3R'S IMPLEMENTATION VACCINE BATCH RELEASED IN ASEAN-INDONESIA

Directorate of Animal Health

Directorate of General Livestock and Animal Health Services

Ministry of Agricuture Republic of Indonesia

2022

Current Regulation and Policy (ASEAN-Indonesia)

- Manual of ASEAN Standards of Animal Vaccines
  - ✓ Sterility testing : Bacteria, Mycoplasma, Salmonella, Fungi (no animal testing)
  - ✓ Testing for extraneous viruses : using embryonated chicken eggs, chicken inoculation test, tissue culture inoculation test, test for avian leucosis virus (chicken embryo fibroblast (CEF) cell cultures)
  - ✓ Potency test by sero-conversion : potency tests based on in-vivo challenge in the target species may be substituted by sero-conversion provided that such serological values are correlated to immunogenicity in the target species.
- Manual of the ASEAN Standard of Good Manufacturing Practice (GMP) for Animal Vaccines
  - ✓ The identification test can often be conveniently combined with the batch potency test to avoid unnecessary use of animals. For a given vaccine, a validated *in vitro* test can be used to avoid the unnecessary use of animals.
  - ✓ Use the minimum number of animals and to cause the least pain, suffering, distress or lasting harm.
  - ✓ Alternative test methods may be used to demonstrate compliance and the use of such tests is particularly encouraged when this leads to replacement or reduction of animal use or reduction of suffering.
- Indonesia Veterinary Drug Pharmacopoeia (Biological Agent)
- Ethical Clearance Commission (replace, reduce, refine, reuse, and rehabilitate)

Harmonization Regulation Authority (ASEAN-Indonesia)

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Manual of ASEAN Standards for Animal Vaccines

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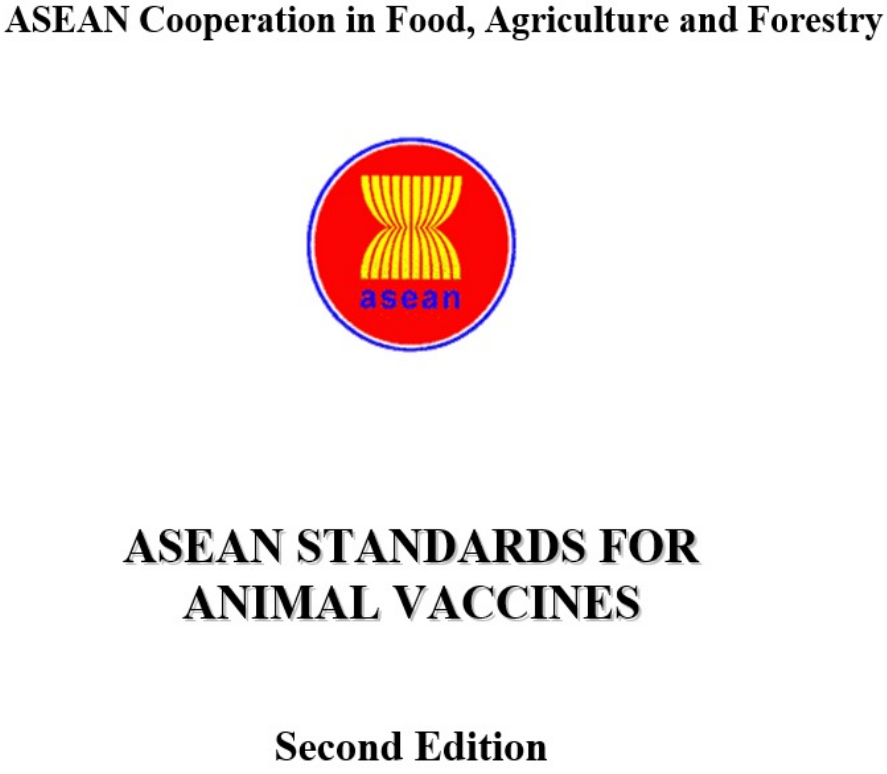
Manual of ASEAN Standards for Animal Vaccines

Author:ASEAN Secretariat

Hardcopy available

ASEAN Manual Standard for Animal Vaccine

a. **Manual of ASEAN Standards of Animal Vaccines**
b. **Manual of the ASEAN Standard of Good Manufacturing Practice (GMP) for Animal Vaccines**
c. Manual of ASEAN Accreditation Criteria for Animal Vaccine Testing Laboratories
d. Manual of ASEAN Rules and Procedures for the Registration of Animal Vaccines



CERTIFICATE OF APPROVAL

This is to certify that the

National Veterinary Drug Assay Laboratory (NVDAL)
Gunung Sindur, Bogor, Indonesia

has been approved by the ASEAN Member States and endorsed by the ASEAN Ministers on Agriculture and Forestry (AMAF) in accordance with the requirements of

PROTOCOL FOR RECOGNITION OF ASEAN REFERENCE LABORATORIES FOR ANIMAL VACCINE TESTING
for
the testing of the following animal vaccines:

Re-accreditation:

a. Newcastle Disease Vaccine, live
b. Newcastle Disease Vaccine, inactivated
c. Marek's Disease Vaccine, live
d. Infectious Laryngotracheitis Vaccine, live
e. Infectious Bronchitis Vaccine, live
f. Infectious Bronchitis Vaccine, inactivated
g. Egg Drop Syndrome '76 Vaccine, inactivated
h. Fowl Cholera Vaccine, inactivated
i. Haemophilus paragallinarum Vaccine, inactivated

Approval Certificate No. : ASEAN/Vaccine/006
Date of Approval : 21 October 2020
Certificate Expiry : 21 October 2025

SECRETARY-GENERAL OF ASEAN

DATO LIM JOCK HOI

PROGRESS OF INITIATIVES UNDER THE COOPERATION

Regularization of Products and Utilization of Animal Vaccines ------ Recognition of Animal Vaccine Testing Laboratories :

BBPMSOH

National Veterinary Drugs Assay Laboratory (NVDAL), Gunung Sindur, Bogor, Indonesia

AVIAN VACCINES

AVIAN ENCEPHALOMYELITIS	LIVE
AVIAN ENCEPHALOMYELITIS	INACTIVATED
DUCK PLAGUE	LIVE
EGG DROP SYNDROME 76	INACTIVATED
FOWL POX	LIVE
FOWL CHOLERA	BACTERIN
HAEMOPHILUS PARAGALLINARUM	BACTERIN
INFECTIOUS BRONCHITIS	LIVE
INFECTIOUS BRONCHITIS	INACTIVATED
INFECTIOUS BURSAL DISEASE	LIVE
INFECTIOUS BURSAL DISEASE	INACTIVATED
INFECTIOUS LARYNGOTRACHEITIS	LIVE
MAREK'S DISEASE	LIVE
MYCOPLASMA GALLISEPTICUM	BACTERIN
NEWCASTLE DISEASE (LENTOGENIC STRAIN)	LIVE
NEWCASTLE DISEASE (MESOGENIC STRAIN)	LIVE
NEWCASTLE DISEASE	INACTIVATED
RIEMERELLA ANATIPESTIFER	BACTERIN
VIRAL ARTHRITIS	LIVE

SMALL ANIMAL VACCINES

CANINE CONTAGIOUS HEPATITIS	INACTIVATED
FELINE PANLEUCOPENIA	LIVE
FELINE PANLEUCOPENIA	INACTIVATED
LEPTOSPIRA	BACTERIN
RABIES FOR DOGS AND CATS	INACTIVATED

SWINE VACCINES

ACTINOBACILLUS PLEUROPNEUMONIAE	BACTERIN
AUJESKY'S DISEASE	LIVE
AUJESKY'S DISEASE	INACTIVATED
BORDETELLA BRONCHISEPTICA	BACTERIN
FOOT-AND-MOUTH DISEASE FOR PIGS	INACTIVATED
SWINE E. COLI	BACTERIN
SWINE ERYSIPELAS	BACTERIN
SWINE FEVER VACCINE (CELL CULTURE ORIGIN)	LIVE
SWINE FEVER VACCINE (LAPINISED)	LIVE
SWINE PASTEURELLA MULTOCIDA	BACTERIN

RUMINANT VACCINES

ANTHRAX SPORE	LIVE
BRUCELLA ABORTUS	LIVE
BLACKLEG	INACTIVATED
BOVINE VIRAL DIARRHOEA	INACTIVATED
FOOT-AND-MOUTH DISEASE FOR CATTLE AND BUFFALOES	INACTIVATED
HAEMORRHAGIC SEPTICAEMIA FOR CATTLE AND BUFFALOES	BACTERIN
INFECTIOUS BOVINE RHINOTRACHEITIS	LIVE
INFECTIOUS BOVINE RHINOTRACHEITIS	INACTIVATED
OVINE ECTYMA (ORF)	LIVE

MANUAL OF ASEAN STANDARDS OF ANIMAL VACCINES

AVIAN VACCINES
SWINE VACCINE
RUMINANT VACCINES
SMALL ANIMAL VACCINES

APPENDIX
- APPENDIX 1
- APPENDIX 2
- APPENDIX 3
- APPENDIX 4

General requirements:

1) Seed and Production Substrate Requirements
2) Quality Control Requirements
3) Other Requirements

MANUAL OF ASEAN STANDARDS FOR GOOD MANUFACTURING PRACTICES (GMP) FOR ANIMAL VACCINES

- APPENDIX 1
- APPENDIX 2
- APPENDIX 3 --- Veterinary Vaccine

SEED AND PRODUCTION SUBSTRATE REQUIREMENTS

SEED VIRUS

a. **Master** and **working seed viruses** are produced in **Specific-Pathogen-Free (SPF) embryonated eggs in seed lot system**.
b. The seed viruses must satisfy **sterility, purity, safety and potency tests** before they are used for vaccine production.

PRODUCTION SUBSTRATE

Embryonated eggs used throughout the production of the vaccine **must be derived from SPF flocks** complying with tests that appear as Appendix 1 in GMP Manual.

1. **Any batch of such materials which does not comply with the specification shall be rejected**.
2. **The consistent production of pure, safe, potent, and efficacious vaccines requires quality assurance procedures** to ensure the **uniformity** and **consistency** of the production process.
3. **Consistent product quality (batch-to-batch uniformity) must be built in at each stage**.
4. **Final product testing** is used as a check to verify that the controls on the production procedures have remained intact and that the released product meets the specification.

QUALITY CONTROL

BACTERIAL VACCINES	VIRAL VACCINES	VECTOR VACCINES
1. Bacterial vaccines and bacterial toxoids are prepared from **cultures grown on suitable solid or liquid media**, or by other suitable means; the requirements of this section do not apply to bacterial vaccines prepared in cell cultures or in live animals. The strain of bacterium used may have been modified by genetic engineering. The identity, antigenic potency and purity of each bacterial culture used are carefully controlled. 2. Bacterial vaccines contain inactivated or live bacteria or their antigenic components; they are liquid preparations of various degrees of opacity or they may be freeze-dried.	1. Viral vaccines are prepared by growth in suitable **cell cultures, in tissues, in micro-organisms, in fertilised eggs** or, where no other possibility is available, in live animals, or by other suitable means. The strain of virus used may have been modified by genetic engineering. They are liquid or freeze-dried preparations of one or more viruses or viral subunits or peptides. **2. Live viral vaccines** are prepared from **viruses of attenuated virulence or of natural low virulence** for the target species. 3. Inactivated viral vaccines are treated by a validated procedure for inactivation of the virus and may be purified and concentrated.	Vector vaccines are liquid or freeze-dried preparations of one or more types of live micro-organisms (bacteria or viruses) that are non-pathogenic or have low pathogenicity for the target species and in which have been inserted one or more genes encoding antigens that stimulate an immune response protective against other micro-organisms.

VACCINE PRODUCTION

A.1. Substrates for production

1. **Cell cultures** used in the **production of vaccines for veterinary use** comply with the requirements.
2. Where a documents refers to chicken flocks free from specified pathogens (SPF), these flocks comply with the requirements.
3. For **production of inactivated vaccines**, where vaccine organisms are **grown in poultry embryos, such embryos are derived either from SPF flocks** or from healthy non-SPF flocks free from the presence of certain agents and their antibodies, as specified in the document. For the production of a master seed lot and for all passages of a micro-organism up to and including the working seed lot eggs from SPF flocks are used.
4. Where it is **unavoidable to use animals or animal tissues** in the production of veterinary vaccines, such animals shall be free from specified pathogens, as appropriate to the source species and the target animal for the vaccine.

A.2. Media used for seed culture preparation and for production

1. At least the qualitative composition must be recorded of media used for **seed culture preparation** and for production.
2. The addition of antibiotics during the manufacturing process is normally restricted to cell culture fluids and other media, egg inocula and material harvested from skin or other tissues.

CHOICE OF VACCINE COMPOSITION AND STRAIN

- For the choice of vaccine composition and choice of vaccine strain, important aspects to be **evaluated include safety, efficacy and stability**. These requirements may be made more explicit or supplemented by the requirements of specific documents.
- For **live vaccines**, a **maximum virus titre or bacterial count acceptable from the point of view of safety** is established during development studies. This is then used as the **maximum acceptable titre for each batch of vaccine at release**.

MANUFACTURER'S TESTS

1. **Residual live virus/bacteria and/or detoxification testing**
2. **Batch potency test**

a. For most vaccines, the tests cited under **Potency or Immunogenicity** are **not suitable for the routine testing** of batches.
b. For live vaccines**, the minimum acceptable virus titre or bacterial count** that gives satisfactory **results in the potency test and other efficacy studies** is established during development. For routine testing it must be demonstrated for each batch that the titre or count at release is such that at the end of the period of validity, in the light of stability studies, the vaccine, stored in the recommended conditions, will contain not less than the minimum acceptable virus titre or bacterial count determined during development studies.
c. For **inactivated vaccines**, if the **test described under potency** is **not used for routine testing**, a **batch potency test is established during development**. The aim of the batch potency test is to ensure that each batch of vaccine would, if tested, comply with the test described under Potency and Immunogenicity.

BATCH

a. Only a batch that complies with each of the requirements given below under 3 Batch tests or in the relevant individual monograph may be released for use.
b. The identification test can often be conveniently combined with the batch potency test **to avoid unnecessary use of animals**. **For a given vaccine, a validated *in vitro* test can be used to avoid the unnecessary use of animals**.
c. It is recognised that for an established vaccine the routine application of the safety test will be waived by the competent authority in the interests of **animal welfare** when a sufficient number of consecutive production batches have been produced and found to comply with the test, thus demonstrating consistency of the manufacturing process.

ANIMAL TESTS

- Tests must be carried out in such a way as to **use the minimum number of animals** and to cause the **least pain, suffering, distress or lasting harm**.
- The criteria for judging tests in monographs must be applied in light of this. For example, if it is indicated that an animal is considered to be positive, infected etc. when typical clinical signs occur then as soon as it is clear that result will not be affected the animal in question **shall be either euthanised or given suitable treatment to prevent unnecessary suffering**.
- **Alternative test methods** may be used to demonstrate compliance and the use of such tests is particularly encouraged when **this leads to replacement or reduction of animal use or reduction of suffering**.

BATCH TESTS

All hen eggs, chickens and chicken cell cultures for use in quality control tests shall be derived from an SPF flock.

Extraneous agents

These measures include:

- production within a seed-lot system and a cell-seed system, wherever possible;
- extensive testing of seed lots and cell seed for extraneous agents;
- requirements for SPF flocks used for providing substrates for vaccine production;
- testing of substances of animal origin, which must, wherever possible, undergo an inactivation procedure;
- for live vaccines, testing of the final product for infectious extraneous agents; such tests are less extensive than those carried out at earlier stages because of the guarantees given by in-process testing.

Mycoplasmas

Live viral vaccines comply with the test for mycoplasmas **(culture method)**

BATCH TEST

Safety

The immune status of animals to be used for the safety test is specified in the individual monograph. For most vaccines, one of the 3 following categories is specified:

1. the animals must be free from antibodies against the virus/bacterium/toxin etc. contained in the vaccine;
2. the animals are preferably free from antibodies but animals with a low level of antibody may be used as long as the animals have not been vaccinated and the administration of the vaccine does not cause an anamnestic response;
3. the animals must not have been vaccinated against the disease that the vaccine is intended to prevent.

As a general rule, **category 1 is specified for live vaccines**. For other vaccines, category 2 is usually specified but where most animals available for use in tests would comply with category 1, this may be specified for inactivated vaccines also. **Category 3 is specified for some inactivated vaccines** where determination of antibodies prior to testing is unnecessary or impractical**. For poultry vaccines, as a general rule the use of SPF birds is specified**.
For avian vaccines, the **safety test is generally carried out using 10 SPF chickens**, except that for vaccines not recommended for use in chickens it is carried out using 10 birds of one of the species for which the vaccine is recommended, the birds being free from antibodies against the disease agent for which the vaccine is intended to provide protection.

Potency

The vaccine complies with the requirements of the test mentioned under Immunogenicity when administered by a recommended route and method.

CONCLUSION

- Implementing 3R in ASEAN-Indonesia have been regulated in some manuals for animal vaccine and refer to the Pharmacopoeia and implementation ethical clearance in each ASEAN member states
- The batch potency test can used to avoid unnecessary use of animals. For a given vaccine, a validated *in vitro* test can be used to avoid the unnecessary use of animals
- Alternative test methods may be used to demonstrate compliance and the use of such tests is particularly encouraged when this leads to replacement or reduction of animal use or reduction of suffering
- Regularization of products and utilization of animal vaccines, ASEAN have been recognition of animal vaccine testing reference laboratory as quality control approach


Thank you!