe to Part 2 with details and results of the validation studies where appropriate.)

The batch release specification must indicate the following:

- provision for identification of the batch undergoing test and the test date
- the name of each test
- the company test reference
- limits of acceptance of results.

2. F Batch to batch consistency

A summary of the results of tests on three consecutive batches of finished product must be provided to support the application for registration of the product to demonstrate batch to batch consistency. These batches may be pilot or production batches. If they are pilot batches, they must be representative of the production method described in Part 2 B. Full details of the results of the batch tests demonstrating conformity with the specifications should be included in the Annex to Part 2.

2. G Stability

The proposed shelf life of the product shall be stated.

2. G.1 Shelf life of Final Finished Product

Stability data should be provided for at least 3 batches of finished product stored in the final containers. The storage temperature should be stated together with the results of tests on the batches.

If the immunological veterinary product contains a preservative(s) the efficacy of the preservative throughout the product's shelf life should be established.

2. G.2 In-use shelf life

Stability data should be provided to support the in-use-shelf life of the reconstituted product to determine what the associated loss of titre or potency could be. In support of the proposed in-use shelf-life, data from at least two different batches of finished product should be provided. This data shall demonstrate compliance with the critical stability-indicating parameter(s) when the primary container is first opened and reconstituted and again at the end of the proposed in-use shelf.

2. H Other Information
Provide information relating to the quality of the product not covered by the previous sections.

PART 3: SAFETY

3. A Laboratory Tests

3. A.1 Safety of a single dose.

3. A.2 Safety of an overdose

3. A.3 Safety of a repeated dose

3. A.4 Other Safety studies, for live vaccines

-Spread of the vaccine strain
Spread of the vaccine strain from vaccinated to unvaccinated animals

-Dissemination in the vaccinated animal
Studies to demonstrate if the vaccine strain is present in animal secretions or the body of the vaccinated animal must be provided.

-Safety of a live, attenuated vaccine from Reversion to Virulence

-Recombination or genomic re-assortment of strains
Discuss the probability of recombination or genomic reassortment with field or other strains.

3. B Field Safety
The safety of the immunological product should be evaluated during field trials. Both safety and efficacy may be assessed during the same trial. Batches used in the trials must be manufactured according to the method described under Part 2 B.

3. C Other Safety issues to be considered

-Safety to the user

-Safety to the environment

-Safety of residues
Residues studies are not normally required for immunological veterinary products, however the effects of residues of constituents of the vaccine such as adjuvants or live zoonotic organisms used as antigens should be considered if necessary. Propose a withdrawal period if necessary.

-Interactions
Safety if administered at the same time as other immunological veterinary products

PART 4: EFFICACY

4. A Laboratory efficacy

Provide evidence of efficacy under reproducible controlled conditions. Efficacy will normally be demonstrated by administering a challenge infection with a heterologous strain. If protection against challenge infection has been shown to correlate with serology it may be possible to demonstrate efficacy by serological methods.

The batch(es) used in laboratory efficacy studies will be manufactured and tested according to the methods described in Part 2 of the dossier. It will be administered to the target species at the recommended dose by the recommended route of administration.

4. B Field efficacy

The immunological veterinary product should be tested in controlled field trials. The batch(es) used in field trials will be manufactured and tested according to the methods described in Part 2 of the dossier. It will be administered to the target species at the recommended dose by the recommended route of administration.

PART 5: BIBLIOGRAPHICAL REFERENCES