agriculture,
forestry & fisheries

Department:
Agriculture, Forestry and Fisheries
REPUBLIC OF SOUTH AFRICA

DIRECTORATE: AGRICULTURAL INPUTS CONTROL

GUIDELINES FOR REGISTRATION OF VETERINARY BIOLOGICALS

This guideline has been prepared for applicants to indicate minimum requirements for registration of veterinary biological in terms of Act No. 36 of 1947. It incorporates aspects of quality, safety and efficacy that are essential in the dossier and includes various aspects applicable in other countries. The guidelines are not intended as an exclusive approach and alternative approaches may be used but must be scientifically justified. The DAFF is committed to ensure that all medicines gaining market approval will be of the required quality, safety and efficacy and in doing so reserves the right to make amendments in keeping with the knowledge which is current at the time of consideration of data for market approval of veterinary products.

REGISTRAR OF ACT NO. 36 OF 1947

J M MUDZUNGA

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PURPOSE

The purpose of these guidelines is to detail the requirements for registration of veterinary biologicals in terms of Act 36 of 1947, in order to prove that the use of the product according to label claims (as far as recommended age, dosage, route of administration and type of species are concerned) should have the desired effect as claimed on the label.

PLEASE NOTE THAT THESE GUIDELINES PROVIDE THE MINIMUM DATA REQUIRED. PLEASE ENSURE THAT, PRIOR TO SUBMISSION, THE DOSSIER COMPLIES WITH THESE MINIMUM REQUIREMENTS, OR THE DOSSIER WILL BE REJECTED, WHICH WILL UNNECESSARILY DELAY THE PROCESS.

These guidelines do not preclude the use of other recognised guidelines, e.g. VICH, EU guidelines and directives, USDA/APHIS Code of Federal Regulations (CFR), etc.

GENERAL

Guidelines will be updated from time to time, where necessary.
Deviations from these guidelines will not generally be acceptable, unless **scientifically motivated and permission requested.**
Additional requirements with regard to specific contaminating agents (e.g. TSE/BSE) prescribed in other documents should also be complied with.
Registration and use of veterinary biologicals should not be in conflict with the provisions of any other Act, e.g. Animal Diseases Act, 1984 (Act No. 35 of 1984), Genetically Modified Organisms Act, 1997 (Act No. 15 of 1997).
It is the applicant's responsibility to present requested data for both Directorate: Animal Health and Directorate: Biosafety/Genetic Resources where veterinary biologicals contain vaccine organisms or strains not previously registered in this country, or contains new genetically modified strains that have not previously been registered in this country. The Registrar of Act 36 of 1947 must receive this correspondence before further evaluation can proceed.
Contact person at Directorate: Animal Health – Dr M Maja (Director)
Information required: application form (fully completed) and package insert. Certain data may be requested if required by Dr Maja.
Contact person at Directorate: Genetic Resources – Ms NC Netnou-Nkoana (Noluthando)
Information required: application form (fully completed) and data detailing genetic processes involved.

Letters will be supplied by both Directorates, indicating whether the vaccine may be registered for use in this country. A copy of the letter must accompany the application for registration.

DATA REQUIREMENTS

A. GENERAL INFORMATION

1. Table of Contents
2. Purpose of Application
3. Justification of new vaccine/new use

4. Summary
5. Foreign registration status and proof thereof.
6. GMP certification of manufacturer and proof thereof.
7. Approved International package insert (text in English) and proposed South African package insert.
8. Written approval for use of the vaccine by Directorate: Genetic Resources and Directorate: Animal Health (where applicable)

B. PRODUCTION AND QUALITY CONTROL OF THE VACCINE

The quality of the vaccine is of prime importance, as consistency and reproducibility of the finished product will influence the safety and efficacy of the product. Section B of the Data Requirements has been adapted in these guidelines to make provision for Production and Quality Control of the vaccine.

Wherever possible, immunobiological production should be based on a seed lot system and on established cell banks.

1. MASTER SEED AND WORKING SEED PRODUCTION

MASTER SEED

The most important aspects to be addressed are as follows:

- History of development of the Master Seed Lot, including date of isolation, origin and source of the cell line, strain/s of organism/s, identification of strain and media used for their multiplication, storage conditions, passage history of all seed materials including purification and characterisation procedures.
- Minimum and maximum number of passage levels from Master Seed to production level (should not exceed 5 unless scientific justification is provided).
- Storage conditions of MS (Master Seed) aliquots must be detailed.
- Identification of organism and strain of MS by e.g. morphological, serological, biochemical tests.
- Strain/s of organism/s of MS must be confirmed.
- Preparation, manipulation of strain/s.
- Controls and tests performed on the MS must detail specifications as well as methodology:
    - Purity
    - Identification of organism and strain
    - Proof of freedom/absence of contaminants and extraneous organisms
    - Titre/s of organism/s (range or minimum titres)
    - Virulence (safety)
    - Immunogenicity (efficacy)
- A release specification for the MS must be provided.

WORKING SEED/PRODUCTION SEED

The most important aspects to be addressed are as follows:

- Method of preparation and description of the Working Seed Lot.
    - Method and frequency of identification of the organism/s in cultures/media.
    - The range of passage levels to be used for production.

- Composition and reaction of cultures/media used for seed and production cultures.
- Details of containers used for growing cultures.
- Methods of preparing suspensions for seeding and inoculation.
- Technique of inoculation.
- Observations and characterisation of growth.
- Details of attenuation – if applicable for the vaccine.
- Harvesting, including handling and preparation of the cultures and media for harvesting, minimum and maximum time between inoculation and harvest, specification for acceptable harvest material (minimum titre), handling discarded material.
- Time and conditions of incubation and storage details.

- Quality controls and tests performed on the WS must detail specifications as well as methodology:
  - Purity
  - Identification of organism and strain
  - Proof of freedom/absence of contaminants and extraneous organisms
  - Titre/s of organism/s (range or minimum titres)
  - Virulence (safety)
  - Immunogenicity (efficacy)
- Storage conditions of WS aliquots must be detailed.
- A release specification for the WS must be provided.

2. FORMULATION

- Active constituents: maximum and/or minimum release titres and end of shelf life titres must be provided. Units and proof of the specifications for the biological component must be supplied.
- Adjuvant/s: if applicable must be detailed and specifications provided.
- Excipients: including diluents, preservatives, stabilisers, emulsifiers, colourants and markers where applicable.
- Reference to standards, e.g. pharmacopoeial references, in-house standards, regulatory requirements where applicable.
- Function of each ingredient.
- Percentage residual moisture (and specifications) in the case of live vaccines must be supplied.
- Percentage inactivant (and specifications) in the case of inactivated vaccines must be supplied.
- Quantity of each ingredient in the formulation and the appropriate units must be provided, e.g. $TCID_{50}$, CCU, CFU, mg, mℓ per dosage unit.
- **Important:** it must be confirmed that this was the formulation utilised for clinical trial purposes.
- Products of animal origin used in the formulation **must** comply with international guidelines (e.g. TSE/BSE status) and a certificate from the supplier as proof of compliance must be submitted.

3. STARTING MATERIALS

There are essentially three classes of cell substrate/production medium:

1. **Live animal culture, e.g. specific pathogen-free (SPF) eggs, chickens, cattle**
2. **Tissue culture (continuous cell lines or primary cells)**
3. **Microbiological media.**

- Specifications and functions of all starting materials must be supplied.
- The specifications must be properly presented by the manufacturer and/or QA laboratory i.e. on a letterhead, dated and signed by the responsible person. Certificates of analysis must be recent (not older than batches utilised in the manufacture of the last 3 batches of finished product). CoA's must be on a letterhead, dated and signed by the responsible person. Only CoA's compliant with all specifications will be acceptable.
- Specifications must be qualified i.e. pharmacopoeial or non-pharmacopoeial:
- **Pharmacopoeial references:**
  - Name, origin, code and scientific name of the starting material/s.
  - Copies of the reference/s must be supplied in the dossier and must include the title of the monograph and year of publication, together with the certificate of analysis.
- **Non-pharmacopoeial references:**
  - Scientific justification for using non-pharmacopoeial references must be included in the dossier with copies of the specifications, controls and tests performed on the starting materials.
  - Name, origin, code and scientific name of the starting material/s.
- For most mammalian vaccines, the use of primary cells is not acceptable for the manufacture of vaccines. If a vaccine has to be produced on primary cells, they should be obtained from a specific pathogen free herd or flock with complete protection from introduction of diseases.
- All materials of animal/biological origin used prior to or during manufacture of a veterinary biological must be tested and certified free of any contaminating material or organism. Indicate methods of tests used to determine that starting materials of animal/biological origin are free of contaminants (or supply relevant documentation). Wherever practical, manufacturers are encouraged to minimise the use of such substances.

❖ **If cell substrate/production medium consists of SPF eggs, primary SPF chicken cells or other SPF cells, the following information must also be provided:**

- The source of SPF eggs or chickens or other animals.
- SPF status or applicable tests to confirm this.
- History.
- Disease prevention protocols.
- Disease/agent monitoring procedures and testing specifications.

❖ **If cell substrate/production medium consists of tissue culture substrates (continuous cell lines), the following information must be provided:**

- Source of the master seed
- Treatment of the master seed since origin
- Seed lot system
- Designation/identification of master seed
- Master seed testing method for sterility, and freedom from extraneous agents and specific adventitious virus contamination
- Proof of freedom from Mycoplasma (where applicable)
- Evidence that master cell seed tests comply with pharmacopoeia (where applicable).

- **If the cell substrate/production medium consists of microbiological media:**

    - Name of the medium and composition
    - Raw material specifications including any tests required for freedom from specific agents
    - Method of preparation and sterilisation

- **Media preparation**

    - Methods of preparation and method of sterilisation of all media used in such a way that they become ingredients of the product, including the controls applied, the testing carried out and the certificates of analysis of ready-to-use media.

- **Preservatives**

    - The efficacy of preservatives in multidose containers should be demonstrated.
    - Immunological veterinary products in single dose containers do not normally contain a preservative.
    - The concentration of the preservative in the final filled vaccine and its persistence throughout shelf life must be checked.
    - If no preservative is included, the applicant should demonstrate that the product remains acceptable for its recommended period of use after broaching the vial.
    - Preservatives may not be added to products that are to be freeze-dried, though they may be present in the diluent for reconstitution when the innocuousness of the preservative for the lyophilised product has been proven.
    - The test procedures and microorganisms employed for demonstrating preservative efficacy should conform to pharmacopoeial specifications, e.g. Ph. Eur. Monograph “Efficacy of Antimicrobial Preservation”.
    - Additional evidence of microbiological safety, for example by a multiple vial broaching test is recommended.
    - The finished product specification for any preparation containing a preservative should include tests for both the identity and concentration of the preservative. In the case of concentration, a specification within ± 15% of label claim at time of release is acceptable.
    - For products containing a preservative, the confirmation of preservative for the period of the shelf life should be demonstrated during the stability studies.

4. MANUFACTURING PROCEDURE

- **Manufacturer**

    - GMP status of the manufacturing facility and proof of compliance with GMP.
    - In the case of local manufacturers, if no GMP certification has been granted, a GMP auditor nominated by either DAFF or MCC authorities may inspect the premises and all records. An official report can be issued.
    - International manufacturers must submit a current and acceptable certificate of GMP from the regulatory authority based on a satisfactory audit by that authority.
    - Evidence that the product is manufactured to a standard comparable with international standards, such as VICH, USDA – CVB (9 CFR), APVMA requirements for Veterinary Biologicals may be submitted, if a scientific justification and motivation is supplied.

- **Manufacturing process of the final product**

  - A flow chart of the manufacturing process, showing each step from production of the active constituent to formulation of the final product in final containers. Flowchart should show the stages at which critical in-process control tests are carried out.
  - Detailed description of each process step in the flow chart, e.g. amplification/culture, harvesting, purification, inactivation procedures (**see ✹ below**), blending, adjuvanting, bulk antigen storage, filling of containers, lyophilisation, as relevant.
  - Critical in-process quality control and terminal control testing must be provided.

✹ **Inactivation:**

The following procedures must be followed:

- Each pilot production batch must be shown to have been appropriately detoxified or inactivated using relevant test standards wherever available.
- The inactivating agent and the inactivation procedure shall be shown, under conditions of vaccine manufacture, to inactivate the vaccine organism.
  Normally the organism shall be shown to be inactivated within a time period equivalent to not more than 67% of the inactivation process used during manufacture.
  - Aziridine. If an aziridine compound is used as the inactivating agent then it must be demonstrated that no inactivating agent remains at the end of the inactivation procedure. This may be accomplished by neutralising the inactivating agent with thiosulphate and demonstrating residual thiosulphate in the bulk harvest at the completion of the inactivation procedure.
  - Formaldehyde. If formaldehyde is used as the inactivating agent, free formaldehyde testing should be carried out. Not more than 0.05% of free formaldehyde shall be present in the vaccine unless this higher concentration has been shown to be safe.
  - Betapropriolactone. Where betapropriolactone (BPL) is used as the inactivant, it must be demonstrated, at the end of the inactivation procedure, that no significant amount of BPL is present in the inactivated bulk.

- **In-process control tests during production**

  - All critical analytical test procedures performed for each control stage, including title, timing and frequency, function of test, description of test, must be provided.
  - Procedures must be validated where appropriate and the results of validation studies on all key procedures, as identified by the manufacturer, must be provided.
  - Where applicable, current pharmacopoeial monographs must be used.

5. CONTAINERS AND PACKAGING

- The **specifications** for the immediate container and stoppers/closures (including acceptable tolerances) must be supplied.
- **Diagrams/sketches with measurements** must accompany this data.
- The **material** used for the immediate container must be clearly detailed.
- **Filling volume** of product, e.g. 1 mλ, 1000 mλ, etc.
- The **method, type and material of closure** must be clearly detailed.
- **Additional packaging**, e.g. cartons, and containers per carton, must be described.
- **Diluent containers and packaging** (where relevant) must be described.

6. FINISHED PRODUCT

Control tests on the finished product:

- The assay methodology for detoxified, inactivated or live veterinary biologicals must be thoroughly detailed, the limit of detection specified and validation of analytical techniques provided.
- In the case of sub-batches which differ only due to their processing after bulk blending, for example in the filling session or vial size, some tests may be carried out on the final bulk or on one of the sub-batches.
- Detailed information on final product tests performed on each batch or sub-batch of vaccine produced, including the batch release specifications, must be provided:
  - Identification assay for active components – titres
  - Safety
  - Purity of active components
  - Sterility
  - Potency
  - Identification assay for adjuvants
  - Moisture (if applicable)
  - Percentage inactivant (if applicable)
  - Confirmation that finished product is free of all extraneous agents (including Mycoplasmas, Salmonella and other bacterial or fungal contaminants)
  - pH
  - Other parameters, as required, for a specific vaccine
  - Diluent sterility confirmed, if applicable
- Final product release control results from at least two, preferably 3, consecutive most recent production batches must be submitted. Specifications and certificates of analysis of finished product must be submitted.

PLEASE NOTE: **IMPORTANT POINTS TO REMEMBER WHEN PRESENTING DATA**

- **ASSAY RESULTS ALONE ARE NOT ACCEPTABLE. RESULTS FOR ALL PARAMETERS MUST BE PRESENTED.**
- **SPECIFICATIONS AND PARAMETERS MUST BE CLEARLY DETAILED – CERTIFICATES OF ANALYSIS MUST REFLECT ALL PARAMETERS & LIMITS ACCORDING TO SPECIFICATIONS.**
- **THE TERM "COMPLIES" IS NOT ACCEPTABLE FOR REGISTRATION DATA PURPOSES – THE VALUE OR DESCRIPTION OF THE RESULT MUST BE DETAILED.**

7. STABILITY

- Real-time studies must be carried out
  - **On the formulation as applied for**
  - **In the container material(s) and size(s) as applied for**
- When shelf-lives of less than one year are expected, real-time/real-temperature stability studies should be conducted approximately monthly during the first three months and at three-month intervals thereafter, so as to generate multiple measurements (a minimum of five tests three months apart) for the purpose of assessment.

- For products with expected shelf-lives of greater than one year, the studies should be conducted every three to four months during the first year of storage, every six months during the second year, and annually thereafter.
- A summary of the proposed shelf-life, storage conditions and justification for the proposed shelf-life.
- Information must be supplied for at least three batches:
    - Packaging of stability test product, especially confirmation of immediate container and details of container size, material, type, method of closure.
    - Details of storage conditions (temperature, relative humidity).
    - Parameters evaluated and tests performed according to the stability protocol. Specifications must also be clearly detailed, referenced and/or motivated. Details of time-points when tests conducted must be clearly detailed.
    - For multi-dose formulations, preservative efficacy testing to validate inclusion of the preservative chosen. Tests should be consistent with those indicated on the batch release specification.
    - Titre(s) of vaccine/toxoid units etc., sterility and safety tests (as included on the batch release specification) at the final time-point specified in the stability test protocol.
    - Tabulated results including the batch number, date of manufacture, dates of testing and storage conditions.
    - For inactivated multi-dose products which may or may not require reconstitution or dilution before use, stability data to support the in-use stability (recommended time and conditions after broaching) may be submitted. If not, labelling must indicate to destroy unused contents and packaging.
    - Where an applicant provides in-use stability for a vaccine requiring reconstitution prior to administration, the vaccine shall be reconstituted with the diluent as recommended and the resulting mixture titrated or tested for potency immediately after reconstitution and again after recommended usage/storage (whichever is applicable).
    - Information on the effect of external influences, such as sunlight and heat, on the stability of the product when being used (where applicable).
    - Stability data for a multivalent formulation may be extrapolated to formulations of lower valency provided that the quantity of each antigen, adjuvant and excipients of each combination immunobiological under consideration are approximately identical, and providing that the market packaging and recommended storage conditions are also identical. Variation in any of these parameters will require the generation of separate stability data for each formulation.

8. ANALYSIS AND VALIDATION OF METHODS OF ANALYSIS

Analyses for any step of the manufacturing process should be conducted by an accredited QA laboratory with suitably qualified staff members, trained specifically in all aspects of analytical techniques and validation of such techniques.

For data dossiers submitted, the name and physical address of the analytical laboratory, proof of GLP accreditation and details of staff member(s) (including CV's) must be provided.

The responsibility of submitting correct and detailed analytical data lies with the applicant. It must be ensured that all relevant parameters for each analysis are included, according to specifications. Reports (including validation reports) and certificates of analysis must be provided.

CLINICAL STUDIES
Laboratory and field clinical trials may be necessary.
Applicant must index safety and efficacy trials under relevant sections.

GENERAL:

1. Use the recommended dose (except in the case of overdose studies) and vaccination schedule per proposed label instructions.
2. The dose to be used shall contain the required titre or potency for which the application is submitted.
3. Representative batches should be manufactured using procedures outlined in the dossier.
4. Route, method, administration schedule, target species including the most sensitive class or members of the target species.
5. Any adverse reactions should be documented.
6. Methods should be fully described and validated where necessary.
7. Detailed discussion and conclusions must be provided, based on the results of the pen/laboratory studies and clinical/field trials.
8. Unless otherwise justified, the efficacy trial should compare a group of vaccinated animals with an equivalent group of unvaccinated or placebo-vaccinated controls.

C. TARGET ANIMAL SAFETY STUDIES

Safety studies should include:

- Single dose studies
- Repeat single dose studies (where applicable)
- Overdose studies 2X for inactivated vaccines and 5X or 10X (depending on data available) for live vaccines.
- Shed/spread of the vaccine organism in the case of live vaccines.
- Reversion to virulence in the case of live vaccines.
- Immunological effects.
- Reproductive effects (if applicable).
- Compatibility or non-compatibility with other vaccines or medication (if known or data available). Special precautionary measures must be stated on labelling where relevant.
- Environmental effects.
- Data in non-target species (if available).

Single dose safety studies

1. Each animal species and category, including animals of the minimum age at which the product is to be used, must be tested with a single dose taken from either a pilot or production batch.
2. Adverse systemic and/or local reactions must be documented.
3. The single dose should investigate possible systemic side-effects of vaccination with the product, e.g. allergic reactions, mortality, anorexia, pyrexia, changes in behaviour, weight gain

Repeat dose and overdose safety studies

1. The interval between repeated administrations must not be longer than that recommended for field use.
2. This test would not be required where the product is administered only once in a lifetime. Using the recommended dose based upon the maximum release titre, an overdose is usually 2× for inactivated vaccines and 5X or 10X for live vaccines.

Overdose and repeat administration studies may be carried out as follows:

1. Rectal or other temperature monitoring must be done for one day before vaccination, one day after vaccination and thereafter weekly to check for elevated temperatures. If there is no evidence of elevated temperature reactions, may then this may be discontinued. Monitoring of signs of systemic or local site reactions must be done. Performance monitoring, including appetite and general disposition, should be carried out daily.
2. Examination of injection sites at regular intervals for 24 to 96 hours after administration. If significant lesions are still present at the end of 96 hours, observation should continue daily until lesions have subsided to an insignificant level.
3. Examination of the administration site by inspection and palpation for signs of inflammation by inspection and palpation must be done. The dimensions of palpable lesions should be recorded. The injection site should be checked on the final day of clinical observation.

INTERACTIONS WITH OTHER PRODUCTS

Claims that the vaccine can be administered simultaneously or in combination with other products must be substantiated. Any known interactions with other products must be declared.

D. ENVIRONMENTAL AND OCCUPATIONAL HEALTH AND SAFETY

Potential occupational health and safety risks associated with the manufacture and use of the product include:

- Safety instructions
- Use of personal protective equipment
- First aid instructions
- Information for medical practitioners

Environmental risks to be addressed include:

- Extent of exposure of the product, its active constituents or relevant metabolites to the environment.
- Proposed disposal methods for unused material or waste products.

E. TARGET ANIMAL EFFICACY STUDIES

Efficacy studies should include:

- Minimum protective dose and vaccination schedule.
- Immunogenicity - confirmation of protection against challenge in the target species.
- Influence of passively acquired and/or maternally derived antibodies on efficacy, if applicable.
- Onset of immunity.
- Duration of protection.

- Timing of, and response to, booster vaccination.

Establishment of the minimum protective dose and vaccination schedule

1. This can be undertaken as a dose-response study or as a study to confirm that the chosen dose and vaccination schedule is efficacious in the target species. From this study the end of shelf-life titre may be established. Allowance may need to be given for assay variation in setting the end of shelf-life from the minimum protective dose.
2. The method for determining the minimum protective dose must be justified, particularly if a suitable laboratory challenge model or serological (or other) marker of protection is not available. A pharmacopoeial standard is appropriate where that standard has a long history of satisfactory use.

Interactions with other products

1. Studies of immunological compatibility shall be undertaken when simultaneous administration is recommended either by the applicant or in a usual vaccination schedule. If a product is recommended for administration in combination with or at the same time as another veterinary chemical product including a vaccine, compatibility, efficacy and safety must be demonstrated.
2. Any known interactions with other products must be declared.

Duration of protection

1. The results from vaccination-challenge trials under laboratory or clinical conditions may be used.
2. End-point studies should demonstrate the actual duration of protection provided.
3. Where the primary vaccination course involves more than one administration and/or a follow-up or booster vaccination is required, the level of protection afforded between administrations should be assessed.
4. The duration of protection provided by the primary vaccination schedule should be demonstrated by a challenge of vaccinated animals just before the recommended time for the start of re-vaccination.

E. RESIDUE STUDIES

For veterinary biological products, it will normally not be necessary to undertake a study of residues. However, where adjuvants and/or preservatives are used in the products, consideration shall be given to the possibility of any residue remaining in the foodstuffs. If necessary, the effects of such residues shall be investigated.

Residue depletion studies are thus not required for veterinary biologicals. However, certain ingredients in an injectable veterinary biological are irritant and may cause a local injection site reaction (especially inactivated vaccines). Also sero-conversion with live vaccines could result in vaccine reactions.

Thus a minimum withdrawal period of 21 days has been established for vaccines.

REFERENCES:

PLEASE NOTE: All the information and guidelines listed below may be referred to in data dossiers. Such information may be valuable to both the applicant and evaluator.
The applicant may also refer to guidelines not referred to hereunder, but which are internationally accepted.

1. **Guidelines for Inactivated Veterinary Vaccines. Dr A C E Pienaar.**

2. **Efficacy of Veterinary Biologicals. MCC Guidelines.**

3. **General Requirements for the Production and Control of Live Mammalian Bacterial and Viral Vaccines for Veterinary Use. Supplement to Directive 81/852/EEC, as amended by Directive 92/18/EEC.**

4. **United States Department of Agriculture (USDA) (1999). Code of Federal Regulations, Title 9, Parts 1-199. US Government Printing Office, Washington D.C., USA.**

5. **Office International des Epizooties (OIE) Manual of Standards for Diagnostic Tests and Vaccines, 2017.**

6. **European Agency for the Evaluation of Medicinal Products (EMA, 2007) 30 Churchill Place, Canary Wharf, London, E14 4HB, UK.**

7. **VICH - Veterinary Biologicals Guidelines.**

8. **APVMA - Veterinary Biologicals Guidelines.**

9. **East African Veterinary Biologicals Guidelines.**