REGULATORY JOURNEY OF VACCINE DEVELOPMENT IN THE PHILIPPINES

Abstarct

A vaccine is a biological preparation that induces active acquired immunity against a specific infectious disease.Vaccination is widely regarded as one of humanity's most significant achievements of the twentieth century. In terms of absolute significance, it is regarded as being on stake with some of the most significant medical science discoveries.vaccines for infectious diseases typically take years to develop because they are produced either by chemical inactivation of the virus or pathogen attenuation, processes that can take a long time to validate and also require the live pathogen.

Vaccines have been credited with reducing or eliminating a variety of infectious diseases, including smallpox, measles, and diphtheria. Vaccines proved to be timely interventions, particularly in countries such as the Philippines, where a large number of infectious diseases were prevalent. The Philippines FDA oversees the vaccine approval process in the Philippines.

Vaccines are subjected to rigorous testing and oversight throughout the development life cycle, from preclinical studies to post-licensure. To ensure vaccine quality, manufacturers must follow good manufacturing practises and control procedures.

This work attempted to outline the vaccine development journey and regulatory process beginning with the formulation and process development and concluding with commercialization (distribution).

Keywords

FDA (Philippines Food and Drug Administration) , Vaccine, Formulation, GMP, GDP, GCP.

Introduction

Scientists choose which sort of vaccination to develop based on a variety of variables. Vaccines come in a variety of forms, including:

A. Inactivated vaccines
B. Live-attenuated vaccines
C. mRNAvaccines
D. Subunit, recombinant, polysaccharide, and conjugate vaccines
E. Toxoid vaccines
F. Viral vector vaccines

A. Inactivated Vaccines

- An inactivated vaccine is one that is made up of virus particles, bacteria, or other pathogens that have been grown in culture and then killed to remove their ability to cause disease. Live vaccinations, on the other hand, use germs that are still living. [1]

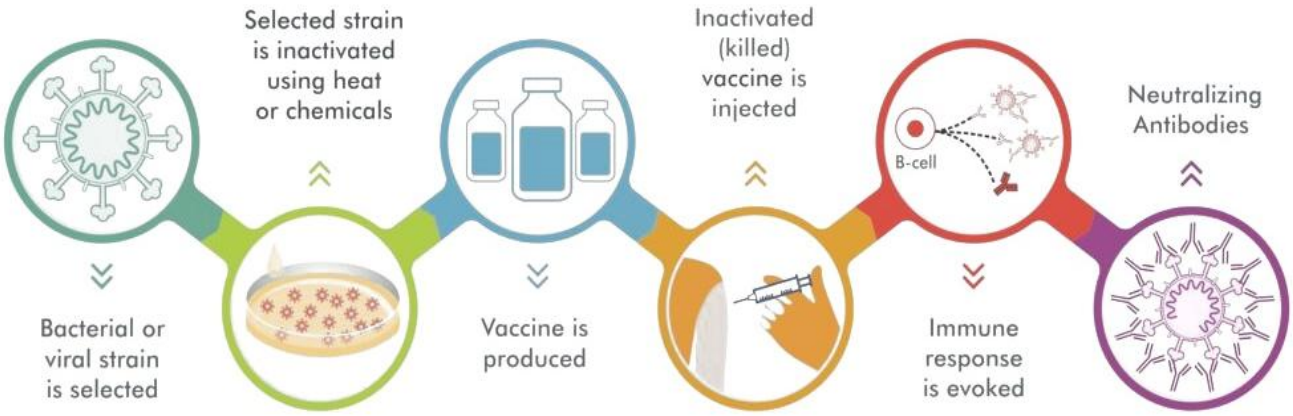


Figure: The Emergence of Inactivated Vaccines [2]

Inactivated vaccinations use a dead version of the disease-causing bacterium.

Inactivated vaccines rarely produce the same level of immunity (protection) as live immunizations. As a result, you may require multiple doses over time (booster injections) to maintain continuous protection against illnesses.

Inactivated vaccines are used to protect against:

- Hepatitis A
- Flu
- Polio
- Rabies

B. Live-attenuated Vaccines

Live-attenuated vaccines differ from traditional inactivated vaccines in that the pathogen is not "killed," and as the name implies, the pathogen remains active in live vaccines. However, the pathogen is attenuated or modified in such a way that it cannot cause disease but can elicit a strong immune response. In comparison to inactivated vaccinations, live vaccines typically result in a stronger, longer-lasting, and more robust immune response.

Reverse genetics, which includes RNA, can be used to create live-attenuated vaccinations. To summarise, live-attenuated vaccines are created using reverse genetic methods. Current (novel) virus genes are mixed with genes from previously altered (attenuated) viruses from the same generic strain. [3]

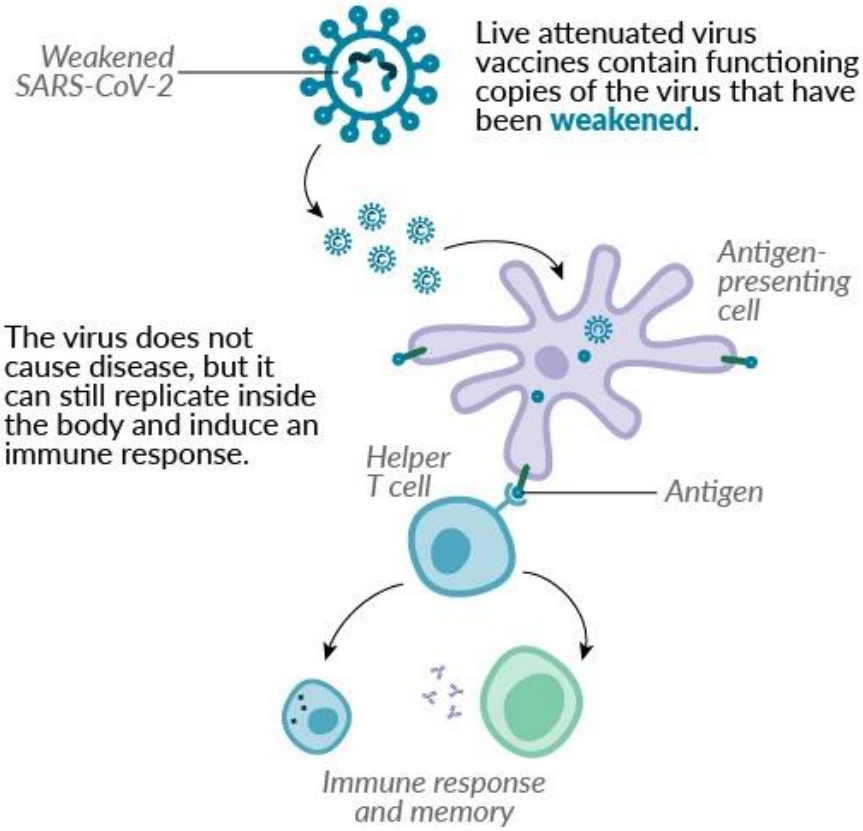


Figure: Live Attenuated Virus Vaccine [4]

Live attenuated vaccines contain a weakened version of the living virus that does not cause serious illness in those who have a good immune system.

Live vaccines employ a weakened (or attenuated) version of the disease-causing bacterium.

These vaccines elicit a powerful and long-lasting immune response because they are so identical to the natural infection they help prevent. Most live vaccines can provide lifetime protection against a germ and the disease it causes with just one or two doses.

However, live vaccines have some drawbacks. As an example:

- Because they include a small quantity of the attenuated live virus, some people, such as those with weaker immune systems, long-term health problems, or those who have had an organ transplant, should see their health care practitioner before taking them.
- Because they must be kept chilled, they do not travel well. As a result, they can't be used in places where refrigerators are scarce.

Live vaccines are used to protect against:

- Measles, mumps, rubella
- Rotavirus
- Smallpox
- Chickenpox
- Yellow fever

C. mRNA Vaccines

An mRNA vaccine is a type of vaccine that produces an immunological response by using a copy of a molecule called messenger RNA (mRNA). The vaccine introduces antigen-encoding mRNA molecules into immune cells, which use the tailored mRNA as a blueprint to make a foreign protein that would otherwise be produced by a disease (such as a virus) or a cancer cell. [5]

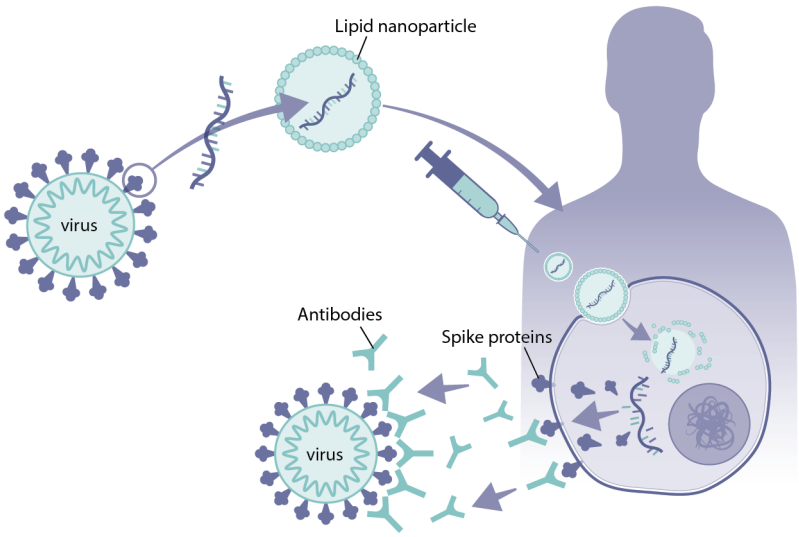


Figure: mRNA Vaccine Development for Covid-19 [6]

mRNA vaccines are a novel vaccine type. They don't utilize a live virus to stimulate the immune system. Instead, they instruct your cells on how to produce a protein that will activate your immune system. Your body produces antibodies after being stimulated. If the true virus enters your body in the future, these antibodies will help you fight it.

mRNA vaccines function by injecting a small amount of mRNA that corresponds to a viral protein, usually a protein located on the virus's outer membrane.

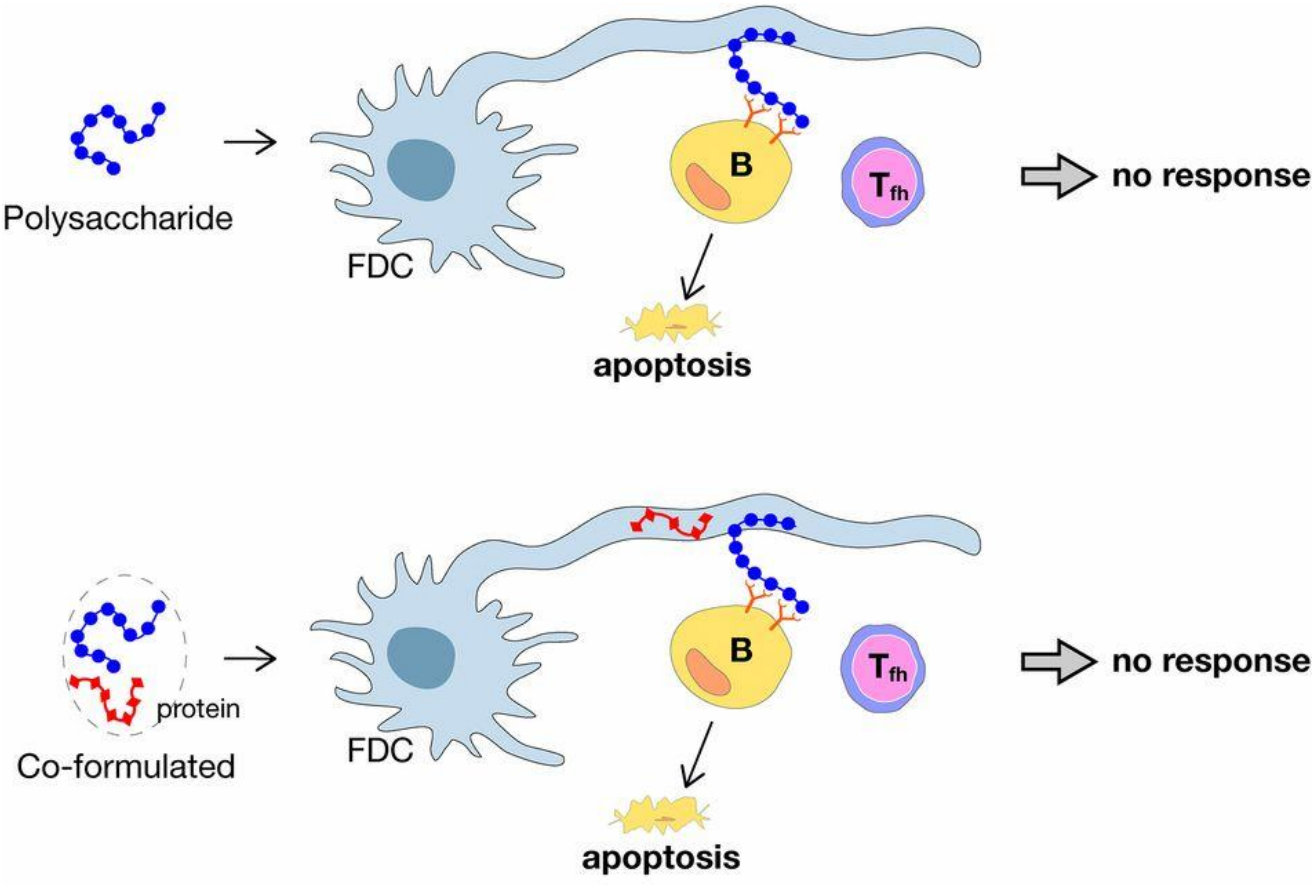
mRNA vaccines are used to protect against:

- COVID-19

D. Subunit, recombinant, polysaccharide, and conjugate vaccines

Specific components of the germ - like its protein, sugar, or capsid—are used in subunit, recombinant, polysaccharide, and conjugate vaccines (a casing around the germ).

These vaccines produce a powerful immune response that is targeted to specific portions of the germ since they only use certain pieces of the germ. They can also be used on practically everyone who requires them, including those with compromised immune systems and long-term health issues.



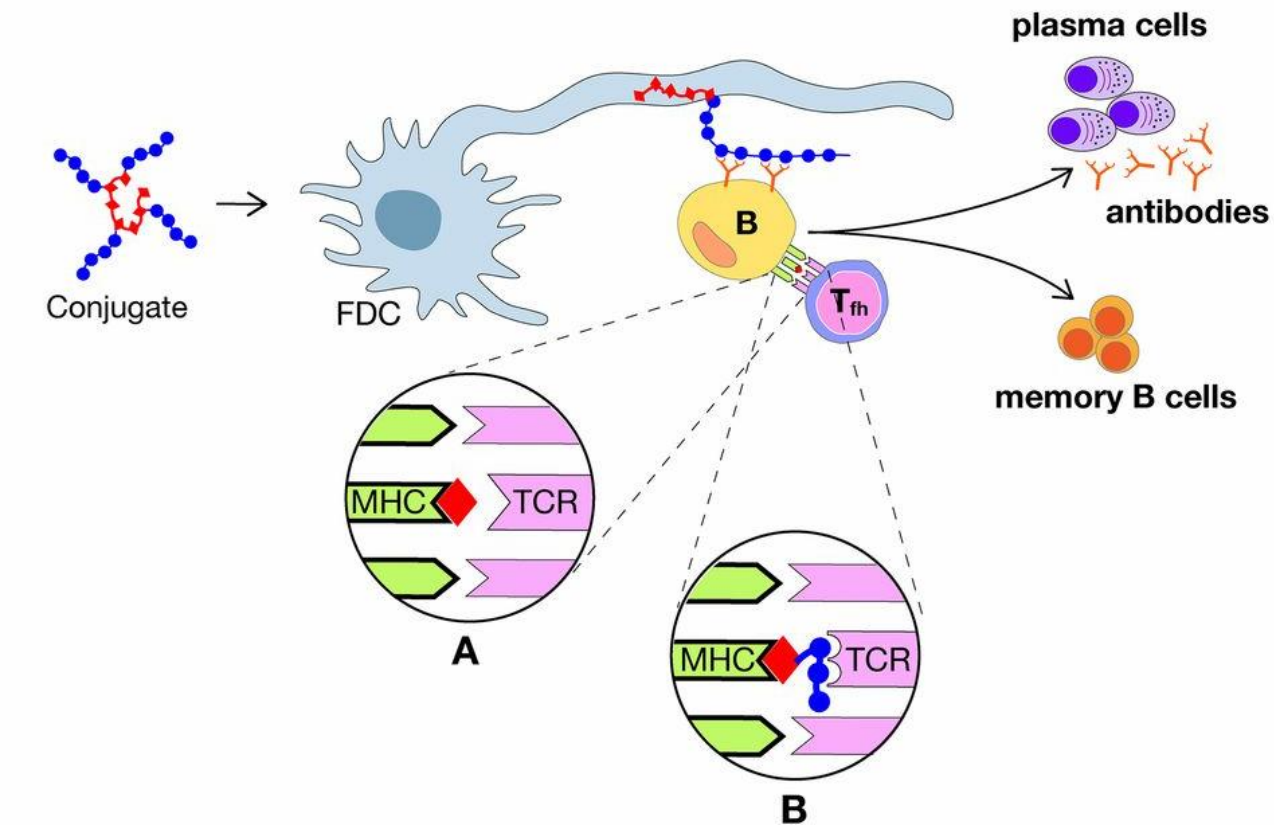


Figure: The Emergence of Subunit, recombinant, polysaccharide, and conjugate vaccine. [7]

Where;

1. FDC – Follicular Dendritic Cells
2. B- B Cells
3. T_{fh}– Follicular helper T Cells
4. MHC – Major Histocompatibility Complex
5. TCR – T Cell Receptor

One disadvantage of these vaccinations is that they may require booster shots in order to provide continued protection against diseases.

These vaccines are used to protect against:

- Haemophilus influenzae type bdisease
- Hepatitis B
- Human papillomavirus
- Whooping cough
- Pneumococcal disease
- Meningococcal disease
- Shingles

D. Toxoid Vaccines

A toxoid is an inactivated toxinwhose toxicity has been suppressed by chemical or heat treatment while maintaining other properties, such as immunogenicity. Toxins are produced by bacteria, whereas toxoids are modified versions of toxins that are not produced by bacteria. As a result, when utilized during vaccination, an immune response is elicited and immunological memory is created against the toxoid's molecular markers without the toxin causing sickness. An anatoxin is another name for such a substance. [8]

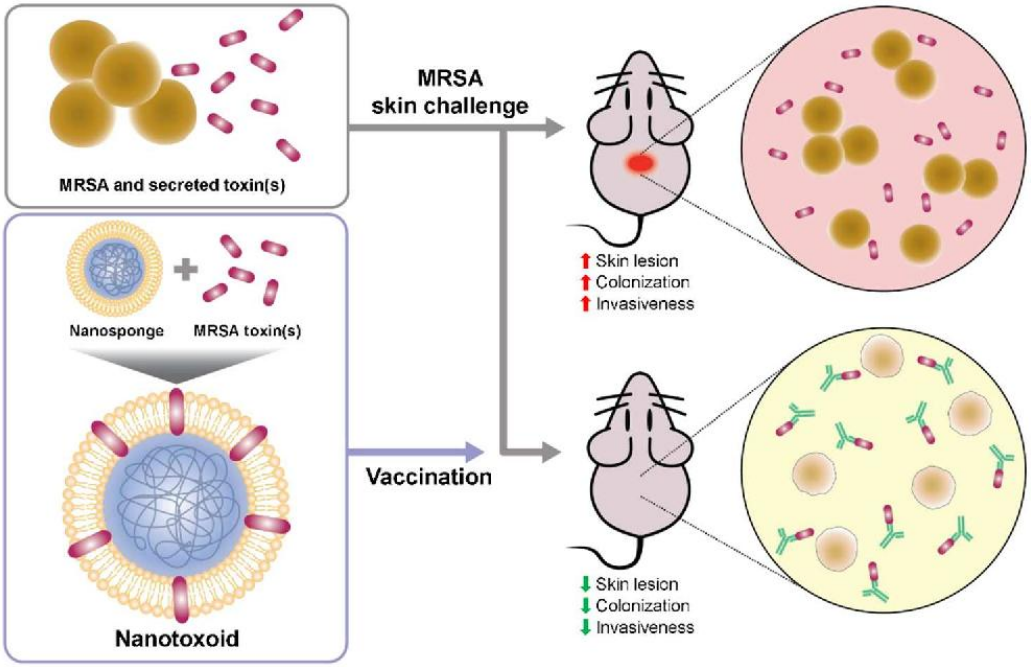


Figure: Toxoid Vaccine against Bacterial Infection [9]

A course of toxoid vaccines, which produce an immune response to weaker copies of certain bacterial toxins called toxoids, induces long-lasting protection against bacterial illnesses such as tetanus and diphtheria. [10]

Purification of bacterial exotoxin is used to create toxoid vaccines. To generate toxoids, the toxicity of purified exotoxins is reduced or inactivated using heat or formaldehyde.

Toxoid vaccines use a toxin (harmful substance) produced by the disease-causing bacterium. Instead of the germ itself, they generate immunity to the components of the germ that cause disease. That is, the immune reaction is directed at the poison rather than the entire germ.

Booster doses, like several other forms of vaccines, may be required to maintain disease protection.

Toxoid vaccines are used to protect against:

- Diphtheria
- Tetanus

E. Viral Vector Vaccines

To send vital instructions to our cells, viral vector vaccines use a modified version of a virus that is not the virus being targeted. A vector virus is a virus that has been changed in some way. [11]

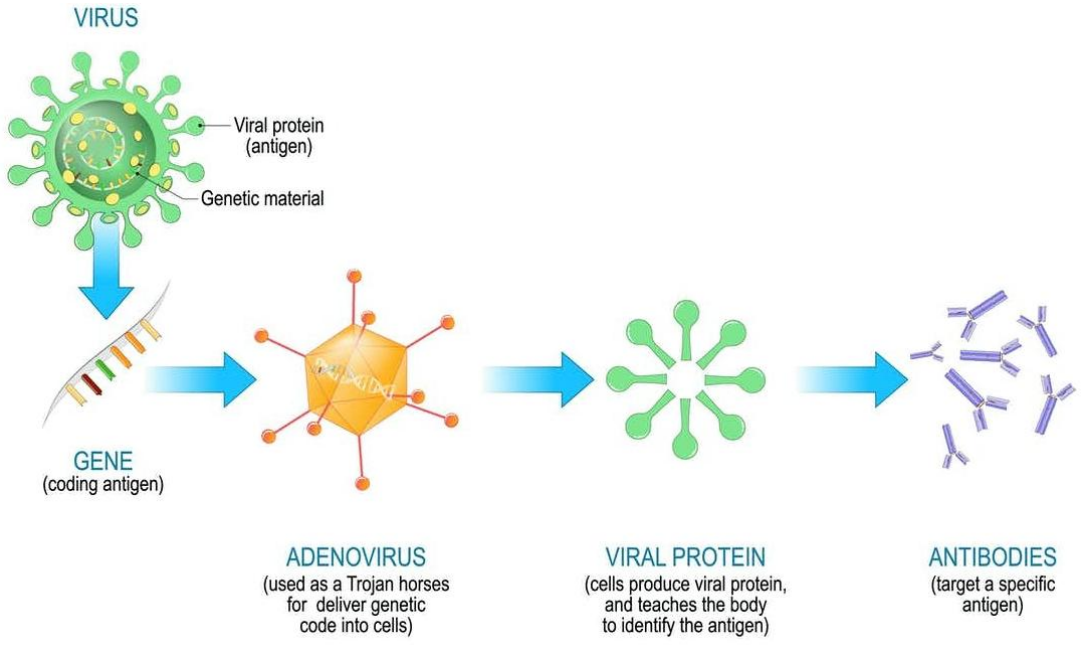


Figure: MOA of Viral Vector Vaccines [12]

A vaccine that uses a viral vector to transmit genetic material coding for the desired antigen into the recipient's host cells is known as a viral vector vaccine. Six viral vector vaccines have been approved for human use in at least one nation as of April 2021: four COVID-19 vaccines and two Ebola vaccines. [13]

Virus vector vaccines have been explored for decades. Virus vector technology was recently applied in several Ebola vaccinations, and a number of studies have focused on viral vector vaccines for other infectious diseases like Zika, flu, and HIV. COVID-19 vaccines were also developed using this method.

To give protection, viral vector vaccines use a modified version of a separate virus as a vector. Viruses such as influenza, vesicular stomatitis virus (VSV), measles virus, and adenovirus, which causes the common cold, have all been utilized as vectors. One of the viral vectors employed in certain COVID-19 vaccines in clinical trials is an adenovirus.

Viral vector vaccines are used to protect against:

COVID-19 [14]

Discussion

TYPES OF ROUTES OF ADMINISTRATION OF VACCINES

- Example:

- Oral Polio Vaccine
- Rotavirus Vaccine

ORAL

- Example:

- Hepatitis A Vaccine
- Hepatitis B Vaccine
- TT

INTRAMUSCULAR

- Example:

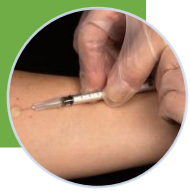
- Measles Vaccine
- yellow fever Vaccine
- varicella Vaccine

SUBCUTANEOUS

- Example:

- BCG Vaccine

INTRADERMAL



HOW DO VACCINES WORK

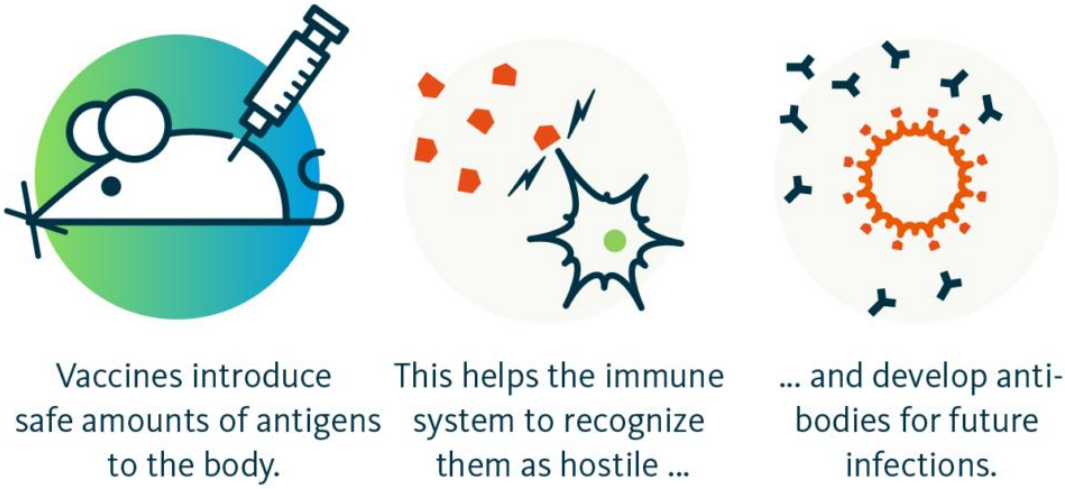


Figure: Process of development of immunity against viruses [15]

Vaccines minimize the risk of infection by assisting the body's natural defenses in developing disease immunity in a safe and effective manner.

Step 1: A disease that has been weakened or killed is injected into the body.

Step 2: Antibodies are produced by the body to fight infections.

Step 3: If the body is ever attacked by disease germs, the antibodies will return to eliminate them. [16]

Herd Immunity - Herd immunity is a type of indirect protection from infectious disease that can occur with some diseases when a large enough percentage of a population has become immune to an infection, either through previous infections or vaccination, reducing the likelihood of infection for those who have not been exposed to it. [17]

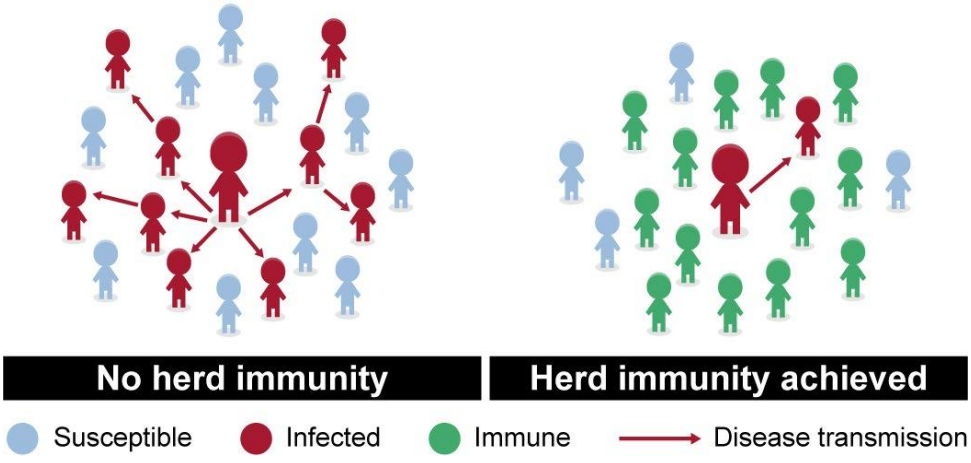


Figure: Illustration of Herd Immunity [18]

FORMULATION & PROCESS DEVELOPMENT

Figure: Formulation and Process Development Stages of Vaccine in Philippines [19]

GOOD MANUFACTURING PRACTICE (GMP)

I.RATIONALE/BACKGROUND		
II. SCOPE/COVERAGE		
III. DEFINITION OF TERMS		
IV. GENERAL GUIDELINES	A. GMP ORGANIZATION	1. Organization, Qualification, and Responsibilities
		2. Training
	B. PREMISES	1. Grounds
		2. Plant Construction and Design
	C. EQUIPMENT	
	D. SANITATION & HYGIENE	1. Personnel
		2. Education and training
		3. Supervision
		4. Sanitary Facilities
		5. Maintenance and sanitation
	E. PRODUCTION & PROCESSES CONTROLS	1. Production Processes and Controls
	F. QUALITY CONTROL	1. Quality Management
		2. Testing of Reprocessed Products
		3. Testing of Returned Goods
		4. Testing of Returned Goods
		5. Laboratory Facilities and Controls
	G. DOCUMENTATION	
	H. QUALITY AUDITS	
	I. WAREHOUSING AND DISTRIBUTION	
	J. PRODUCT RECALL	
	K. RETENTION OF SAMPLES	
	L. SUB-CONTRACTING OF MANUFACTURE	
V. REPEALING CLAUSE		
VI. EFFECTIVITY		

Table: Good Manufacturing Practice for Vaccine Development in Philippines [20]

GMP Inspection Process:

A. Inspection Team

A team of inspectors consists of at least two people, with one designated as the lead. When necessary, a subject matter expert (SME) from a roster of approved Specialists who are designated based on their qualification and competency may be called upon. Similarly, the lead inspector may include 1 or 2 trainees/observers.

B. Frequency

A risk-based approach is used to determine the frequency of inspection based on the inherent risk associated with the product and manufacturing process, as well as the manufacturer's compliance history.

C. Manner of Inspection

Inspection can either be:

I. Announced Inspection-

Establishments eligible for pre-notification must meet all of the requirements listed below:

- CSL has had no product recalls, product complaints, or OOS results in the last three (3) years;

II. Unannounced Inspection-

Pre-notification is not provided in the following situations:

- if the establishment does not meet the criteria under the announced inspection,
- subject to investigation,
- subject to special assignments; or
- routine inspection for establishments with a high-risk level determined during the previous inspection.

D. Inspection Process

At the start of an inspection, the lead inspector discusses the inspection agenda, which includes the purpose, scope, standards to be used, duration of the inspection, roles of each member of the team, and the inspection process. As needed, appropriate changes to the agenda can be made.

The inspection process will include document review, a walkthrough, and interviews with people involved in the manufacturing. To cover the manufacturing site, the team may either go in pairs as individuals or break into smaller groups if there are more than four members. They will ask questions and request evidence to determine whether the company is in compliance with relevant GMP standards. If a finding is made, they may want to see more evidence if it is requested.

The team will discuss and consolidate the findings (deficiencies or observations for improvement) at the end of the inspection, classify deficiencies, and prepare an inspection report. A closeout meeting is held, and the inspection report is presented for discussion to the manufacturer. Deficiency classification is based on FDA Circular No. 2019-003, "Guidelines for the Classification of Deficiencies Observed During Inspection of Drug Manufacturers" [21]

In the event that a critical deficiency is discovered, the lead inspector recommends appropriate actions to the manufacturer based on the degree of harm that the deficiency may cause to patients. The lead inspector directs the submission of a CAPA Plan and objective evidence of compliance, as well as major and other deficiencies.

The lead inspector may decide to end the inspection if critical findings are identified as a result of cross-contamination, mix-up, fraud, or other determining factors, and/or if there are unresolved disputes or disagreements between the inspector and company staff or officers.

E. Period of Inspection

The length of the inspection period will be determined by the complexity of the manufacturing process/es that must be covered.

In most cases, an inspection will take between 1 and 5 working days.

F. Deliberation

If there is a critical deficiency that was not identified in the list of deficiencies and/or if there is a concern about the classified major deficiency after the inspection, deliberation may be pursued prior to the submission of the inspection report.

- The deliberation and action will take place at the FDA office.
- The deliberation will take place with the inspection team members; an independent qualified inspector and a senior qualified inspector.

The outcome of the deliberation will be communicated to the manufacturer in the form of a formal response.

G. Compliance Period

Following the inspection, the manufacturer receives a post-inspection letter outlining the deficiencies discovered during the inspection. For all deficiencies, the establishment receives two submissions of the CAPA plan. The plan must include details on corrective and preventive actions, as well as compliance deadlines.

The response should be concise and comprehensive, with a reasonable time frame for resolving the issues. It is considered their commitment, and the response is used by the lead inspector to determine whether compliance was met in a timely and effective manner. Once accepted, it is expected that actions will be carried out exactly as described. Any significant changes or implementation delays should be communicated to the Lead Inspector. Failure to implement corrective actions will be identified at the next re-inspection and may have an impact on the manufacturer's re-inspection frequency.

Responses are typically reviewed within two weeks of receipt, and if accepted, a follow-up inspection may be scheduled. If necessary, additional information, evidence, or clarification may be requested. Any such request will be passed on to the manufacturer. Otherwise, the CAPA report is completed and the risk assessment form is completed to determine the frequency of inspection.

The manufacturer is notified in writing that the inspection has been completed, and a copy of the final report is available upon request.

GOOD LABORATORY PRACTICE & GOOD CLINICAL PRACTICE

A. GLP

The OECD Principles define Good Laboratory Practice as "an organizational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived, and reported." The purpose of the GLP Principles is to promote the development of high-quality test data and to provide a tool for ensuring a sound approach to laboratory study management, including conduct, reporting, and archiving. The principles can be viewed as a set of standards for ensuring study quality, reliability, and integrity, as well as the reporting of verifiable conclusions and data traceability.

Fundamentals of GLP- The GLP Principles outline the requirements for conducting appropriate nonclinical safety studies. This enables the researcher to carry out his or her work in accordance with his or her pre-established scientific design. GLP Principles aid in the definition and standardization of research institutions' planning, performance, recording, reporting, monitoring, and archiving processes. [22]

GLP emphasizes the importance of the following main points, regardless of the industry targeted:

1. Organization, personnel, facilities, and equipment;
2. Characterization of test items and test systems
3. Protocols and standard operating procedures (SOPs) are examples of rules.
4. Outcomes: raw data, final report, and archives
5. Quality Control: Independent oversight of research processes.

I. RESOURCES	1. Organisation and Personnel
	2. Facilities and Equipment
	3. Characterization
II. RULES	1. Protocol or Study Plan
	2. Written Procedures
III. RESULTS	1. Raw Data
	2. Study Report
	3. Archives
IV. QUALITY ASSURANCE	

Table: Good Laboratory Practice Requirement for Vaccines in the Philippines

B. GCP

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting human subject trials. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, in accordance with the principles enshrined in the Helsinki Declaration, and that clinical trial data are credible.

1. GLOSSARY	
2. THE PRINCIPLES OF ICH GCP	
3. IRB/IEC	1. Responsibilities
	2. Composition, Functions, and Operations
	3. Procedures
	4. Records
4. INVESTIGATOR	1. Investigator's Qualifications and Agreements
	2. Adequate Resources
	3. Medical Care of Trial Subjects
	4. Communication with IRB/IEC
	5. Compliance with Protocol
	6. Investigational Product
	7. Randomization Procedures and Unblinding
	8. Informed Consent of Trial Subjects
	9. Records and Reports
	10. Progress Reports
	11. Safety Reporting
	12. Premature Termination or Suspension of a Trial
	13. Final Reports by Investigator
5. SPONSOR	1. Quality Management
	2. Quality Assurance and Quality Control
	3. Contract Research Organization (CRO)
	4. Medical Expertise
	5. Trial Design
	6. Trial Management, Data Handling, and Record-Keeping
	7. Investigator Selection
	8. Allocation of Responsibilities
	9. Compensation to Subjects and Investigators
	10. Financing
	11. Notification/Submission to Regulatory Authority
	12. Confirmation of Review by IRB/IEC
	13. Information on Investigational Product(s)
	14. Manufacturing, Packaging, Labelling, and Coding Investigational Product(s)
	15. Supplying and Handling Investigational Product(s)
	16. Record Access
	17. Safety Information
	18. Adverse Drug Reaction Reporting
	19. Monitoring • Purpose • Selection and Qualifications of Monitors • Extent and Nature of Monitoring • Monitoring Procedures • Monitoring Report • Monitoring Plan
	20. Audit

	• Purpose • Selection and Qualification of Auditors • Auditing Procedures
	21. Noncompliance • Premature Termination or Suspension of a Trial • Clinical Trial/Study Reports • Multicentre Trials
6. CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)	1. General Information
	2. Background Information
	3. Trial Objectives and Purpose
	4. Trial Design
	5. Selection and Withdrawal of Subjects
	6. Treatment of Subjects
	7. Assessment of Efficacy
	8. Assessment of Safety
	9. Statistics
	10. Direct Access to Source Data/Documents
	11. Quality Control and Quality Assurance
	12. Ethics
	13. Data Handling and Record-Keeping
	14. Financing and Insurance
	15. Publication Policy
	16. Supplements
7.INVESTIGATOR'S BROCHURE	1. Introduction
	2. General Considerations • Title Page • Confidentiality Statement
	3. Contents of the Investigator's Brochure • Table of Contents • Summary • Introduction • Physical, Chemical, and Pharmaceutical Properties and Formulation • Nonclinical Studies • Effects on Humans • Summary of Data and Guidance for the Investigator
	4. APPENDIX 1
	5. APPENDIX 2
8. ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL	1. Introduction
	2. Before the Clinical Phase of the Trial Commences
	3. During the Clinical Conduct of the Trial
	4. After Completion or Termination of the Trial

Table: Good Clinical Practice Requirement for Vaccines in Philippines [22 and 23]

REQUIREMENTS FOR CLINICAL TRIALS

Regulations Governing the Conduct of Clinical Trials for Investigational Drugs:

I. RATIONALE	• Republic Act No. 9711
II. OBJECTIVES	• Safeguarding human subjects' rights and safety, as well as the integrity of clinical trial data • Ensure an efficient and effective C.T. approval process. • Establish standards and requirements for the regulation and importation of Investigational Products.
III. SCOPE AND COVERAGE	
IV. DEFINITION OF TERMS	
V. GENERAL GUIDELINES	
VI. SPECIFIC GUIDELINES	1. Clinical Trial Application
	2. Investigational Products and Clinical Trial Import License
	3. Labelling of Investigational Products
	4. Uploading to the Clinical Trial Registry
	5. Amendments
	6. Safety Reporting
	7. Interim/Annual Report
	8. Termination of Clinical Trial
	9. Promotions
	10. Inspections
	11. Records and Archiving
VII. FEES	
VIII. PENALTIES	
IX. TRANSITORY PERIOD	
X. REPEALING CLAUSE	
XI. SEPARABILITY CLAUSE	
XII. EFFECTIVITY	

Table: Clinical Trial Requirement for Vaccines in Philippines [23]

Clinical Trial Approval Process Flow Chart

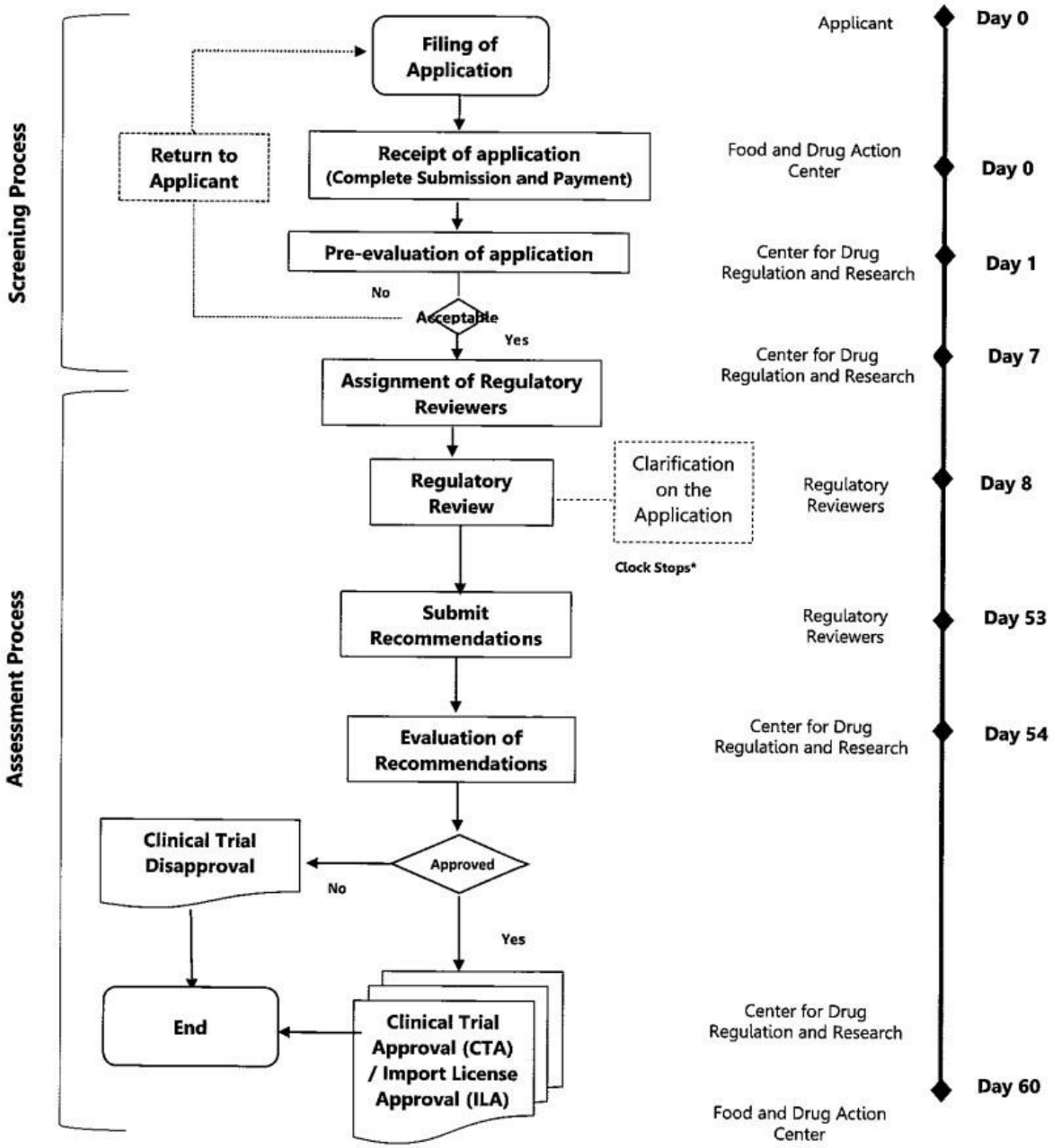


Figure: Clinical Trial Approval Process in Philippines [23]

STABILITY STUDIES: DEVELOPMENT & ONGOING

ICH Guideline - Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products (Q5C) is adopted by FDA Philippines.

I. PREAMBLE	
II. SCOPE OF THE ANNEX	
III. TERMINOLOGY	
IV. SELECTION OF BATCHES	1. Drug Substance (Bulk Material)
	2. Intermediates
	3. Drug Product (Final Container Product)
	4. Sample Selection
V. STABILITY-INDICATING PROFILE	1. Protocol
	2. Potency
	3. Purity and Molecular Characterization
	4. Other Product Characteristics
VI. STORAGE CONDITION	1. Temperature
	2. Humidity
	3. Accelerated and stress conditions
	4. Light
	5. Container/closure
	6. Stability after Reconstitution of Freeze-Dried Product
VII. TESTING FREQUENCY	
VIII. SPECIFICATIONS	
IX. LABELLING	
X. GLOSSARY	

Table: Requirements for Stability Studies on Vaccines in Philippines [24]

PRODUCT DOSSIER REQUIREMENTS

To be able to market a drug product in the Philippines, a company must first obtain a marketing authorization in the form of a Certificate of Product Registration (CPR). A CPR covering a specific drug product is prima facie evidence of the registrant's marketing authority for the said drug product in connection with the activities permitted by the issuance (License to Operate).

The process starts with the submission of an electronic copy application using the Integrated application Form at the Public Assistance, Information, and Receiving (PAIR), by appointment schedule of an applicant company (which could be a licensed manufacturer, trader, or distributor).

When an applicant submits a dossier, the CDRR evaluates the documents to determine whether the product meets the standards for safety, efficacy, and quality. If the product meets these requirements, a CPR is issued that is valid for five (5) years. If flaws are discovered,

depending on their severity, a Notice of Deficiency (NOD) or Letter of Disapproval (LOD) may be issued. [19]

The FDA rejects products on the following grounds:

- According to the application requirements, the drug product does not meet the required technical requirements or appropriate standards.
- The applicant made false statements, entered false data, or withheld any relevant information.
- Significant inconsistencies in the registration dossier's information.
- Significant queries in the NOD compliance that were not clarified or addressed satisfactorily by the applicant company; and
- Significant inconsistencies in the NOD compliance and the registration dossier.

The Republic of the Philippines' Department of Health (DOH) adopted the ASEAN CTD (ACTD) and Common Technical Requirements (CTR) for the registration of pharmaceutical products for human use.

Asian Common Technical Document (ACTD)

The Common Technical Document is organized into four parts as follows:

Part I. Table of Contents, Administrative Data, and Product Information

Part II. Quality Document

Part III. Nonclinical Document

Part IV. Clinical Document

Part I: Table of Content Administrative Information and Prescribing Information

Part I begins with the overall Table of Contents for the entire ACTD, which provides a general overview of the information that can be accessed. Second, the next content is Administrative Data, which includes detailed documentation such as application forms, labels, package inserts, and so on. The final section of this section is Product Information, which includes required information such as prescribed information, mode of action, side effects, and so on.

A general introduction to the pharmaceutical should be included, as well as its pharmacologic class and mode of action.

Section A: Introduction

Section B: Overall ASEAN CTD Table of Contents

Section C: Documents required for registration

Part II. Quality Document

Part II should include an overall summary, followed by the research reports. As much as possible, the quality control document should be described in detail.

Section A: TOC

Section B: Quality overall summary

Section C: Body of data

Part III. Nonclinical Document

Part III should include a Nonclinical Overview, followed by a Nonclinical Discussion. Nonclinical Tabulated summaries are written summaries. This part's documentation is not required for generic products, minor variation products, and some major variation products. If the original products are already registered and approved for market authorization in Reference countries, ASEAN member countries may not require this section's study reports for NCE, Biotechnological Products, and other Major Variation Products. As a result, the authority that requires specific Study reports should request the required documents.

Section A: Table of Contents

Section B: Nonclinical Overview

Section C: Nonclinical Written and Tabulated Summaries

1. Table of Contents
2. Pharmacology
3. Pharmacokinetics
4. Toxicology

Section D: Nonclinical Study Reports

1. Table of contents
2. Pharmacology
3. Pharmacokinetics
4. Toxicology

Part IV. Clinical Document

Part IV should include a clinical overview as well as a clinical summary. For generic products, minor variation products, and some major variation products, this document is not required. If the Original Products are already registered and approved for market authorization in reference countries, ASEAN member countries may not require the Study Reports in this section for NCE, Biotechnological Products, and other Major Variation Products. As a result, the authority that requires specific study reports should request the required documents.

Section A: Table of Contents

Section B: Clinical Overview

Section C: Clinical Summary

1. Summary of Biopharmaceutics and associated analytical methods

2. Summary of Clinical Pharmacology Studies

3. Summary of Clinical Efficacy

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5. Synopses of Individual Studies

Section D: Tabular Listing of All Clinical Studies

Section E: Clinical Study Reports

Section F: List of Key Literature References

GOOD DISTRIBUTION PRACTICE

1. Introduction	• Pharmaceutical distribution is a critical activity in the integrated supply-chain management of pharmaceutical products.
2. Scope of the document	• This document establishes guidelines for pharmaceutical product distribution.
3. General principles	• GDP principles should also be followed in the case of donated pharmaceutical products.
4. Regulation of the distribution of pharmaceutical products	• National legislation should be in place to regulate the activities of individuals or entities involved in pharmaceutical product distribution.
5. Organization and management	• Within the organization, a designated person should be appointed with defined authority and responsibility for ensuring that a quality system is implemented and maintained.
6. Personnel	• An adequate number of competent personnel should be involved in all stages of pharmaceutical product distribution to ensure that product quality is maintained.
7. Quality system	• Quality assurance is used as a management tool within an organization. There should be a documented quality policy describing the distributor's overall intentions and quality requirements, as formally expressed and authorized by management.
8. Premises, warehousing, and storage	• Good storage practices (GSP) apply in all situations where pharmaceutical products are stored, as well as throughout the distribution process.
9. Vehicles and equipment	• Vehicles and equipment used to distribute, store, or handle pharmaceutical products must be fit for purpose and properly equipped to avoid exposing the products to conditions that could compromise their stability and packaging integrity, as well as

	prevent contamination of any kind.
10. Shipment containers and container labeling	• Pharmaceutical products should be stored and distributed in shipment containers that have no negative impact on product quality and provide adequate protection from external influences, including contamination.
11. Dispatch and receipt	• Pharmaceutical products should only be sold and/or distributed to individuals or entities who are authorized to obtain such products under applicable national, regional, and international law.
12. Transportation and products in transit	• Products and shipment containers should be secured to prevent unauthorized access or to provide evidence of such access. Vehicles and operators should be outfitted with additional security, as needed, to prevent product theft and misappropriation during transportation.
13. Documentation	• Written instructions and records documenting all activities relating to pharmaceutical product distribution, including all applicable receipts and issues (invoices), should be available. Unless otherwise specified in national or regional regulations, records should be kept for seven years.
14. Repackaging and relabelling	• Procedures for the secure disposal of original packaging should be in place.
15. Complaints	• A written procedure for handling complaints should be in place.
16. Recalls	• A system, including a written procedure, should be in place to effectively and promptly recall pharmaceutical products that are known or suspected to be defective or counterfeit, with a designated person(s) in charge of recalls.
17. Returned products	• A distributor should accept pharmaceutical product returns or exchanges in accordance with the terms and conditions of the distributor-recipient agreement.
18. Counterfeit pharmaceutical products	• To avoid confusion, counterfeit pharmaceutical products found in the distribution chain should be kept separate from other pharmaceutical products.
19. Importation	• The WHO guidelines on pharmaceutical product import procedures should be taken into account, and the number of ports of entry in a country for the handling of pharmaceutical product imports should be limited by appropriate legislation. The state could designate such ports.
20. Contract activities	• Any activity relating to the distribution of a pharmaceutical product that is delegated to another person or entity must be carried out by parties who are appropriately authorized for that function and in accordance with the terms of a written contract.

21. Self-inspection	• Self-inspection should be carried out independently and thoroughly by a designated, competent person.

Table: Good Distribution Practices for Vaccine Development in Philippines [25]

Conclusion

Vaccines are a relatively new class of pharmaceuticals that are designed to boost immunity to a specific disease. Traditionally, they are composed of disease-causing microbes that have been weakened or killed, as well as their toxins or one of their surface proteins. They allow the body to produce highly specific antibodies by activating adaptive immune systems and through immunological memory against potential future infections.Vaccines are critical tools for protecting public health from the mortality and morbidity caused by the prevalence of infectious diseases. Manufacturers in the Philippines are currently developing and marketing a large number of vaccines. These vaccines are used by a vast percentage of respondents. To prevent contagious and serious diseases, numerous vaccines with high potential have been developed. Vaccine development for emerging and re-emerging diseases is a critical issue that is being actively addressed by both researchers and regulators, and the Philippines FDA is undertaking several initiatives to encourage vaccine developers to work on diseases that do not yet have a treatment.

The primary responsibility of regulators is to ensure that pharmaceutical products are of high quality, safe, and effective. Implementing a strong regulatory system will assist in meeting these objectives, which are especially important for vaccines, which are inherently more difficult to develop, characterise, and manufacture than most pharmaceutical products.In terms of regulating vaccine production, the Philippines FDA has taken the most stringent measures. To ensure regulatory oversight at all stages of vaccine research, the regulatory aspects of vaccine development have established a coordinated review system.

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