GUIDELINES FOR THE SUBMISSION OF VETERINARY VACCINE DOSSIER

PRESENTATION

A cover letter stating clearly the purpose of the application must accompany TACB 1 form (*Official Form for Submission of Dossier / Dossier Check List for Registration of Animal Vaccines in Malaysia*). The form must be filled, signed and dated by the applicant.

Two copies of the vaccine's dossier must be paginated throughout, suitably bound and clearly identified. All material submitted must be in English and clearly legible. An authorized English translation must accompany any material not published in English. Arrangement of information in the dossier shall follow the format as stated in TACB 1.

PART 1: GENERAL INFORMATION

a) Name of vaccine (Trade and Generic Name)
   i. With details on type / serotype/ strain of organism

b) Name and address of the manufacturer

c) Name and address of manufacturing facility/ premise (if different from (b))

d) Country of origin

e) Copy of manufacturing/ establishment license or registration certificate of the manufacturer in the country of origin
   i. Malaysian manufacturer
      - All vaccine manufacturers in Malaysia must comply with the Malaysian veterinary code of Good Manufacturing Practices and has been accredited by DVS for GMP. They also must hold a current license from the local authority to manufacture veterinary vaccines.
   ii. Overseas manufacturer
      - Applicant must provide acceptable evidence that the vaccines are manufactured to a standard that comparable with Malaysian standards or other international standards (i.e. OIE, ASEAN, USA, EU, JAPAN etc.).
      - A current GMP certificate from the competent authority in the country of origin must be provided

- Copy of certificates must be certified by the competent authority in the country of origin.

f) Name and address of local agent/ Malaysian company

g) Copy of letter of attorney or authorization letter by the manufacturer
   i. Letter of authorization from the manufacturer to the appointed local agent shall be valid for at least 5 years.
   ii. Copy of letter of attorney must be certified by the competent authority in the country of origin or by Commissioner of Oaths

PART 2: OTHER INFORMATION AND SUPPORTING DOCUMENTS

a) Copy of assay certificate or certificate of release for 3 latest batches.
   i. All tests must be conducted in laboratory with Good Laboratory Practice (GLP) status.

b) Copy of registration certificate or free sale certificate from country of origin
   i. Including license number of company and vaccine details
   ii. Certificates must be valid at the time of the application and shall be accompanied by a valid English translation.
   iii. Copy of certificates must be certified by the competent authority in the country of origin.

c) Copy of registration certificate from 2 other countries
   i. Each certificate must be valid at the time of the application and shall be accompanied by a valid English translation.
   ii. Copy of certificates must be certified by the competent authority in the country of origin.

PART 3: VACCINATION REGIME

a) Vaccination schedule

b) Target age/ group

c) Dosage and route of vaccination
   i. The dosage should be expressed in terms of a veterinary medicinal product

ii. Route of vaccination should also include directions of proper use by the veterinarian, farmer or owner. Any special equipment needed for administration of the product should be mentioned

d) Diluents
   i. Name of the diluent
   ii. Packaging quantity
   iii. Name and address of the manufacturer
   iv. Any warning/ pre-cautions
   v. Data for vaccine stability at RT for 1 to 2 hours

PART 4: PACKAGING INFORMATION

a) Description of container
   i. Fill volume/ weight of container
   ii. Type of container
   iii. Material of the primary container
   iv. Type and material of stopper

b) Doses per package/ Pack sizes
   i. Should also include all pack sizes, number of units and number of doses for multi-dose vaccines

c) Instruction pamphlet and specimen of label
   i. Full instructions for the proper use of the product including vaccination schedules, warnings and cautions

d) Storage conditions
   i. Should contains information necessary for the correct storage of the product: temperature, light and humidity
   ii. Should also mentioned if there is special precautions for storage

e) Indications and contra-indications
   i. The indications should be clearly defined for the target species and should be substantiated by data in the dossier
   ii. Contraindications may be linked with a target species or a sub-group of the target species, the administration of the product by a particular route or administration in conjunction with other products. Furthermore, particular clinical diagnoses, concomitant diseases, age or sex may constitute contraindications. Other veterinary medicines or

classes of secutive should only be stated here, if such use has serious consequences (e.g. fatalities)

f) Side effects and precautions
   i. Precautions for use shall include precautions for use in animal and to the person administering the vaccines to the animals.
   ii. Precautions for use in animals- to provide clear information on how to ensure the safe use of the product in target animals
   iii. Precautions to be taken by the person administering the vaccines to the animals- risk resulting from the nature of the product, its preparation and use of any risks resulting form the particular characteristics of the user should be stated here.
   iv. Side effects/ adverse reactions – should include information on side effects/ adverse reactions attributed to the product when used as recommended. This section should also include information about any action that may be taken by the animal owner or the veterinarian in case of adverse reactions.

g) Batch serial number & expiry date
   i. Batch serial number & expiry date should appear on the label drafts

PART 5: TECHNICAL INFORMATION

5.1 Vaccine Production, control and shelf life

a) Master seed history (MS)/ Master Cell Stock (MCS) (when cell cultures are used for product preparation)
   i. Scientific name (for bacterial seed lots), pathotype, serotype and strain for the bacteria/ virus
   ii. History of acquisition of master seed lot (Origin of master seed, data of isolation, data of propagation)/ source of the cell line and its passage history
   iii. Storage of master seed
   iv. For genetically modified microorganisms, the source of the gene(s) for the immunogenic antigens and the vector microorganism should be identified. The gene sequences introduced into the seed microorganism genome during construction of the modified seed should be provided.

b) Vaccine attenuation process (for live/ attenuated vaccine)

i. Working seed for the production of vaccine – number of passages. The number of passages should be determined by data.

c) Master seed genetic/ master cell stock stability
   i. Genetic stability of the master seed/ master cell stocks should be demonstrated.
   ii. For genetically modified seed should also be tested to ensure stability and safety of the inserted gene sequences.

d) Master seed identity
   i. Methods of identification of MS to the genus and species level by laboratory tests shall be sufficient to distinguish the virus/ bacteria from other similar virus/ bacteria.
   ii. Data/ report and certificate of analysis of the MS should be attach as reference.

e) Master seed/ master cell stock purity
   i. Free of extraneous bacteria, fungi, mycoplasma and viruses
   ii. Data/ reports and certificate of analysis of the MS should be attach as reference.
   iii. MCS (Cell cultures) free from tumourigenicity

f) Substrate for propagation (including Master cell stock information)
   i. Substrate composition
   ii. Substrate purity, sterility & safety
   iii. Cell cultures free from oncogenicity and tumorigenicity

g) SPF status of production support (eggs, primary cell culture)
   i. For SPF eggs: reliable source (certificate of SPF eggs should be attached); tested for at least 21 pathogens

h) Other starting material of animal origin
   i. Source of the ingredients (type of animal) and country of origin of the animal(s) must be declared.
   ii. Samples of each lot of ingredient of animal origin which is not subjected to heat sterilization or other sterilization methods shall be shown free of bacteria and fungi
   iii. Each lot of ingredient of animal origin, except porcine trypsin must show to be free from cytopathogenic and/or haemadsorbing-inducing agents or other extraneous viruses
   iv. If porcine trypsin is used, test results must show that it must be free from porcine parvovirus

v. Media derived from bovine products from Europe- Freedom from BSE prion proteins. BSE free certificate must be attached.
vi. Vaccines meant for livestock for Muslim consumption – materials used are free from porcine origins.

i) Vaccine inactivation process (for killed/ inactivated vaccine)
   i. Data/ result of inactivation kinetics & safety margin for each organism must be shown
   ii. Inactivation test for each organism at each release must be shown
   iii. The virus/ bacteria shall be killed by an appropriate agent

j) Inactivation kinetic studies information (for inactivated antigens)

k) Chemical starting material
   i. Chemical composition of vaccine: chemical starting materials used in adjuvant/ emulsion/ suspension/ antibiotic, etc.
   ii. Identification and purity of each starting material should be given
   iii. Controls and test performed on the starting material and/or certificates of analysis
   iv. Levels of toxic components
   v. Antigenic mass per dose/ titer per dose of each organism and compare with minimum immunogenic dose
   vi. Antibiotics as preservatives: only one antibiotic shall be used as a preservative except for some permitted combinations (according to international standards). Antibiotic level in one ml of the vaccine shall be given.

5.2 Quality control on finished product

l) Sterility Tests
   i. Freedom from extraneous organisms.
   ii. Data/ results and certificate of analysis of the finished product must be attached

m) Inocuity Tests (For live vaccines)
   i. 2 times and 10 times field doses at recommended routes for all species of intended host
   ii. Validation are from field trial results
   iii. Overdose test is required for live vaccines shown to retain residual pathogenicity by induction of disease specific signs or lesions.
   iv. Other vaccines do not require overdose testing.

n) Moisture contents (for live vaccine)
   i. The maximum percent moisture in desiccated vaccines shall be stated in the Outline of Production and moisture content for the final container samples must be tested and found to be in accordance with the percent provided before.
   ii. Data/ results and certificate of analysis of the finished product must be attached

o) Viscosity of vaccine (for inactivated vaccines)
   i. Stability results for validation
   ii. Accelerated stability tests acceptable if confirmed by efficacy tests after expiry and 3 months beyond.

p) Purity tests for live vaccines
   i. Shall be tested for the presence of extraneous viable bacteria and fungi

q) Composition of final product
   i. The quantitative and qualitative composition for the active substance(s), excipients, adjuvant(s)
   ii. The usual name or chemical description shall be used

r) Nature of final products
   i. Type of vaccine: Lyophilised/ inactivated/ live attenuated/ recombinant/ DNA/ transgenic/ combination
   ii. Strength and presentation

5.3 Stability study

s) Stability study;
   i. Test must be done in three consecutive batches/ serials of completed product
   ii. Test must be done three months beyond the designated expiry date
   iii. Standard requirements and procedures must be attach in the dossier
   iv. Satisfactory test results should be demonstrated for all three batches/serials. Each subsequent batch/serial should be tested in the same manner.
   v. Stability test reports should include;
      - Product name
      - Batch number (3 consecutive batches) and manufacture date

- Storage condition
- Initial, interval and end date of test
- Name and signature of personnel conducting the test
- Parameters tested should be on purity, safety and potency
- Results

5.3 Vaccine safety

t) Field trials
   i. Must be done in different farms with different locations and different managements
   ii. Number of animals must be statistically significant

   iii. Safety Tests;
      - Vaccines organisms not pathogenic for intended host at recommended ages and routes of vaccination
      - Reversion to virulence
      - Vaccine inocuity at 10 to 100 times field dose (for live vaccines) or 2 times field doses (for inactivated vaccines)
      - Clinical signs exposure dosage

5.4 Vaccine Efficacy

u) Potency/ Challenge tests
   i. Must be done in intended host and/or progeny
   ii. Correlation data must be given
   iii. Vaccination to include all recommended routes and ages in intended hosts of various species and breeds
   iv. Appropriate challenge organisms, dose, route & duration post vaccination
   v. For efficacy test in other hosts: correlation data is required
   vi. Challenge results: Clinical signs typical disease under test & scoring system for clinical signs

v) Minimum immunogenic dose (Procedure for determination of MID)
   i. Vaccination challenge tests in intended hosts for each recommended route for each vaccine component

w) Immune levels and duration (challenge and serology results)
   i. Studies carried out in the intended hosts for all recommended routes of administration at all the recommended ages

x) Transmitted passive immunity in progeny (serology and or challenge) – when relevant

y) Shelf life
   i. Shelf life of the vaccine as packaged for sale
   ii. Shelf life after first opening the immediate packaging (where relevant)
   iii. Shelf life after dilution or reconstitution according to directions (where relevant)
   iv. Shelf life after incorporation into meal or pelleted feed/ broached/ open container (where relevant)

PART 5: GENETICALLY ENGINEERED VACCINES REGISTRATION – ADDITIONAL INFORMATION

a) Registration of genetically engineered vaccines must follow the same procedure of the conventional vaccine with additional information as stated below.

   i. Source materials
      - Identification, sources and strains of parental organism
      - Source, description and function of foreign genetic material

   ii. Construction of recombinant organisms
      - Name, origin, replicon function, regulator elements
      - Genes for and method of selection
      - Mode of introduction into producer strain
      - Constitutive and controlled expression
      - Cloning and fusion (if relevant)

   iii. Description of producer strain or cell line
      - Name, origin and identification
      - Potential microbial and/ or viral contaminants

   iv. Genetic stability
      - Genetic stability, phenotypic stability and potential combination. Host range/ specificity, tissue tropism and shed/ spread capabilities
      - Comparison of the modified organism to parental properties
      - Route of administration and admission

v. Safety studies

- May include studies documenting non-pathogenically and non-reversion to virulence by a number of back passages in the host animals, study to determine the fate of the microorganism when injected into the host and the ability or the organism to multiply, shed transmit and maintain itself in target and non-target animal populations
- Stability and survival of the organism in the environment
- The organism's host range, specificity and tissue tropism, as well as it stability to adapt and to affect other species.

- Human Safety
  - Probability of human exposure
  - Possible outcomes of human exposure
  - Pathogenicity of parent microorganisms in man
  - Effect of gene manipulation on pathogenicity in man
  - Risk associated with widespread use of the vaccine

- Animal Safety
  - Fate of the vaccine in target and non-target species
  - Potential for shed and/or spread from vaccinate to contact target and non-target animals
  - Reversion to virulence resulting from back passage in animals
  - Effect of overdose in target and potential non-target species
  - Relative safety when compared to conventional vaccines
  - The extent of the host range and the degree of mobility of the vector
  - Safety in pregnant animals and to offspring nursing vaccinated animals

- Environment safety
  - Persistence of the vector in the environment/ cumulative impacts
  - Extent of exposure to non-target species
  - Behaviour of parent microorganisms and vector in non-target species
  - Potential of the vector to infect non-vertebrate organisms

- Physical and chemical factors which can affect survival, reproduction and dispersal of the vector

PART 5: AUTOGENOUS VACCINES REGISTRATION – ADDITIONAL INFORMATION

a) Registration of autogenous vaccines must follow the same procedure of the conventional vaccine with additional information as stated below.

b) Shall be prepared from cultures of microorganisms which have been inactivated or non-toxic.

c) Shall be prepared only for use by or under the direction of a veterinarian under the direction of a veterinarian-client-patient relationship

d) Each serial of autogenous vaccines shall meet the requirements in this section;

   i. Seed requirements- The microorganisms used shall be from microorganisms isolated from sick or dead animals in the herd of origin and which there is reason to believe are the causative agent(s) of the current disease outbreak
   ii. Under normal circumstances, microorganisms from one herd must not be used to prepare an autogenous vaccine for another herd unless there are proofs that there is risk of infection with the same microorganism(s).

e) To obtain an authorization from DVS to produce autogenous vaccines, producer must first submit;
   i. Name and address of producer
   ii. Name and address of the herd of origin
   iii. Veterinarian name and address
   iv. Animal species and number in herd of origin
   v. Identification of microorganism(s), at least to genus
   vi. Diagnosis or clinical signs of the disease observed
   vii. Name and address of person/ laboratory who isolated the microorganism(s) and the date of isolation
   viii. Microbial isolates: characterization to demonstrate purity and identity
   ix. Reference Special Outlines
   x. Material of animal origin
   xi. Efficacy/ immunogenicity data

xii. Safety data – protocol for i) laboratory animal safety test, ii) target animal safety test
xiii. Number of doses of autogenous biologic requested and vaccination schedule
xiv. For preparation of autogenous vaccine for use in herd that are not adjacent to the herd of origin, the requested information are i) The geographic designations of the area involved and, ii) A summary of the epidemiology of the disease situation that links to the designated geographic areas with the herd of origin

f) Under normal circumstances, microorganism(s) used for the production of autogenous vaccines may not be older than 15 months form the date of isolation, or 12 months form the date of harvest of the first serial of product produced from the microorganism(s).

g) Inoculation
   i. Methods of preparing suspensions for inoculation
   ii. Technique of inoculating seed/ production media and results at 10-100x doses for each recommended age and route
   iii. Incubation process