GUIDELINES FOR REGISTRATION OF VETERINARY DIAGNOSTIC TEST KITS IN MALAYSIA

DEPARTMENT OF VETERINARY SERVICES
MINISTRY OF AGRICULTURE AND AGR0-BASED INDUSTRY

DECEMBER 2017

To be read in conjunction with
Procedures for Registration of Veterinary Biologics (Excluding Vaccines)/ Diagnostic Test Kits for Animal Use In Malaysia (Review 2016), Animal Act 1953, Animal Act (Amendment 2013)

ABBREVIATIONS

DVS	Department of Veterinary Services
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GQC	Good Quality Control
HSST	High Standard of Safety Test
HACCP	Hazard Analysis and Critical Control Point
MAQIS	Malaysian Animal Quarantine & Inspection Services
TACB	Technical and Advisory Committee on Biologics
TACB 6	Official Form for Submission of Dossier/ Dossier Check List for Registration of Local Agent of Veterinary Vaccines in Malaysia
TACB 10	Official Form for Submission of Dossier/ Dossier Check List for Registration of Veterinary Diagnostic Test Kits

Table of Content

- THE END -

i. INTRODUCTION

This guideline sets out the procedure to register a veterinary diagnostic test kits/ assays and provides guidance to submit data in a logical way so that scientific reviewers, appointed by DVS, can assess the diagnostic kits against the criteria of validation and fitness for purpose.

ii. SCOPE

The purpose of this guideline is;

(a) To ensure that all diagnostic test kits/ assays to be registered are validated, properly developed, optimized and standardized for an intended purpose.
(b) To bring coherence to the validation process for all types of diagnostic test kits/ assays by focusing on the criteria that must be fulfilled during assay development and validation of all assay types.
(c) To establish the "fitness for purpose" of a veterinary diagnostic test kit.

This guideline shall apply only to Peninsular Malaysia and Federal Territory of Labuan.

iii. DEFINITION

(a) **"local agent"** means any organization that has been appointed and authorized by the manufacturer to import and distribute the product.

(b) **"dossier"** means a collection of documents containing detailed information about a particular vaccine.

(c) "**diagnostic test kit**" means the product used to determine the health status of an animal or diagnosis of animal disease/ condition

GUIDELINE FOR REGISTRATION OF VETERINARY DIAGNOSTIC TEST KITS

PART 1. APPLICATION

1.1. Applications to register veterinary diagnostic test kits must be made in writing by registered local agent to:

Director General of Veterinary Services
Department of Veterinary Services
Ministry of Agriculture and Agro-Based Industry,
Wisma Tani, Podium Block, Lot 4G1, Precinct 4,
Federal Government Administration Centre,
62630 Putrajaya, Malaysia
(Attn : TACB Secretariat)
Tel : 03 – 88702000
Fax : 03 - 8888 6472

1.2. Specific guidance on types of documents needed to support this application is provided under PART 2 within this document.

1.3. This document is to be read together with Procedures for Registration of Veterinary Biologics (Excluding Vaccines)/ Diagnostic Test Kits for Animal Use In Malaysia (Review 2016), Animal Act 1953, Animal Act (Amendment 2013) and with reference to OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals: Chapter 1.1.6, Principles and Methods of Validation of Diagnostic Assays for Infectious Diseases (Version May 2013).

1.4. Applications shall be made using TACB 10 Form and be supported by all data required for the registration described in PART 2 in this document. Please submit one (1) hardcopy and one (1) softcopy of the original dossier.

1.5. The registration is valid for 5 years and renewable. The success in registration will depend on supplying quality controlled validation data to demonstrate the fitness of the kit to fulfill a defined task or tasks.

PART 2.

2.1 GENERAL INFORMATION

(a) Name of Product
   (i) To include trade name and details of type/ serotype/ strain of organism that which to be detected

(b) Name and address of manufacturer (Headquarters)
(c) Name and address of manufacturing facility/ premise (if different from (b)
(d) Country of origin
(e) Copy of manufacturing license or registration certificate of the country of origin, accreditations or certificate status of manufacturer are as below:
   i. A current GMP certificate/ GLP/ ISO certificate from the competent authority in the country of origin must be provided
   ii. Copy of certificates must be certified by the competent authority in the country of origin.

(f) Name and address of local agent/ Malaysian company
   i. Company need to provide prove of registration with Suruhanjaya Syarikat Malaysia (SSM), along with contacts details of company (eg. Email, phone)
(g) Copy of letter of attorney or authorization letter by manufacturer
   i. Letter of authorization from the manufacturer to the appointed local agent shall be valid
   ii. Copy of letter of attorney must be certified by the competent authority in the country of origin or by Notary Public of Country of Origin

2.2 PURPOSE OF DIGNOSTIC KIT

(a) Type of method
   (i) Please state type of methods used: eg Indirect or competitive ELISA, conventional or real-time PCR, etc.

(b) Detection method for

(i) Please state detecting for antibody, antigen, nuclei acid or others. If others, please specify.

(c) Detection ability or type

(i) Singleplex means the test kit only detects one analyte.

(ii) Multiplex means the test kit detects more than one analyte.

(d) Intended purpose(s) of the test

(i) Please describe the intended purpose of the test and include also descriptions of the following:

- Demonstrate freedom from infection in a defined population (country/zone/compartment/herd)
- Demonstrate disease free with vaccination
- Historical freedom from disease
- Re-establishment of freedom after outbreaks
- Certify freedom from infection or agent in individual animals or products for trade/movement purposes
- Eradication of infection from defined populations
- Confirmatory diagnosis of suspect or clinical cases (includes confirmation of positive screening test)
- Estimate prevalence of infection to facilitate risk analysis (Screening/ surveys/herd health schemes/disease control)
- Determine immune status in individual animals or populations (post-vaccination)
- Establish the individual animal freedom from infection/ health condition
- Other [please specify]:

2.3 TEST DESCRIPTION AND REQUIREMENTS (AT END USER)

(a) Protocol of the test

(i) Include the commercial leaflet/ working protocol as would be given to laboratory/ consumer.

(b) Disease target/ analyte target

(i) State targets in analytical terms (eg. antibody isotype and specificity, gene sequence and associations, etc)

(c) Species and specimens

(i) Species and specimens that can be examined (eg. swine serum, bull semen, fish kidney). List only those that have been validated sufficiently. Decribe briefly the recommended

procedures for acquiring, preserving and shipping specimens for the test.

(d) Controls included
  (i) Describe the positive and negative control materials in the test, including source and test activity.

(e) Laboratory requirements
  (i) Describe minimum laboratory requirements for optimal test performance; include environmental, equipment, chemical and/ or biological requirements (not specified in the protocol or included in the test)

(f) Computational requirements (if applicable)
  (i) Describe the hardware and software requirements for test kits operation and data processing. Indicate what is supplied and what is not.

(g)Test kit format (if applicable)
  (i) For commercial tests, outline the number of samples that can be tested with one kit. Describe any flexibility in kit formats that would accommodate various test throughout volumes (eg. multi-well plate vs. strip formats).

(h)General precautions/ safety aspects/ disposal of reagents
  (i) List potential health hazards and the safety precautions, refer to Material or Biological Safety Data Sheets if necessary.

(i) Assay interpretation
  (i) Provide details on methods to generate results
  (ii) Provide criteria on validity of data (Eg. Lateral flow rapid test kit results are only valid if control line is present and has to be read within 20 minutes)

2.4 TECHNICAL INFORMATION ABOUT THE DIAGNOSTIC TEST

(a) Chemical reagents
  i. List all chemical reagents specified in the test protocol or supplied with test, indicate their use and briefly describe composition and characteristics in chemical terms (eg. buffer formula, molarity, pH, etc). Provide Material Safety Data Sheets (MSDS) where applicable.

(b) Equipment and consumables included (if applicable)
    i. List all pieces of equipment supplied with the test, indicate their use and briefly describe operating characteristics (eg. accurary, precision, etc)

(c) Biological components used in test
    i. List each biological component, its function in the test and briefly describe its origin, composition, presentation in biological terms (eg. affinity purified, rabbit anti-bovine IgG, etc.)

(d) Control of the final product of the test (if applicable)
    i. Briefly describe the method used to document and approve a serial or batch release of the test, include description of (reference) reagents/ panels used to assess test performance.

(e) Shipping requirements
    i. List conditions and precautions required for shipping, include critical factors that may adversely affect test performance
    ii. Include storage conditions

(f) Troubleshooting and technical support (if applicable)
    i. Indicate scope, format and availability of technical support.

2.5 DEVELOPMENT AND VALIDATION

(a) Fitness of assay for its intended purpose
    i. Provide study protocol that gives a brief description of how you see the test being applied in support of a specific type(s)of testing programme. Test applications may be relatively broad or highly specific depending on the diagnostic application being targeted. The design of the test must be consistent with its intended purpose and the population for which its is intended. Please refer to the discussion of this topic in Chapter 1.1.6 Principles of validation of diagnostic assays for infectious diseases of the OIE Manual of Diagnostic Tests and Vaccines for Terrestial Animals, for an overview of 'reasons for test'.

(b) Design, development, optimization and standardization of the assay.
   i. Test kit design, development, optimization and standardization, as well as, validation must be based on sound scientific principles and carried out using best practices, leading to a validated test kit that is published in peer reviewed journals.
   ii. Where applicable, the statistical methods and conclusion reached in drawing inferences relative to reagent optimization/ standardization or results interpretations should be submitted.

2.6 VALIDATION PATHWAY STAGE 1: ANALYTICAL CHARACTERISTICS

(a) Stage 1. Repeatability data
   i. Repeatability is level of agreement between replicates of a sample both within and between runs of the same test method in a given laboratory.
   ii. A minimum of three in-house samples representing activity within linear range of assay.
   iii. Within run tests (quadruplicates preferred).
   iv. Between run tests (a minimum of 20 runs total, two or more operators preferably on separate days, where runs are independent).
   v. Between serial repeatability, ideally three production batches.
   vi. Data should include mean, SD, upper and lower control (UCL and LCL) on unprocessed and processed data.

(b) Stage 1. Analytical specificity data
   i. Document cross-reactivity by comparing samples from animals infected with organisms with similar clinical presentations and organisms that are genetically closely related. The higher the analytical specificity, the lower level of false- positives.
   ii. Documentation affirming serotype or group specificity.

(c) Stage 1. Analytical sensitivity data
   i. Analytical sensitivity is synonymous with 'Limit of detection', smallest detectable amount of analyte that can be measured with a defined certainty.

ii. Specify standard of comparison (i.e. currently accepted test method).
- Comparison may include: end-point titrations; earliest time of detection post-exposure.
- Duration of detection post-exposure (if applicable).

(d) Stage 1. Standard of comparison

i. For provisional acceptance, the standard method(s) of comparison (reference standard) should be run in parallel on small but select group of highly characterized test samples representing the linear operating range of the new method(s). Identify and cite the reference method(s) and protocol(s) used in the study.

(e) Stage 1. Preliminary evaluation of reproducibility

i. Reproducibility is the ability of a test method to provide consistent results when applied to aliquots of the same sample tested by the same method in different laboratories. For provisional acceptance where it is not possible to complete Stages 2 or 3, a preliminary evaluation of reproducibility must be presented. Laboratories participating in this type of study should be known to the test developer and may be in close geographic proximity

2.7 STAGE 2- DIAGNOSTIC CHARACTERISTICS

(a) Study design(s)

i. Aim to determine the diagnostic sensitivity and specificity estimates. Reference samples may be obtained from the field or from experimentally infected animals as appropriate to the nature of the disease. Their key characteristic is that their true status (positive/negative etc) should be independently verified by a different technique.

ii. Give an overview of the chosen approach used for determination of diagnostic specificity and sensitivity estimates. Include rationale for statistical design, choice of populations, animal models, or other suitable models (eg. tissue culture/ embryonated eggs), numbers of animals used to generate confidence intervals for sensitivity and specificity etc.).

(b) Stage 2. Negative reference animals/ samples

i. Negative refers to lack of exposure to, or infection with, the agent in question.

ii. Provide a complete description of age, sex, breed, immunological status etc. of the negative reference animals/ samples and the relatedness to intended target population. Selection criteria including historical, epidemiological and/or clinical data.
iii. Pathognomonic and/or surrogate tests used to define status of animals or prevalence within population. Sampling plan and procedures.

(c) Stage 2. Positive reference animals/ samples
i. Positive refers to known exposure to, or infection with, the agent in question.
ii. Provide a complete description of age, sex, breed, immunological status etc. of the positive reference animals/ samples and the relatedness to intended target population. Selection criteria including historical, epidemiological and/or clinical data.
iii. Pathognomonic and/or surrogate tests used to define status of animals or prevalence within population. Sampling plan and procedures.

(d) Stage 2. Experimental animals (where used)
i. Experimental animals maybe be used when it is not possible to define or obtain sufficient positive reference animals from the field.
ii. Provide a complete description of the age, sex, breed, immunological status. etc. of the experimental animals used and its relatedness to intended target population.
iii. Provide details of the exposure
- Inoculum, source, dose, etc.
- Type of exposure – inoculation, aerosol, contact, etc.
- Sampling plan and procedures.

(e) Stage 2. Threshold determination
i. Complete description of method used to determine thresholds (cut-off(s)) used to classify animals as test positive, negative or indeterminate (if relevant). Include statistical calculations, frequency distributions, etc., as applicable.

(f) Stage 2. Diagnostic sensitivity and specificity estimates – with defined reference animals

i. Diagnostic sensitivity is the proportion of known infected reference animals that test positive in the assay; infected animals that test negative are considered to have false-negative results.
ii. Diagnostic specificity is the proportion of known uninfected reference animals that test negative in the assay; uninfected reference animals that test positive are considered to have false-positive results.

(g) Stage 2. Diagnostic sensitivity and specificity estimates – without defined reference animals
   i. This applies to diseases where sourcing positive reference sample is difficult (eg. Anthrax). Provide a complete description of latent class model used (eg. Bayesian or maximum likelihood). Describe rationale for use of this approach, and sources of priors (e.g. experts and published papers) for Bayesian models providing relevant, supporting data. Population selection criteria should be presented, including prevalence estimates. Other test methods evaluated should also include the standard method of comparison. The source data tables with cross-classified test results should be presented for each test population. Using best available priors, choose test populations with appropriate prevalences and select animals in sufficient numbers to generate estimates of sensitivity and specificity with an allowable error of ± 5% at a level of 95% confidence. If multiple laboratories are involved in the study design, data on reproducibility should be presented in analysis of reproducibility

(h) Stage 2. Comparison of performance between tests
   i. Provide statistical measures of agreement between the reference method(s) and the new test being validated and suggest explanations for results not in agreement.

2.8 Stage 3- Reproducibility (if applicable)

Reproducibility is the ability of a test method to provide consistent results when applied to aliquots of the same sample tested by the same method in different laboratories. This is the same definition found in Stage 1. Preliminary evaluation of reproducibility; however, Stage 3 is more international in scope and is a better indicator of the ruggedness of the test method. Ruggedness is a measure of an assay's capacity to remain unaffected by substantial changes or substitutions in test conditions anticipated in multi-laboratory utilization, part of fitness studies and reproducibility assessments (e.g. shipping conditions, technology transfer, reagents batches, equipment, testing platforms and/or environments).

(a) Stage 3. Laboratory identification

i. Selection criteria for laboratories involved in the reproducibility study should include:
   - Location, i.e. country.
   - Status, i.e. regional, national, provincial/state.
   - Level of expertise, familiarity with technology.
   - Accreditation status.
   - State the number of laboratories included (minimum of three) which should also include OIE Reference Laboratories where they exist.

(b) Stage 3. Evaluation panel

i. Description of test panel used for independent reproducibility study (interlaboratory comparisons).

(c) Stage 3. Analysis of reproducibility

i. Description of reproducibility study and interpretation of results.

2.9 Stage 4- Application (if applicable)

Stage 4 validation is recognized as an ongoing process that continues for the lifetime of the assay. Although this section gives important information regarding the validation of the diagnostic test, it is not a compulsory requirement for the OIE evaluation. Please complete where the information is available.

(a) Stage 4. Test applications

(Note: This Section applies to tests that have been incorporated into routine diagnostic regimens.)

iii. Describe functional test applications (i.e. screening, confirmatory, supplemental applications) and integration with other tests into diagnostic regimen. Include flowcharts and decision trees where applicable.

(b) Stage 4. Laboratories

i. List laboratories where this test method is in current use.
- Location, i.e. Country.
- Status, i.e. Regional, national, provincial/state.
- Accreditation status.

ii. For each laboratory, indicate purpose of test, integration with other tests and status of test, i.e. official test, supplementary, etc.

(c) Stage 4. International reference standards

i. List type and availability of international reference reagents, source, negative, weak/strong positive reference reagents and other key biologicals, e.g. antigens, antibodies, etc.

(d) Stage 4. Inter-laboratory testing programmes

i. Describe programmes involving inter-laboratory comparisons using this test method. (Eg. National, international). Describe eligibility and number of laboratories participating.

(e) Stage 4. International recognition

i. List internationally recognized reference laboratory responsible for this test method and/or biologicals. List international standards containing this test method. List international programmes employing this test method.

2.10 Packaging Information

(a) Instructional pamphlet and specimen of label

i. Usage instructions/ indications/ precautions/ storage conditions/ batch number/ expiry date

(b) Composition of final product

2.11 Reference cited in the dossier

List the scientific literature related to the diagnostic test described in this application and cited in this dossier. Use a consistent reference style throughout.

PART 3 ENQUIRY

Enquiries and further details pertaining to variation to registered veterinary vaccines and for importation, sale and use in Peninsular Malaysia and Federal Territory of Labuan can be obtained from:

Director General of Veterinary Services
Department of Veterinary Services
Ministry of Agriculture and Agro-Based Industry,
Wisma Tani, Podium Block, Lot 4G1, Precinct 4,
Federal Government Administration Centre,
62630 Putrajaya, Malaysia
(Attn : TACB Secretariat)

Tel : 03 – 88702000
Fax : 03 - 88886472