Guidelines on Animal Vaccine

Directorate General of Drug Administration
Ministry of Health and Family Welfare
Government of the People's Republic of Bangladesh
2018

Message from the Director General, Directorate General of Drug Administration

It is my pleasure that one of the nine functions of DGDA – "Marketing Authorization" *related guidelines are now regularly published from DGDA for different class of drugs.* On this aspect "Guidelines for Registration of Animal vaccines" is one of the very important guideline which will help Biotech and Animal vaccine Industry, Researchers, Academicians as well as Regulators to ensure quality, efficacy and safety of Animal vaccine registered in Bangladesh.

This guideline is prepared harmonizing with OIE, European, Australian and ASEAN animal vaccine guideline, so that animal vaccine registration would be given in Bangladesh with a high standard to get global recognition as well as protecting the health of animals those are in dire need of vaccines.

I would like to thank the members of Animal Vaccine Guideline preparation committee for their meticulous job.

Major General Md. Mustafizur Rahman
Director General
Directorate General of Drug Administration &
Licensing Authority of Drugs

Members of Animal Vaccine Guideline Preparation Committee

1. Professor Dr. Md. Bahanur Rahman, Department of Microbiology and Hygiene, Bangladesh Agricultural University. Convener
2. Professor Dr. Liaquat Ali, Ex-Vice-Chancellor, Bangladesh University of Health Sciences (BUHS), Mirpur, Dhaka. Member
3. Dr. Md. Giasuddin, Director, National Reference Laboratory for Avian Influenza (NRL-AL), BLRI, Savar, Dhaka. Member
4. Dr. Md. Rezaul Islam, Director, LRI Mohakhali, Dhaka. Member
5. Dr. Begum Noorjahan, PSO, Rabies Vaccine Section & Salmonella Vaccine Section, LRI, Mohakhali, Dhaka. Member
6. Professor Dr. S. M. Lutful Kabir, Head, Department of Microbiology and Hygiene, Bangladesh Agricultural University. Member
7. Chairman, Department of Microbiology and Parasitology, Sher-e-Bangla Agricultural University,Dhaka. Member
8. Dr.A.H.M Saiful Islam Khan, PSO,CDIL,Dhaka . Member
9. Expert representative, M/S Incepta Vaccine Ltd. Member
10. Expert representative, M/S FnF Pharmaceuticals Ltd. Member
11. Mr. Md. Salahuddin, Assistant Director, DGDA. Member-Secretary

Contents

Annexure

Introduction

The role of livestock and fisheries sectors in the development of agro-based economy of Bangladesh is very important and promising. They contribute around 8% to national income, which is 32% of the total agricultural income. About 90% of animal protein in our diet comes from fish and livestock. But, the industry is burdened with a huge loss year after year due to economically important existing, emerging, re-emerging and diseases like; Newcastle, Gumboro, Bronchitis, Fowl Cholera, Fowlpox, Duck Cholera, Duck Plague, Foot and Mouth Disease (FMD), Anthrax etc. Annual loss due to only FMD has been estimated at about 1000 crore taka (US$ 125 million) per year which is almost equivalent to development and non-development budgets combined, for the Ministry of Fisheries and Livestock. For the prevention of major animal diseases, veterinary vaccines can play a vital role for the development of livestock industry and welfare of companion animals in a cost-effective way. Right now, Livestock Research Institute (LRI) manufactures few animal vaccines which are not sufficient to meet the national demand. Most of the animal vaccines are imported from different parts of the world. To import these vaccines, substantial foreign currency is drained every year. Farmers are using imported vaccines keeping potency doubt in their mind whether the vaccines are consistent with the circulated pathogens in the field or not. Moreover, it is difficult to maintain an uninterrupted cold chain system during transportation of these vaccines. This guidance is intended to assist importers, manufacturers and others stakeholders in demonstrating the requirements of animal vaccine development, formulation, manufacturing, quality controlling, testing and marketing in Bangladesh market.

Purpose of the Guideline

The purpose of guideline has evaluated the benefits versus risks of vaccines currently available in Bangladesh. Animal vaccine is a trust sector of livestock industry in Bangladesh. To minimize the use of antibiotic load, animal vaccine can play a vital role. Vaccine seed is a critical factor of quality vaccine without which, quality vaccine manufacturing is impossible. Manufacturing facilities and good manufacturing practice are another two vital factors to ensure quality vaccine. A standard manufacturing facility, good manufacturing practice and quality management system are prerequisite of manufacturing of quality vaccine. This guidance is intended to assist

importers, manufacturers and others stakeholders in demonstrating that a proposed animal vaccine for purposes of the submission of a marketing authorization application under The Drugs Act, 1940, The Drugs Rules, 1945, the Bengal Drug Rules1946 and The Drugs (Control) Ordinance, 1982.

Scope

This guideline addresses the general principles for the Quality, Laboratory test and Field trial development and assessment of the marketing authorization applications of finished animal vaccine products, bulk imported animal vaccine products and imported animal vaccines. In principle, this document can apply to all types of animal vaccines. However, in this case, it applies specifically to live and inactivated vaccines that are well-characterized and of which comparability can be demonstrated through characterization, laboratory studies and field studies. Nevertheless, the principles explained here could apply to other animal vaccines, on a case by case basis. This guideline should be followed for vaccines intended for use in food-producing and companion/pet animals.

Definition/Glossary

Animal Vaccine: Animal Vaccines are products that when administered to the host, provide, induce or change an immune response to a target chemical or biological entity.

Attenuated Live Vaccine: is a vaccine created by reducing the virulence of a pathogen, but still keeping it viable (or live). Attenuation takes an infectious agent and alters it so that it becomes harmless or less virulent. These vaccines contrast to those produced by "killing" the virus (inactivated vaccine).

Killed/Inactivated Vaccine: An inactivated vaccine (or killed vaccine) is a vaccine consisting of virus particles, bacteria, or other pathogens that have been grown in culture and then killed using a method such as heat or formaldehyde.

SPF: Specific-pathogen-free (SPF) is a term used for laboratory animals/eggs that are guaranteed free of particular pathogens. Use of SPF animals/eggs ensures that specified diseases do not interfere with an experiment. For example, absence of respiratory pathogens such as influenza is desirable when investigating a drug's effect on lung function.

Seronegative: giving a negative result in a test of blood serum, e.g. for the presence of a virus.

Sterility Test: Sterility testing. Sterility can be defined as the freedom from the presence of viable microorganisms. In pharmaceutical practice, a container is defined as sterile when the probability is less than one out of one million that it is contaminated with replicating microorganisms. This test is carried out to ensure the vaccine is free of other micro-organism and pyrogens.

Safety Test: An adverse event is a health problem that happens after vaccination that may or may not be caused by a vaccine. By definition, a side effect has been shown to be linked to a vaccine by scientific studies. This test is carried out to ensure safety of animal after vaccination.

Potency Test: The relevance of a potency test to clinical efficacy is fundamental to its use for a combination vaccine. Different test methods, such as assays of physicochemical properties, antigenicity, immunogenicity, infectivity, and protection against infection or disease, are used to measure potency. This test is carried out to ensure the vaccine will provide optimum titer level after vaccination.

Challenge Test: the gold standard test to evaluate the protective efficacy of a vaccine in host animal's body. This test is carried out to ensure the vaccine will prevent the vaccinated animals if it is attacked by vaccine specific pathogens.

Field Trial/Study: A specific investigation of an animal vaccine under field condition and in target animals (in terms of animal species and categories), using the product as recommended.

Good Manufacturing Practices (GMP): are the practices required in order to conform to the guidelines recommended by agencies that control the authorization and licensing of the manufacture and sale of pharmaceutical products. These guidelines provide minimum requirements that a manufacturer must meet to assure that their products are consistently high in quality, from batch to batch, for their intended use. GMP is typically ensured through the effective use of a quality management system (QMS).

Cold Chain System: A cold chain or cool chain is a temperature-controlled supply chain. An unbroken cold chain is an uninterrupted series of refrigerated production, storage and distribution activities, along with associated equipment and logistics, which maintain a desired low-temperature range. It is used to preserve and to extend and ensure the shelf life of products, such

as fresh agricultural produce, seafood, frozen food, chemicals, and pharmaceutical drugs. This is important in the supply of vaccines to distant clinics and chemist shops in hot climates.

ETP: Effluent treatment plant is a process to convert wastewater-which is water no longer needed or suitable for its most recent use-into an effluent that can be either returned to the water cycle with minimal environmental issues or reused. The effluent contains several pollutants, which can be removed with the help of an effluent treatment plant (ETP). The "clean" water can then be safely discharged into the environment.

Lab Animal House: Animal testing, also known as animal experimentation, animal research and in vivo testing, is the use of non-human animals in experiments that seek to control the variables that affect the behavior or biological system under study. The focus of animal testing varies on a continuum from pure research, focusing on developing fundamental knowledge of an organism, to applied research, which may focus on answering some question of great practical importance, such as finding a cure for a disease. For that, a separate animal lab plays a crucial role in a Pharmaceutical manufacturing company.

Contamination: Contamination is the undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or API during production, sampling, packaging or repackaging, storage or transport.

Cross-contamination: The process by which any chemicals, bacteria or other microorganisms are unintentionally transferred from one substance or object to another, with harmful effect.

Bioburden: Bioburden is the level and type (e.g. objectionable or not) of micro-organisms that can be present in raw materials, API starting materials, intermediates or APIs. Bioburden should not be considered contamination unless the levels have been exceeded or defined objectionable organisms have been detected.

Virus: Virus is intracellular replicating infectious agents that are potentially pathogenic, possessing only a single type of nucleic acid (either RNA or DNA), is unable to grow and undergo binary fission, and multiply in the form of their genetic material.

Bacteria: a member of a large group of unicellular microorganisms which have cell walls but lack organelles and an organized nucleus, including some which can cause disease.

Master Seeds: Master Virus Seed Stock. A vaccine virus bank is referred to as the Master Virus Seed Stock (MVSS) and Working Virus Seed Stock (WVSS). The Master Seed and Master Cell

concept is used in the manufacture of vaccines and biological products. A Master Seed may be a bacterium, virus, or recombinant organism, e.g. a plasmid with an exogenous insert, expressed in an E. coli bacterial host.

Immunogenicity: Immunogenicity is the ability of a substance to trigger an immune response or reaction, such as development of specific antibodies, T-cell response, allergic or anaphylactic reaction.

Immunological Properties: The study of the molecular and cellular components that comprise the immune system, including their function and interaction, is the central science of immunology. The immune system has the capability of self and non-self-recognition. An antigen is a substance that ignites the immune response.

Antibody: A protein found in the blood that is produced in response to foreign substances (e.g. bacteria or viruses) invading the body. Antibodies protect the body from disease by binding to these organisms and destroying them.

Immunity: Protection against a disease. There are two types of immunity, passive and active. Immunity is indicated by the presence of antibodies in the blood and can usually be determined with a laboratory test.

Titer: The detection of antibodies in blood through a laboratory test.

Animal Welfare: the protection of the health and well-being of animals. The treatment that an animal receives is covered by other terms such as animal care, animal husbandry and humane treatment.

Excipient: Excipient is an ingredient added intentionally to the drug substance which should not have pharmacological properties in the quantity used.

Quality: Quality is the degree to which a set of inherent properties of a product, system or process fulfills requirements.

Quality System: Quality System is the sum of all aspects of a system that implements quality policy and ensures that quality objectives are met.

Specification: Specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests

described. It establishes the set of criteria to which a drug substance, drug product or materials at other stages of its manufacture should conform to be considered acceptable for its intended use. A drug substance and drug product, when tested according to the listed analytical procedures, will meet the acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

Cell Culture: Cell culture is the process by which cells that are no longer organized into tissues are grown in vitro under defined and controlled conditions. Cell cultures are operated and processed under axenic conditions to ensure a pure culture absent of microbial contamination. In biology, axenic describes the state of a culture in which only a single species, variety, or strain of organism is present and entirely free of all other contaminating organisms.

Cell Line: Cell line is a type of cell population which originates by serial subculture of a primary cell population, which can be banked.

Biological Agent: also called **bio-agent**, **biological threat agent**, **biological warfare agent**, **biological weapon**, or **bioweapon**—is a bacterium, virus, protozoan, parasite, or fungus that can be used purposefully as a weapon in bioterrorism or biological warfare (BW). In addition to these living and/or replicating pathogens, toxins and biotoxins are also included among the bio-agents. More than 1,200 different kinds of potentially weaponizable bio-agents have been described and studied to date.

Biological agents have the ability to adversely affect human health in a variety of ways, ranging from relatively mild allergic reactions to serious medical conditions, including death. Many of these organisms are ubiquitous in the natural environment where they are found in water, soil, plants, or animals.

ELD_{50}- Embryo Lethal Dosage. ELD_{50} unit is the amount of virus that will kill 50 percent of inoculated eggs.

EID_{50}- Embryo Infective Dosage. EID_{50} unit is the amount of virus that will infect 50 percent of inoculated eggs.

$TCID_{50}$- Tissue Culture Infective Dose. $TCID_{50}$ unit is the amount of virus that will produce a cytopathic effect in 50 percent of the cultures inoculated.

CFU- In microbiology, a colony-forming unit (CFU, cfu, Cfu) is a unit used to estimate the number of viable bacteria or fungal cells in a sample. Viable is defined as the ability to multiply via binary fission under the controlled conditions. Counting with colony-forming units requires culturing the microbes and counts only viable cells, in contrast with microscopic examination which counts all cells, living or dead.

PFU- In virology, a plaque-forming unit (PFU) is a measure of the number of particles capable of forming plaques per unit volume, such as virus particles. It is a functional measurement rather than a measurement of the absolute quantity of particles: viral particles that are defective or which fail to infect their target cell will not produce a plaque and thus will not be counted. For example, a solution of tick-borne encephalitis virus with a concentration of 1,000 PFU/µl indicates that 1 µl of the solution contains enough virus particles to produce 1000 infectious plaques in a cell mono-layer, but no inference can be made about the relationship of pfu to number of virus particles.

General Requirements for Vaccine Production (Manufacture)

Principle

Production operations must follow clearly defined approved current procedures; they must comply with the following principles in order to obtain products of the requisite quality and be in accordance with the relevant manufacturing and marketing authorizations.

The manufacture of animal vaccine has special characteristics that should be taken into consideration when implementing and assessing the quality assurance system. Because of the very nature of this manufacture (cultivation steps, lack of terminal sterilization), the products must be particularly well protected against organic or inorganic contamination and cross-contamination. The environment also must be protected, especially when the manufacture involves the use of pathogenic or exotic biological agents, and the worker must be particularly well protected when the manufacture involves the use of biological agents pathogenic to humans.

i) Production should be performed and supervised by competent authorized people. Workers must understand the theory behind and practice of their work to the extent that they can predict and prevent problems within the scope of their responsibility.

ii) All handling of materials and products, such as receipt and quarantine, sampling, storage, labeling, dispensing, processing, packaging and distribution should be done in accordance with approved written procedures or instructions and adequately documented.

iii) All incoming materials should be evaluated to assess the quality impact on manufacturing. Appropriate action should be taken when materials are determined to be compromised.

iv)Incoming materials and finished products should be physically or administratively quarantined immediately after receipt or processing, until they have been released for use or distribution.

v) Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials.

vi)All materials and products should be stored under the appropriate conditions as established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation according to life expectancy.

vii) Checks on yields, and reconciliation of quantities should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.

viii) Operations on different products should not be carried out simultaneously or consecutively in the same room unless there is a negligible risk of mix-up or cross-contamination.

ix) At every stage of processing, products and materials should be protected from microbial and other contamination. A method of measuring bioburden within the production facility should be established. OIE guideline and WHO GMP guidelines for Biological products TRS 996 annex-3, should be complied for production and quality control of animal vaccine.

x) When working with dry materials and products, special precautions should be taken to prevent the generation and dissemination of dust particulates. This applies particularly to the handling of highly active or sensitizing materials.

xi) At all times during processing, all materials, bulk containers, critical items of equipment and where appropriate rooms used should be labeled or otherwise identified with an indication of the product or material being processed, its strength or concentration (where applicable) and batch number. Where applicable, this indication should also mention the stage of production.

xii) Labels applied to containers, equipment or premises should be clear, unambiguous and in the company's approved format. It is often helpful in addition to the wording on the labels to use colors to indicate status (for example, quarantined, accepted, rejected, clean, etc.).

xiii) Checks should be carried out to ensure that pipelines and other pieces of equipment used for the transportation of products from one area to another are connected in a correct manner.

xiv) Any deviation from instructions or procedures should be avoided as far as possible. If a deviation occurs, it should be approved in writing by a competent authorized person, with the involvement of the quality control department as appropriate to evaluate the effect on product quality and the shelf life of the product.

xv) Access to production premises should be restricted to authorized personnel.

xvi) Normally, the production of other products should be avoided in areas destined for the production of animal vaccines (Live and inactivated) and should not use the same equipment.

Prevention of Cross-contamination in Production

i) Contamination of a starting material or of a product by another material or product should be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, vapors, sprays or organisms from materials and products in process, from residues on equipment, residues from excipients or packaging and from operators' clothing, skin and respiratory tract. The significance of this risk varies with the type of contaminant and of a product being contaminated. Amongst the most hazardous contaminants are biological preparations containing living organisms.

ii) Cross-contamination should be avoided by appropriate technical or organizational measures, for example:

a) Production in segregated areas or by campaign (separation in time) followed by appropriate cleaning.

b) Providing appropriate air-locks and air extraction.

c) Minimizing the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air; routine testing of air.

d) Keeping protective clothing inside areas where products with special risk of cross-contamination are processed.

e) Using cleaning and decontamination procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross-contamination.

f) Using "closed systems" of production.

g) Testing for residues and contamination and use of cleaning status labels on equipment.

iii) Measures to prevent cross-contamination and their effectiveness should be checked periodically according to set procedures.

Master & Working Seed Banks

i) A master seed (reference culture, parental strain) should be established for each microorganism used in the production of a product to serve as the source of seed for inoculation of all production cultures. Records of the source of the master seed should be maintained. For each seed, the highest and lowest passage levels that may be used for production should be established and specified in the approved production documents for the relevant regulatory procedure. Full characterization of master seed will be needed, if source is changed.

ii) Working seeds and production seeds may be prepared from the master seed by subculturing. Using a master seed and limiting the number of passages of seed microorganism in this manner assists in maintaining uniformity and consistency in production.

iii) The origin, form and storage conditions of seed material should be described (frozen or desiccated and stored at low temperatures such as –40°C or –70°C, or under other conditions found to be optimal for maintaining viability). Storage containers should be adequately sealed and clearly labeled. Storage conditions should be properly monitored. An inventory should be kept and each container accounted for. Tamper evident tape may be needed for boxes and containers.

Master Cell Stock

When cell cultures are used to prepare a product, a master cell stock (MCS) should be established for each type of cell to be used. Records of the source of the master cell stock should be maintained. For each product, the highest and lowest passage levels of cells that may be used for production should be established and specified in approved documents. Each MCS should be characterized to ensure its identity, and its genetic stability should be demonstrated when subculture from the lowest to the highest passage used for production. The purity of MCSs should be established by testing to ensure freedom from extraneous bacteria, fungi, mycoplasma, and viruses.

Embryonated Eggs

Embryonated eggs are also commonly used in the production of biologicals. They should be derived from SPF (Specific Pathogen Free) chicken flocks that have been intensively monitored for infectious agents and have not been vaccinated; or, where justified (e.g. for production of some inactivated vaccines) and in line with the marketing authorization, from healthy chicken flocks. The route of inoculation of the egg and the choice of egg material to be harvested are dependent on the particular organism that is being propagated.

Quality Control

Principle

Quality control is concerned with sampling, specifications and testing as well as the organization, documentation and release procedures that ensure that the necessary and relevant tests are carried out and those materials are not released for use, nor products released for sale or supply until their quality has been judged satisfactory. Quality control is not confined to laboratory operations but must be involved in all decisions that may concern the quality of the product. The independence of quality control from production is considered fundamental to the satisfactory operation of quality control.

Animal Vaccine Manufacturing General Rules

i) Each holder of a relevant regulatory approval should have a quality control department. This department should be independent of other departments, and under the authority of a person with appropriate qualifications, who has adequate laboratory support. Adequate resources must be available to ensure that all the quality control requirements are effectively and reliably carried out.

ii) The head of the quality control department generally has the following responsibilities:

a) To approve or reject, as he/she sees fit, starting materials, packaging materials, and intermediate, bulk and finished products.

b) To evaluate batch records.

c) To ensure that all necessary testing is carried out.

d) To approve specifications, sampling instructions, test methods and other quality control procedures.

e) To approve and monitor any contract analysts.

f) To check the maintenance of his/her department, premises and equipment.

g) To ensure that the appropriate validations are done.

h) To ensure that the required initial and continuing training of department personnel is carried out and adapted according to need.

iii) The quality control department may have other duties, such as to establish, validate and implement all quality control procedures, keep the reference samples of materials and products, provide training and SOPs or Directives to departments to ensure the correct labelling of containers of materials and products, ensure the monitoring of the stability of the products, and participate in the investigation of complaints related to the quality of the product. All these operations should be carried out in accordance with written procedures and recorded.

iv) Finished product assessment should include all relevant factors, including production conditions, results of in-process testing, a review of manufacturing (including packaging) documentation, compliance with finished product specifications and examination of the finished product.

v) In-process controls ensure the quality of a product. Those controls should be performed at an appropriate stage of production.

vi)There may be a requirement for the continuous monitoring of data during a production process for example, monitoring of physical parameters during fermentation.

vii) Continuous culture of biological products is a common practice and special consideration needs to be given to the quality control requirements arising from this type of production method.

Good Practice for Quality Control in Laboratories

Documentation

i) Laboratory documentation. Following details should be available to the quality control department:

a) Specifications.

b) Sampling procedures.

c) Testing procedures and records (including analytical worksheets or laboratory notebooks).

d) Analytical reports or certificates.

e) Data from environmental monitoring, where required.

f) Validation records of test methods, where applicable.

g) Procedures for and records of the calibration of instruments and maintenance of equipment.

ii) Any quality control documentation relating to a batch record should be retained for 1 year after the expiry date of the batch or at least 5 years after the certification. Records retention requirements may be specified by the relevant regulatory body or national laws.

iii) For some kinds of data (e.g. analytical tests results, yields, and environmental controls) it is recommended that records are kept in a manner permitting trend evaluation.

iv)In addition to the information that is part of the batch record, other original data such as laboratory notebooks or records should be retained and readily available.

Sampling

i) Sampling should be done in accordance with approved written procedures that describe:

a) The method of sampling

b) The equipment to be used

c) The amount of the sample to be taken.

d) Instructions for any required sub-division of the sample.

e) The type and condition of the sample container to be used.

f) The identification of containers sampled.

g) Any special precautions to be observed, especially with regard to the sampling of sterile or noxious materials.

h) The storage conditions.

ii) Instructions for the cleaning and storage of sampling equipment.

iii) Quality control personnel should have access to production areas for sampling and investigation.

iv)Samples are retained; firstly, to provide a sample for analytical testing and secondly to provide a specimen of the fully finished product. Samples may therefore fall into two categories:

a) Reference sample: a sample of a batch of starting material, packaging material or finished product that is stored for the purpose of being analysed should the need arise during the shelf life of the batch concerned.

b) Retention sample: a sample of a fully packaged unit from a batch of finished product.

These are stored for identification and retest purposes during or beyond the shelf life of the product. The number of retention samples may be specified by the relevant regulatory authority, otherwise they should be stored at least in duplicate.

v) Samples should be selected from each batch or serial of product. The selector should pick representative final containers from each batch or serial and store these samples at the storage temperature recommended on the label. The producer should keep these reserve samples at the recommended storage temperature for a minimum of 12 months after the expiry date shown on the label, so that they are available to assist in evaluating the cause of any field problems

reported from the use of the vaccine. The samples should be stored in a secure storage area and be tamper-evident.

vi) It may be necessary to retain samples of intermediate products in sufficient amount and under appropriate storage conditions to allow repetition or confirmation of a batch control.

vii) Samples should be representative of the batch of materials or products from which they are taken. Other samples may also be taken to monitor the most stressed part of a process (e.g. beginning or end of a process).

viii) Sample containers should bear a label indicating the contents, the batch number, the date of sampling and the containers from which samples have been drawn.

Characterization

Extensive characterization studies should be performed to demonstrate that the quality of the vaccine product is comparable to the reference product. Characterization studies should at least include physicochemical properties, biological properties, immunological properties, purity (process-related and product-related impurities), contaminants, potency, and strength. Characterization studies may be performed in accordance with the reference guideline. Characterization studies should be designed to allow direct comparison of the vaccine product and the reference product. However, if characterization studies result in different patterns, the implications of such differences should be evaluated and additional characterization studies may be required.

Structural/Physicochemical Properties

The physicochemical characterization should include the determination of composition, physicochemical properties, and primary and higher order structures of the active ingredient of the vaccine product. If the appropriate higher order structural information cannot be obtained, a relevant biological activity assay may indicate a correct conformational structure. In such instances, the analytical procedures for determination of biological activity should have appropriate precision and accuracy. In addition, if process-related and product-related impurities are generated or if degradation products are identified through stress and accelerated stability

studies, such impurities and/or degradation products should also be evaluated. An inherent degree of structural heterogeneity occurs in proteins due to the process. Therefore, the vaccine product may contain a mixture of modified forms. Appropriate efforts should be made to investigate and identify such forms.

Biological Properties

Since animal vaccines having a wide range of biological properties, various biological assays should be considered in determining the biological activity. Biological assays can be used in determining the action mechanism of the relevant vaccine. Therefore, a set of relevant functional assays designed to evaluate the range of activities of a vaccine with multiple biological activities should be developed and employed. Therefore, the biological assay can also serve as a complement to physicochemical analysis. If a biological assay with appropriate accuracy and precision is used, it is possible to demonstrate that a vaccine product is not significantly different from a reference product in terms of biological functions. However, since the biological activity assay usually has considerable variability, it should be considered that the biological assay may not be able to detect any differences from the reference product. The results of the biological assay should be provided and expressed in units of activity calibrated against an international or national reference standard, when available and appropriate. Such assays should comply with appropriate compendial requirements for biological assays, if applicable.

Immunological Properties

As the purpose of the use of animal vaccine is to trigger immune response, immunological properties are very important to characterize the immunological properties of a vaccine product. If immunological properties are part of the characterization studies (e.g., for antibodies or antibody-based products), the specificity, affinity, binding activity and others of the vaccine product should be evaluated in comparison with those of the reference product. In addition, the results from the immunogenicity studies in animal models should be considered.

Purity (Impurities)

The purity and impurity profiles of the drug substance and the drug product should be assessed both qualitatively and quantitatively by a combination of analytical procedures. Accelerated

conditions, other conditions that may cause degradation, and potential post-translational modifications should be considered in evaluating the impurity profiles. The product-related impurities in the biosimilar product should be identified and compared to the reference product using the appropriate technologies. If possible, application of more than one analytical technology to each should be considered. Since the vaccine product is produced according to its own unique manufacturing process different from that for the reference product, the process related impurities in the vaccine product may be quantitatively and qualitatively different from those in the reference product. Purity supporting data should demonstrate purity of, master seed, bulk, Ingredients and finished product.

Specifications

Specifications should be established for routine quality controls. Product specific tests to be included in the specifications should be selected to assure the quality of the vaccine product and should comply with the requirements as specified in the relevant regulations or guidelines. If a pharmacopoeial monograph such as USP, BP, OIE is available for the vaccine substance or finished product then the specification should be based on pharmacopeia. Each acceptance criterion should be established and justified based on data obtained relevant development data, and data obtained from the comparability studies (quality, safety, and efficacy) and justifications for the methods used and the proposed range should be provided.

Analytical Procedures

In order to demonstrate that the quality of the vaccine product is comparable to the reference product, extensive characterization studies should be applied at animal vaccine product, bulk and seed. Given the complexity of the properties and its inherent heterogeneity, more than one analytical technique may be required for each quality attribute, in order to sufficiently characterize the physicochemical and biological properties. Although validated analytical procedures are not necessarily required, analytical procedures used in the characterization studies should be scientifically sound and be able to produce reliable results. Analytical procedures included in the specifications should be appropriately validated.

Cold Chain System

Cold chain system is one of the prime concerns during storage and transportation of vaccine. Every vaccine (live or killed) need to be stored at a recommended temperature. A well established cold chain system is a must during storage and transportation of vaccine from factory to final delivery.

Lab Animal Treated Area

Animal testing standard house/laboratory is essential for the test of animal vaccines safety and efficacy for manufacturing of animal vaccines. Separate Animal testing standard house/laboratory is very crucial requirements for test result accuracy, personnel safety, environmental safety and controlling of mass contamination of pathogenic organism to the environment.

Guideline for the Registration of Animal Vaccines

This guideline describes the minimum data that are expected to provide in support of an application to register a new Animal Vaccine and the format in which should present this information. In all, there are 5 data should consider submitting:

- Part 1 Application overview
- Part 2 Chemistry and manufacturing
- Part 3 Occupational health and safety
- Part 4 Environment
- Part 5 Efficacy and safety

1. Application Overview

The purpose of the application overview is to provide a brief outline of the application and to lead reviewers through an application. The overview should contain other general information on the product, and a summary of all data in the application.

The executive summary within the overview should include the reasons for the application. For a new product, this should include whether the product contains an active constituent and scientific argument for registration of the product. The argument should outline the importance, prevalence and (if applicable) the regional distribution of the disease or problem the product is intended to control, plus the economic and/or technical advantages of the product.

Applicant should also provide a summary of the detailed information on the product characteristics. The information should include the immunobiological properties and the clinical particulars of the product.

Clinical Particulars

- Target species.
- Indications for use.
- Contraindications.
- Undesirable effects (with reference to frequency and seriousness).
- Precautions for use.
- Dosage and method of administration.
- Overdose.
- Special warnings for each target species.
- Major and minor incompatibilities (if appropriate).
- Withdrawal periods.
- Special precautions for the user/administrator of the product.
- First aid instructions.
- Safety directions.

Registration Status Overseas

Applicant should provide details of any known current or previous applications or approvals in other countries for products containing the same formulation in the application overview. If the product has previously been evaluated, applicant should provide full details of the outcome, along with details of the overseas-approved use pattern (host species, claims, directions for use and withdrawal periods), including any use restrictions. Applicant should provide overseas evaluation reports. Applicant should also provide any other information relevant to the proposed application; for example, approvals for other formulations containing the same active constituents including field trial report in Bangladesh.

2. Chemistry and Manufacturing

GMP Status of the Manufacturing Facility of Animal Vaccine

Applicant should provide evidence that the product is manufactured to a standard comparable with the Good Manufacturing Practice for Veterinary Products. For products manufactured overseas, applicant should supply evidence of compliance with good manufacturing practice.

Formulation or Composition of Animal Vaccine Product

Applicant should supply the following information on the formulation or composition of the product:

- Active constituent(s)—including maximum and minimum release titers and end-of-shelf-life titre.
- Adjuvant(s).
- Excipients—including diluent, preservatives, stabilizers, emulsifiers, coloring matter and markers.
- Reference to standards (where applicable).
- Function of each constituent.
- Quantity of each constituent in the formulation—this should be expressed in appropriate units (eg, TCID50, EID50, ELD50, CFU, PFU, mL, mg).

Containers

Applicant should mention the immediate container, and stoppers and closures that will be used in a final product.

Applicant will need to demonstrate details of used for the immediate container is compatible with the type of product. The choice of material should take into consideration the potential for toxicity because some materials are known to have the potential to leach and/or react with the product and produce substances that can be toxic to the target species.

The Manufacturing Process of the Final Vaccine Product

Applicant should provide 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, including any critical in-process control testing steps.

Production, Control and Testing of Starting Materials

Starting materials mean all components used in the production of the Animal Vaccine. The EP, BP, USP, OIE or CFR requirements, where appropriate monographs exist, should apply to all substances in the product. Applicant should provide documentation from suppliers, such as certificates of analysis and/or raw material specifications.

Raw Materials

Applicant should provide detailed information of specifications and functions of all raw materials. If biological raw materials of animal origin are imported, a copy of the import permit (if available) and the manufacturer's specifications will suffice.

Where appropriate, applicant should indicate the methods used to determine that starting materials of biological origin are free from contaminants.

Materials from defined and reliable sources should be used. The specification should note the manufacturer(s) and origin of the raw material.

Starting Materials Listed in a Pharmacopoeia

- The name and code identifying the starting material.
- The title of the monograph and year of publication, preferably together with a copy of the monograph.
- Certificate(s) of analysis.

Master Seed Organism

Each master seed should be assigned a specific code description for identification purposes.

A record of the seed materials (for example, virus, bacteria, mycoplasma, fungi, rickettsia and protozoa), including purification and characterization procedures should be provided.

Characterization of the microorganism should include as a minimum:

- The genus and species.
- Strain/serotype.

Information on the biological characteristics of the master seed should include information on growth characteristics and environmental distribution.

Applicant should provide details of studies and tests carried out to demonstrate purity, identity of the master seed. Applicant should also demonstrate that the master seed is free from extraneous agents. Tests to demonstrate that the master seed is pure and free from extraneous agents should be performed as per OIE, EP, BP, USP or 9CFR, where monographs exist.

Working Seed Organism

Applicant should provide the method of preparation and description of the working seed lot. The description should include the range of passage levels to be used for production, controls applied; tests carried out on working seed and storage conditions.

Cell Substrate/Production Medium

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

- Live animal culture; eg specific pathogen–free (SPF) eggs, chickens, cattle.
- Tissue culture (continuous cell lines or primary cells).
- Microbiological media.

If the cell substrate/production medium consists of SPF eggs, primary SPF chicken cells or SPF chickens, you should demonstrate compliance with EP, BP or 9CFR.

If the cell substrate/production medium consists of tissue culture substrates (continuous cell lines):

- Evidence that master cell seed tests comply with OIE, EP, BP USP or 9CFR (where applicable).

If the cell substrate/production medium consists of microbiological media, you should provide the following information:

- Name of the medium and composition.
- Raw material specifications, including any tests required for freedom from specific agents such as pestivirus, and prion agents of transmissible spongiform encephalopathies.
- A description of the method of preparation and sterilization under the heading 'Media preparation'.

Media Preparation

Detailed description of the methods of preparation and sterilisation of all media used in such a way that they become ingredients of the product. It will include the control applied, the testing carried out and the certificates of analysis of ready-to-use media.

In-process Control Tests During Production

All critical analytical test procedures in sufficient detail to enable the procedures to be assessed. Procedures should be validated where appropriate and provide the results of validation studies on all key procedures as identified by the manufacturer.

Where applicable, current pharmacopoeial monographs. Give copies of the pharmacopoeial monographs, specifications and certificates in an annex to this part of the application dossier.

With a view to verifying the consistency of the production process and the final product, you should provide a flow chart of the production process showing the stages at which critical in-process control tests are carried out. This may be cross-referenced to the section headed Manufacturing process of the final product if the flow chart is provided there.

Provide information on critical tests performed for each control stage, as follows:

- Title and company test code.
- Timing and frequency.
- Function of test.
- A brief description of the test with details and results of the validation studies as appropriate). The detailed description should contain sufficient information to enable us to assess the adequacy of the test method and (if applicable) whether it is consistent with the cited monograph. Provide a copy of the test procedure document as the detailed description, but this is not compulsory.

Applicant should only provide details of tests that are considered critical to allow the manufacturing process to continue to the next stage.

Applicant should provide in detail the assay methodology for detoxified or inactivated immunobiological products and the limit of detection specified. This may be cross-referenced to the section headed Manufacturing process of the final product if the assay methodology is provided there.

Control Tests on the Final Product

Applicant should provide detailed information on final product tests performed, including the batch release specification. This should include as appropriate:

- Identification assay for active ingredients.
- Identification assay for adjuvants.
- Sterility.

- Moisture (as required).
- Safety when required.
- Extraneous agents including mycoplasmas.

Stability Studies

Long-term stability study should be carried out in order to establish the shelf-life (expiry) period and storage conditions of animal vaccine. Although a comparative stability study (with the reference product) is not necessarily required, accelerated and stress stability studies to establish the impurity profiles at drug substance and drug product levels are often useful in determining the comparability of the vaccine product. The stability studies should be performed on the basis of the representative conditions, including the container-closure system. The stability studies may be designed and performed in accordance reference guideline.

Summary of Test Results

Applicant should provide a summary of results of tests on finished product to support application for registration of the product.

3. Occupational Health and Safety

In application, applicant should address potential occupational health and safety risks associated with the manufacture and use of the product. This may include any or all of the following:

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

4. Environment

Applicant should provide information on the extent of exposure of the product, its active constituents or relevant metabolites to the environment, and proposed disposal methods for

unused or waste product. The Effluent treatment plant, (a process to convert wastewater - which is water no longer needed or suitable for its most recent use - into an effluent that can be either returned to the water cycle with minimal environmental issues or reused) should be available.

5. Efficacy and Target Animal Safety

Efficacy of a vaccine means induction of immunity to provide protection against a specified disease. The nature, degree, onset and duration of immunity are the main parameters of the protection. All claims for the efficacy of vaccines, including the duration of protection and the administration schedules, should be fully supported by data from specific laboratory trials. Field studies should be conducted in case of introducing new vaccines registration both local and imported vaccine. The main reasons for conducting field trials on Animal Vaccines: confirmation that the efficacy and safety of a product demonstrated in laboratory studies is reflected in field conditions.

Supportive Data for Efficacy and Safety of the Vaccine in the Target Species

The number of animals and/or groups used in a trial should be sufficient to enable the trial results to be evaluated for statistical significance which is shown in annexure ------.

In general, the animals to be used should be susceptible to the disease(s) against which the vaccine is being evaluated.

Laboratory Trials

Efficacy Trials

- Establishment of minimum protective dose and vaccination schedule.
- Confirmation of protection against challenge in each target species and representatives of each class of target animal.
- Influence of passively acquired and/or maternally derived antibodies on efficacy, if appropriate.
- Onset of immunity.

- Duration of protection.
- Timing of, and response to, booster vaccination.
- Compatibility with other treatments (vaccines) administered within seven days of administering the product under evaluation.

Safety Studies

- Single-dose studies.
- Repeat single-dose studies (where applicable).
- Overdose studies (10× for live vaccines, 2× for inactivated vaccines).
- Immunological effects.
- Reproductive effects (where appropriate).
- Compatibility with other known products administered within seven days of administering the product under evaluation.

For live vaccines, also include:

- Spread to non-vaccinates.
- Spread to non-target animals.
- Dissemination in the host.
- Reversion to virulence.
- Recombination.

It would be preferable to undertake the above studies under controlled laboratory conditions. However, where a suitable laboratory challenges model or marker of protection is not available, or for other justifiable reasons, you may need to rely on large-scale, well-planned field trials for some or all of these studies. Field trials will usually supplement the data generated from laboratory studies.

Field Trials

Field trials can serve two purposes:

- To demonstrate safety and efficacy of commercially-produced batches of vaccine where safety and efficacy have been determined by laboratory studies (using product at the end-of-shelf-life titre or lower under the recommended conditions of use).
- Used as a method of determining safety and/or efficacy of a product where it is not possible or practical to undertake appropriate laboratory studies. In this case, field efficacy studies should be undertaken using product at the end-of-shelf-life titre or lower under the recommended conditions of use. Field safety studies should be undertaken using product at the maximum release titre.

Safety and Efficacy Trials

The trials should:

- Use the recommended dose and vaccination schedule as per proposed label instructions, using product that is at, or close to, the proposed end-of-shelf-life titre.
- Use representative batches manufactured using procedures outlined in the dossier.
- Replicate the proposed major uses of the product (route, method, administration schedule, target species including the most sensitive class or members of the target species).
- For animals kept under extensive or pastoral conditions, use a minimum of three sites, encompassing different husbandry practices and environments.
- For intensively reared animals, use a minimum of two sites.

The dossier should document any adverse reactions.

These studies should be well planned, controlled, monitored and carried out under conditions where endemic disease is known to occur and challenge rates would be expected to mimic those seen commonly in the field.

Applicant should fully describe and validate all techniques involved, where necessary. Applicant should report all results, whether favorable or not, and applicant should also present statistical analysis, if appropriate to a particular study.

Animal Welfare

Clearance from animal welfare and ethics committee should be taken with the trial protocol in order to respect the welfare of animals used in the trials.

Annexure 1: Animal Vaccines Available in Bangladesh

❖ Poultry Vaccines

i. Newcastle Disease Vaccine (Live & Killed)
ii. Infectious Bursal Disease Vaccine (Live & Killed)
iii. Fowlpox Vaccine (Live)
iv. Fowl Cholera Vaccine (Killed)
v. Egg Drop Syndrome Vaccine (Killed)
vi. Marek's Vaccine (Live)
vii. Infectious Bronchitis (Live & Killed)
viii. Avian Encephalomyelitis (Live)
ix. Infectious Coryza (Killed)
x. Fowl Typhoid (Killed)
xi. Duck Plague (Live)
xii. Salmonella (Killed)
xiii. Mycoplasma (Killed)
xiv. Baby-chick Ranikhet Disease (BCRDV live)
xv. Pigeon Pox Vaccine (live)

❖ Large and Small Animal Vaccines

i. Foot and Mouth Disease (FMD), killed vaccine
ii. Anthrax (Live)
iii. Hemorrhagic Septicemia (Killed)
iv. Peste des petits ruminants (PPR), Live vaccine
v. Black Quarter (Killed)
vi. Rabies (Live/Killed)
vii. Mastitis (Killed)
viii. Goat Pox Vaccine (Live)

Annexure 2: Import Vaccines Available in Bangladesh

i. Newcastle Disease Vaccine (Live & Killed)
ii. Infectious Bursal Disease Vaccine (Live & Killed)
iii. Fowlpox Vaccine (Live)
iv. Fowl Cholera Vaccine (Killed)
v. Egg Drop Syndrome Vaccine (Killed)
vi. Marek's Vaccine (Live)
vii. Infectious Bronchitis (Live & Killed)
viii. Avian Encephalomyelitis (Live)
ix. Infectious Coryza (Killed)
x. Salmonella (Killed)
xi. Mycoplasma (Killed)
xii. Avian Influenza (AI, Killed)
xiii. Foot and Mouth Disease (FMD, Killed)
xiv. Rabies (Killed)
xv. Mastitis (Killed)

Annexure 3: Registration Process Flow for Vaccines Manufactured by Imported Bulk

i. **NOC to Import Samples for R&D.**

ii. **Source Validation for Vaccines:**

a) Principal company profile.

b) Copy of valid biological product manufacturing license.

c) GMP certificate issued by the licensing authority of country of origin.

d) Certificate of Analysis (COA) of vaccine bulk by bulk manufacturer originated from the country of origin.

e) Noninferiority Trial with reference or registered vaccine conducted in the field of Bangladesh.

f) List of vaccine of the principal company.

iii. **Recipe Submission:** Necessary documents

a) Data generated from development of R& D batch.

b) Analytical method development.

c) Process development.

d) 3-month stability (R&D batch).

iv. **Application for an Annexure:**

a) Summary of product characteristics.

b) Clinical Trial Report: (a) Safety data, (b) Efficacy report, (c) Immunogenicity / Sero-conversion rate, (d) Field Trial report.

c) Test method qualification (linearity, precision, accuracy, specificity).

d) Test method validation (robustness).

f) In house full testing (corresponding COA).

g) Formulation screening (excipient selection, formulation stability).

h) Finished product specifications (Reference Pharmacopoeia).

i) Finished Product testing, COA.

j) Process validation protocol and subsequent submission of data. (proof of consistency in process).

k) Stability testing (accelerated and ongoing real-time/real condition.

l) Extractable/Leachable studies based on available public data.

J) Proof of availability of cold chain storage and supply facilities.

v. After Approval of Annexure, Subsequently Approval of Packaging Materials, Price and then MA Certificate is Issued.

vi. Post Marketing Documents:

a) Real time Stability data up to shelf-life.

b) Post marketing observational study report on reasonable number of subjects within 6 months to 1 year.

c) Any change should be submitted as per DGDA requirements.

Annexure 4: Registration Process Flow for Locally Manufactured Animal Vaccine

i. Steps for Registration:

a) Copy of valid biological product manufacturing license.

b) GMP certificate of the manufacturing plant.

c) Recipe Application in prescribed form.

d) Annexure Application with data generated from development of Seed characterization, R& D batch and manufacturing flow chart in brief.

e) Analytical specifications.

f) Analytical methods.

g) 3 months stability studies of bulk and finished product and commitment to submit real time data.

h) Test Samples, COA, Summary Lot Protocol.

i) Pyrogen, Safety, Potency, Sterility and Challenge test report.

j) Proof of availability of cold chain storage and supply facilities.

ii. Application for Marketing Authorization (Annexure Approval):

a) DGDA format CTD dossier for 4 modules.

b) Field trial report.

iii. After Approval of Annexure Subsequently Approval of Packaging Materials, Price and then MA Certificate is Issued.

iv. Post Marketing Documents:

a) Real time stability data up to shelf-life.

b) Post marketing observational study report on a reasonable number of subjects within 6 months to 1 year.

Annexure 5: Registration Process Flow for Import of Animal Vaccine

i. Process Flow:

a) Finished animal vaccine to be imported from if the vaccine is registered with one of the following countries USA, France, Germany, UK, Switzerland, Japan, Australia, Russia, South Korea, Singapore and EU countries.

b) Master Seed characterization.

c) Principal company profile with a copy of GMP certificate issued by the licensing authority of country of origin.

d) Certificate of Analysis (COA) with a specification of each API in packaging materials.

e) Test method qualification (linearity, precision, accuracy, specificity).

f) Safety, Potency, Endotoxin, Sterility, Master seed information, and Challenge test details of bulk as well as finished product (country of origin).

g) NOC to import sample vaccine for field trial.

h) Field trial report generated in Bangladesh.

i) Temperature monitoring record, such as data logger report, shipment validation report.

j) Cold chain storage and supply facilities of local agent should be ensured by inspection.

ii. Application for Marketing Authorization (Annexure Approval):

DGDA format CTD dossier for 4 modules.

iii. After Approval of Annexure, Subsequently Approval of Packaging Materials, Price and then MA Certificate is Issued.

iv. Post Marketing Documents:

Real time stability data up to shelf-life and Post marketing observational study report on reasonable number of subjects within 6 months to 1 year.

Annexure 6: General Equipment List for Vaccine Manufacturing

i. General list of equipment for vaccine bulk manufacturing.

- Autoclave bag sealing machine
- 50 L pressure vessel
- Weighing balance
- Water bath
- Vacuum pump
- Seed fermenter (20L)
- Production fermenter (100L)
- Pipette controller
- pH meter
- Peristaltic pump
- Micropipette
- Magnetic stirrer
- Inverted microscope
- HPHV autoclave
- Horizontal LAF
- HEPA cabinet (hanger)
- Hand sanitizer
- Filtration assembly
- Filter integrity tester
- Dry heat sterilizer
- Refrigerated centrifuge
- Deep freezer (-20 ^{0}C)
- Refrigerator (2-8 ^{0}C)
- Ultra low freeze (-80 ^{0}C)
- Decontamination autoclave
- CO_2 incubator
- Walk-in-incubator
- Shaking incubator
- BOD incubator
- Egg incubator
- Ceiling LAF
- Biosafety cabinet
- Viscometer
- Osmometer
- Bioreactor

- Different types of chromatography system
- Spectrophotometer
- Water purification system
- CO_2 incubator
- Hemocytometer
- Inverted microscope
- Liquid nitrogen freezer (-196 ºC)
- Effluent treatment plant (ETP)
- Separate lab animal treated area (Animal house)

ii. General list of equipment for vaccine fill finish manufacturing

- Mixing vessels
- Sterile filtration system
- Filling machine for syringe
- Filling machine for vial
- Lyophilizer
- Sealing machine
- Labeling machine
- Blister machine
- Printing machine
- Water purification system for WFI
- Autoclave
- Balance
- Storage system (Freezer, Refrigerator)

Annexure 7: General Equipment List for Quality Control

Equipment list for Quality Control

- 2–8 °C refrigerator
- 2W DPB
- Autoclave (Double door)
- Autoclave bag sealing machine
- Automated hand sanitizer
- Bench top culture roller
- Biosafety cabinet
- BOD incubator
- BOD incubator 20–25 °C
- BOD incubator 30–35 °C
- Centrifuge (refrigerated)
- CO_2 incubator
- Compound microscope
- Conductivity meter
- Dry heat sterilizer
- Drying cabinet
- Egg candler
- ELISA reader
- Filtration assembly
- Freezer (–20 °C)
- Freezer (–80 °C)
- Fume hood
- Geldoc system
- Gel-Electrophoresis unit
- Heating block
- HEPA cabinet
- Hot plate
- Incubator 20–25 °C
- Incubator 30–35 °C
- Inverted microscope
- LAF horizontal
- LOD Oven
- Magnetic stirrer
- Microbial air sampler
- Micropipette
- Moisture analyzer

- Multichannel micropipette
- Particle counter
- PCR
- Peristaltic pump
- pH meter
- pH meter printer
- Pocket type pH meter
- Slide calipers
- Stability chamber
- TOC analyzer
- Ultracentrifuge machine
- UV-Spectrophotometer
- UV-Spectrophotometer for DGFU
- Vacuum pump
- Vertical autoclave (Single door)
- Vortex mixer
- Water bath
- Weighing balance
- Image analyzer
- Western/ Southern/ Northern blot
- Viscometer
- Osmometer
- HPLC
- Shaker
- Label free molecular interaction analyzer
- Amino acid analyzer
- Sequencer
- Mass spectrometer

Annexure 8: Human Resources Area of Expertise

i. Microbiology

ii. Veterinary Science

iii. Biotechnology and Genetic Engineering

iv. Biochemistry and Molecular Biology

v. Molecular Genetics and Bioinformatics

vi. Biostatistics

vii. Mechanical / Chemical Engineering

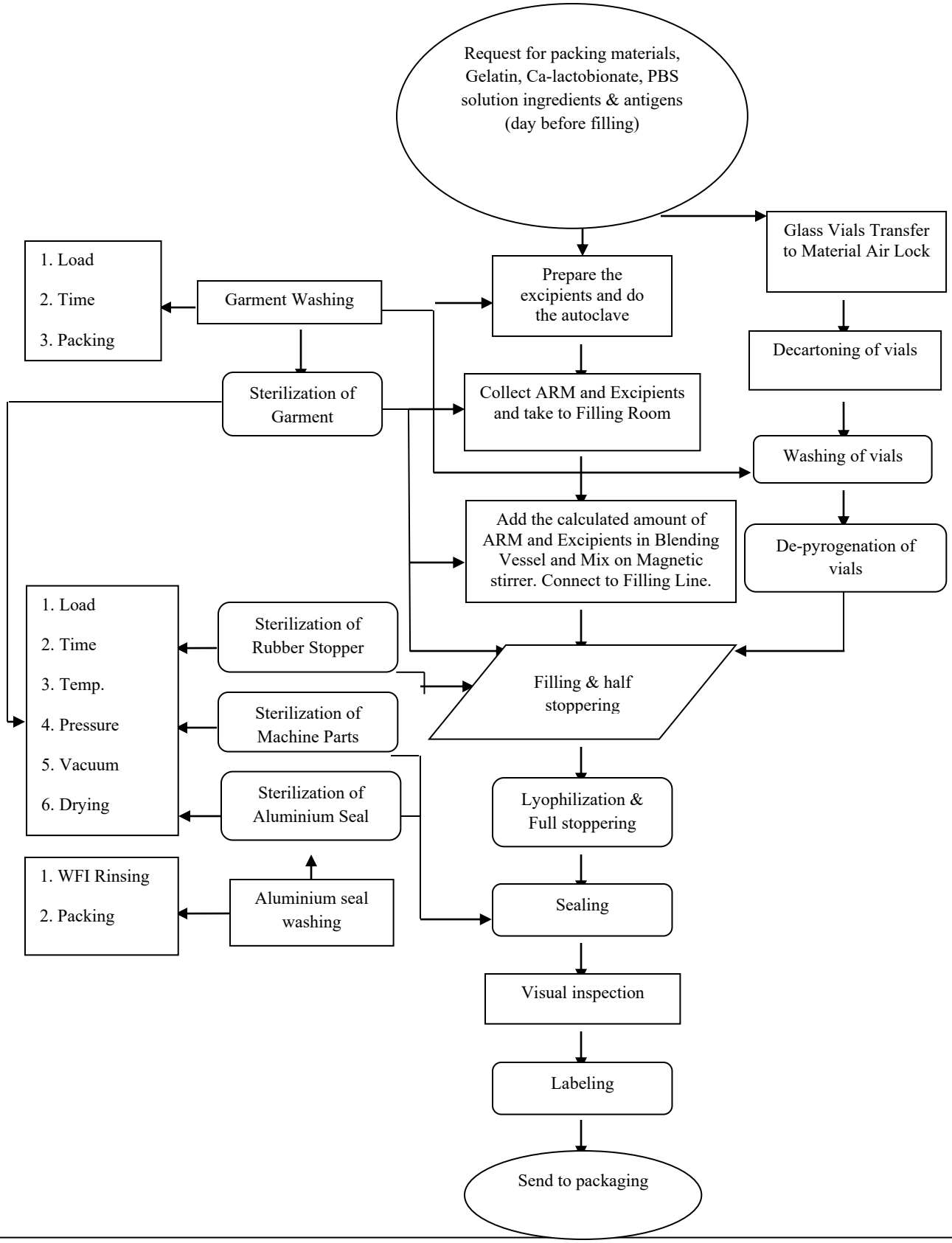
viii. Pharmacy

ix. Chemistry

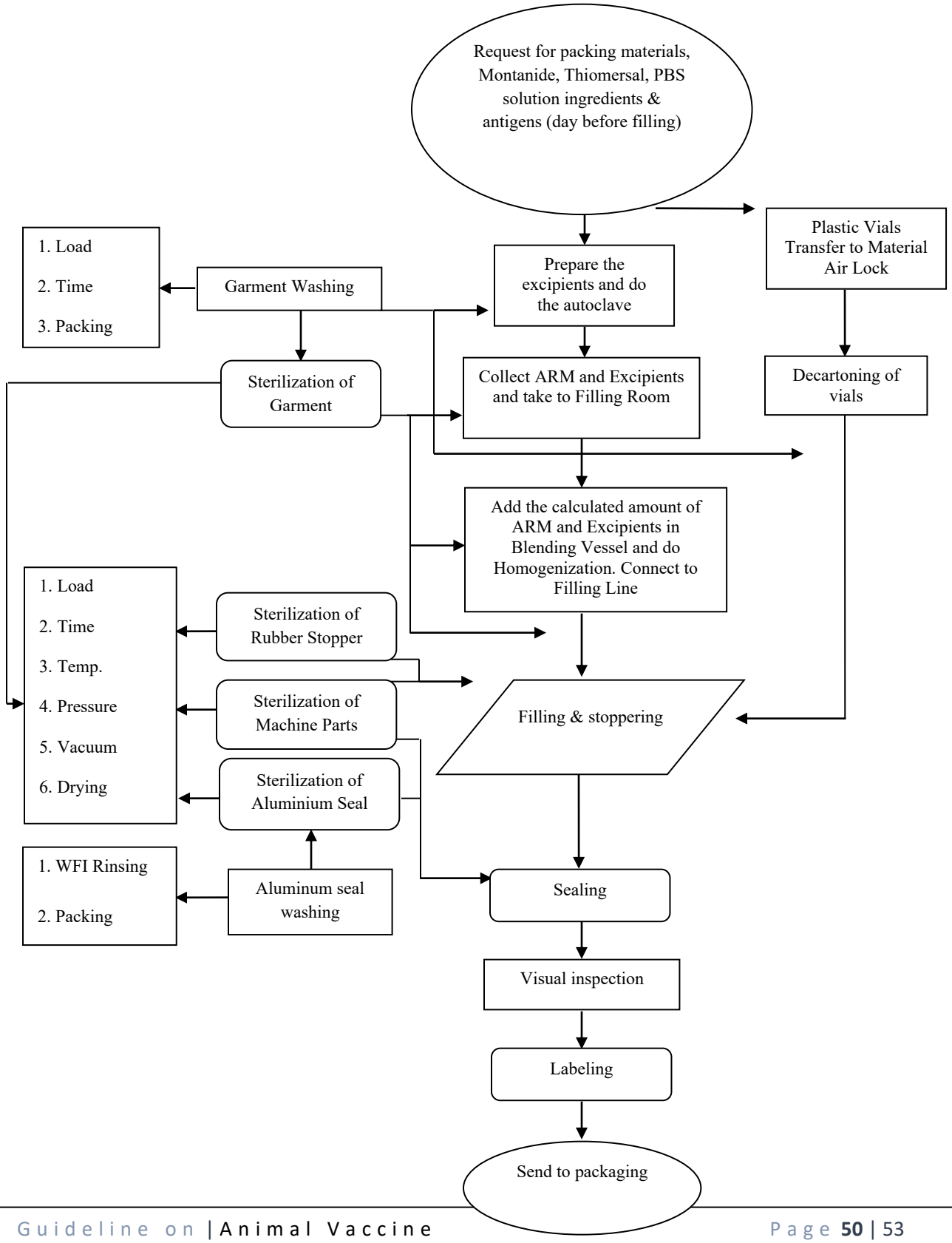
x. Applied Chemistry

xi. Biomedical Engineering

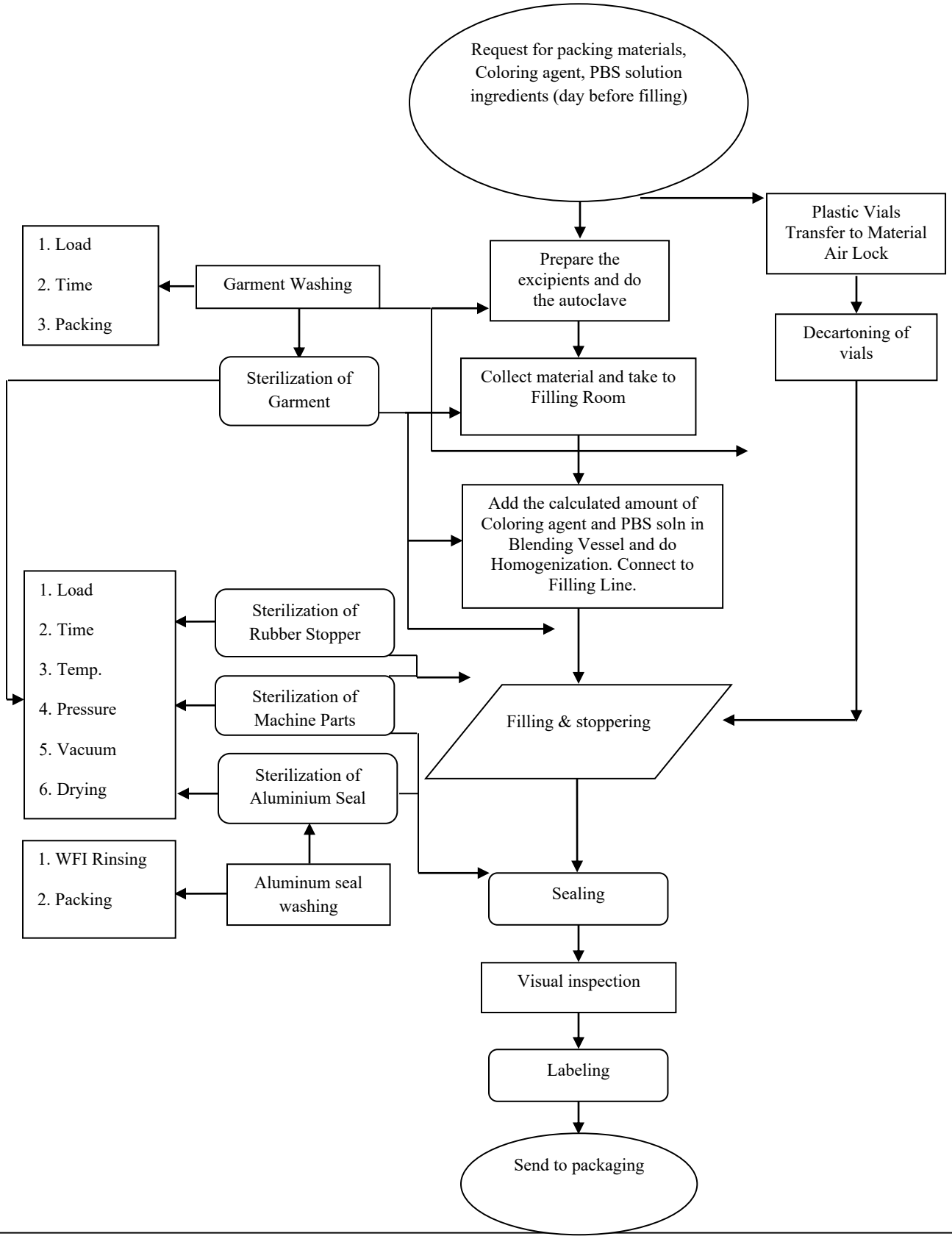
Annexure 9: Process Flow Chart: Live Vaccine



Annexure 10: Process Flow Chart: Killed Vaccine



Annexure 11: Process Flow Chart: Diluent



Annexure 12: Form – 9

Form of undertaking to accompany an application for an import license

Whereas….....of……. intends to apply for a license under the Drugs Rules. 1945 for the import into Bangladesh of the substances specified below manufactured by us. We ……. of……. hereby give this undertaking that for the duration of the said license –

(I) The said applicant shall be our agent for the import of the substances into Bangladesh.

(2) We shall comply with the conditions imposed on a licensee by clauses (a) to (e) of Rule 78 of Drugs Rules, 1945.

(3) We declare that we are carrying on the manufacture of the substances mentioned in this undertaking at the premises specified below and we shall from time to time report any change of premises on which the manufacture will be carried on and in cases where manufacture is carried on in more than one factory any change in the distribution of functions between the factories.

(4) We shall comply with the provisions of Part IX of the Drugs Rules, 1945.

(5) Every substance manufactured by us for import under license into Bangladesh shall as regards strength. Quality and purity conform to the provisions of Chapter III of the Drugs Act, 1940 and of the Drugs Rules, 1945.

(6) We shall comply with such further requirements, if any, as may be specified by rules made by the central government under the Act and of which the licensing authority has given to the licensee not less than four months' notice.

List of Substances

Particulars of premises where manufacture is carried on.

Date: ……. Signed by or on behalf of the manufacturer……..

References

1) Guideline for the registration of new veterinary vaccines. Australian Pesticides and Veterinary Medicines Authority 2014.

2) Minimum Requirements for the production and quality control of Vaccines (OIE Vaccine Recommendation 2018).

3) General Licensing Requirements in the United States. Center for Veterinary Biologics, U.S. Department of Agriculture, Animal and Plant Health Inspection Service, Veterinary Services, 2014.

4) The European Agency for the Evaluation of Medicinal Products. Veterinary Medicines and Information Technology Unit.

5) http://en.ntvbd.com/sci-tech/18122/Bangladesh-invents-anti-FMD-vaccine-for-cattle.

6) Manual of ASEAN rules and procedures for the registration of animal vaccines