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Regulatory Journey of Vaccine Development in the Philippines

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

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).

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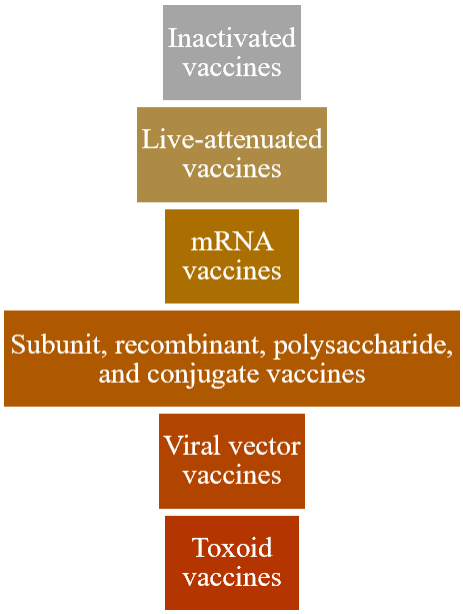
Keywords: FDA (Philippines food and drug administration); vaccine; formulation; GMP; GDP; GCP.

1. INTRODUCTION

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



1.1 Inactivated Vaccines

- An inactivated vaccine is made up of virus particles, bacteria, or other pathogens that have been grown in culture and subsequently destroyed to eliminate their disease-causing potential. Vaccinations using live germs, on the other hand, employ living germs [1].

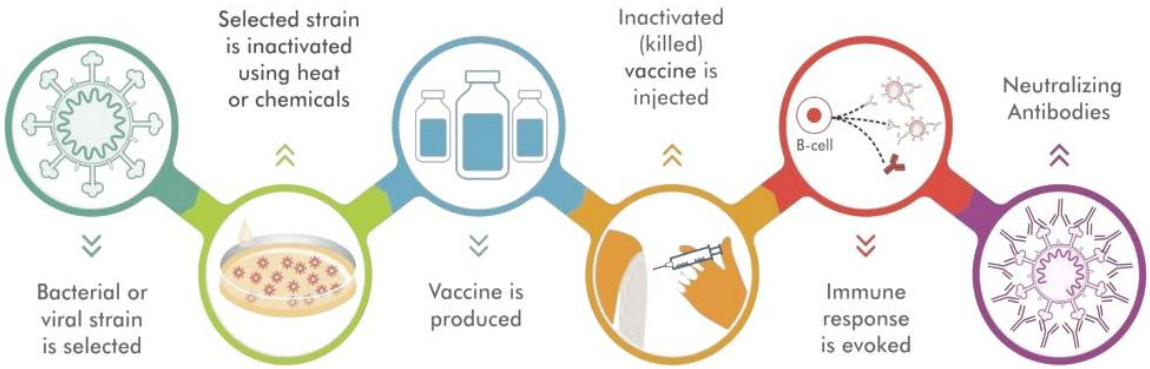


Fig. 1. The emergence of inactivated vaccines [2]

1.2 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 [3].

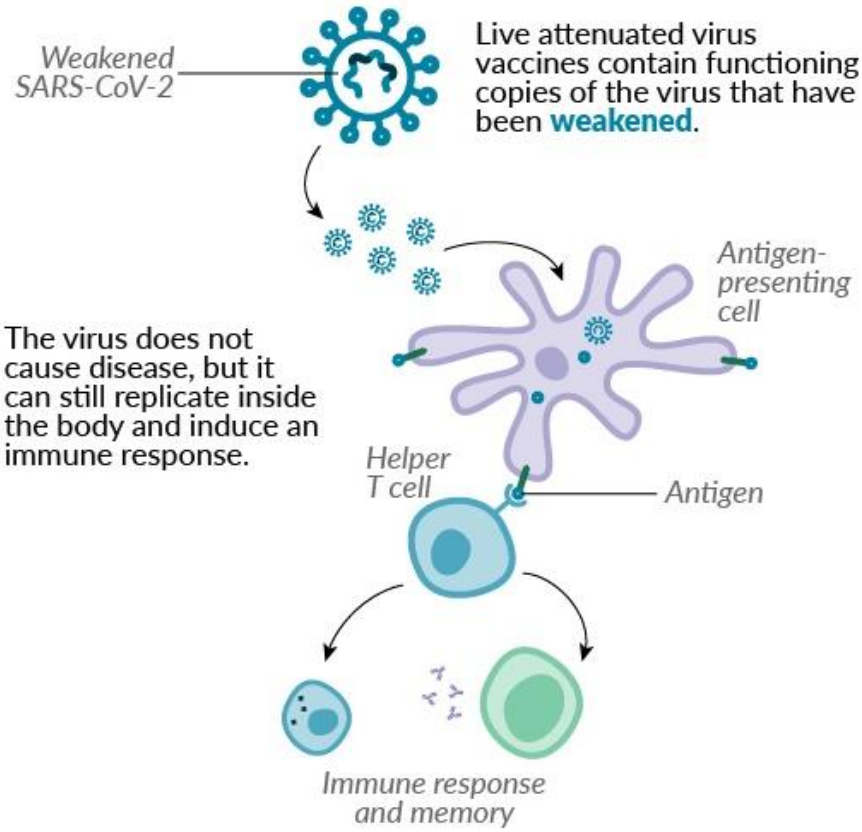


Fig. 2. Live Attenuated Virus Vaccine [4]

1.3 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) [5].

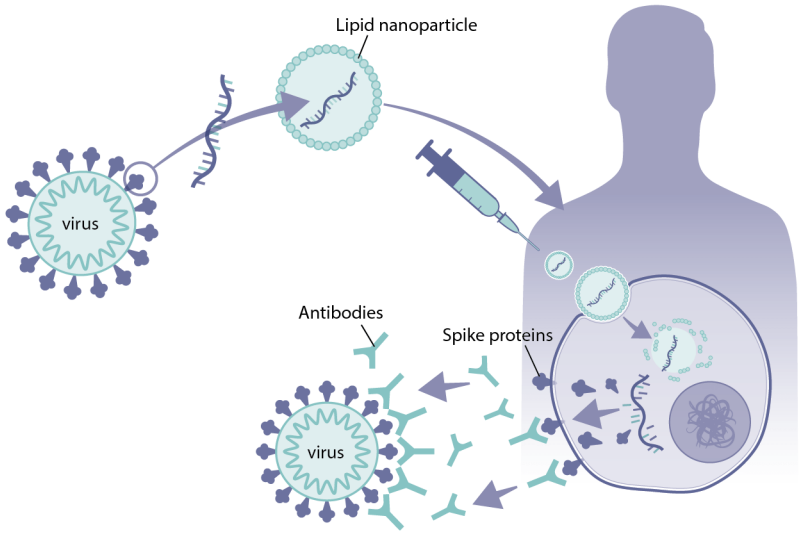


Fig. 3. mRNA vaccine development for COVID-19 [6]

1.4 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).

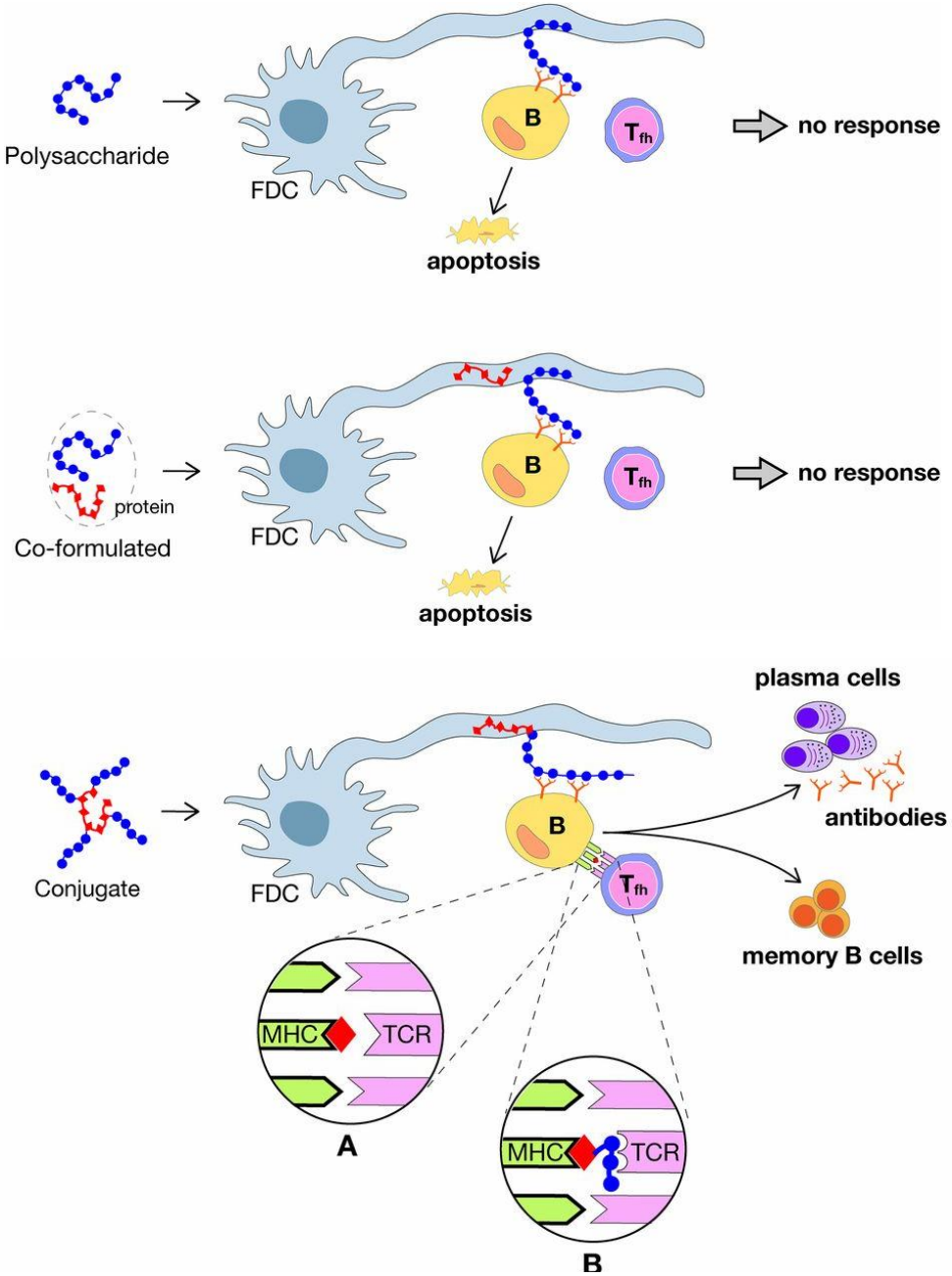


Fig. 4. The Emergence of Subunit, recombinant, polysaccharide, and conjugate vaccine [7]

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

1.5 Toxoid Vaccines

A toxoid is an inactivated toxin whose toxicity has been suppressed by chemical or heat treatment while maintaining other properties, such as immunogenicity [8].

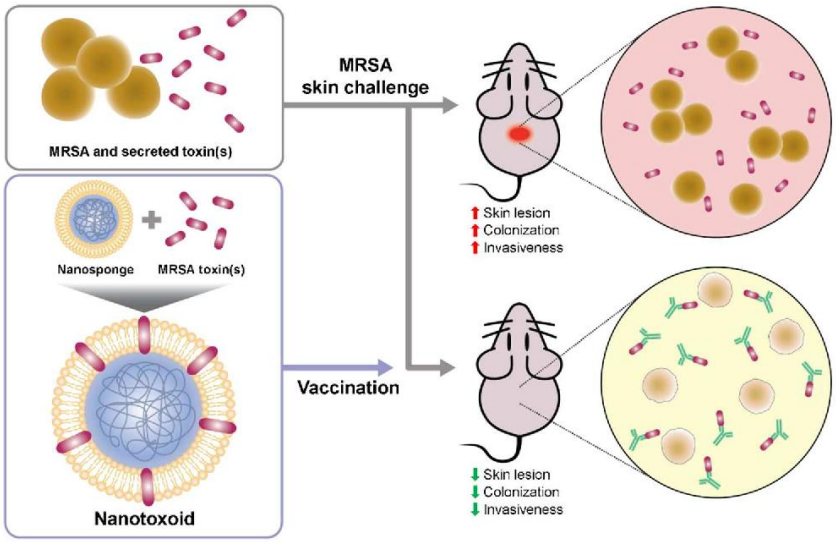


Fig. 5. Toxoid Vaccine against Bacterial Infection [9]

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].

1.6 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 [11].

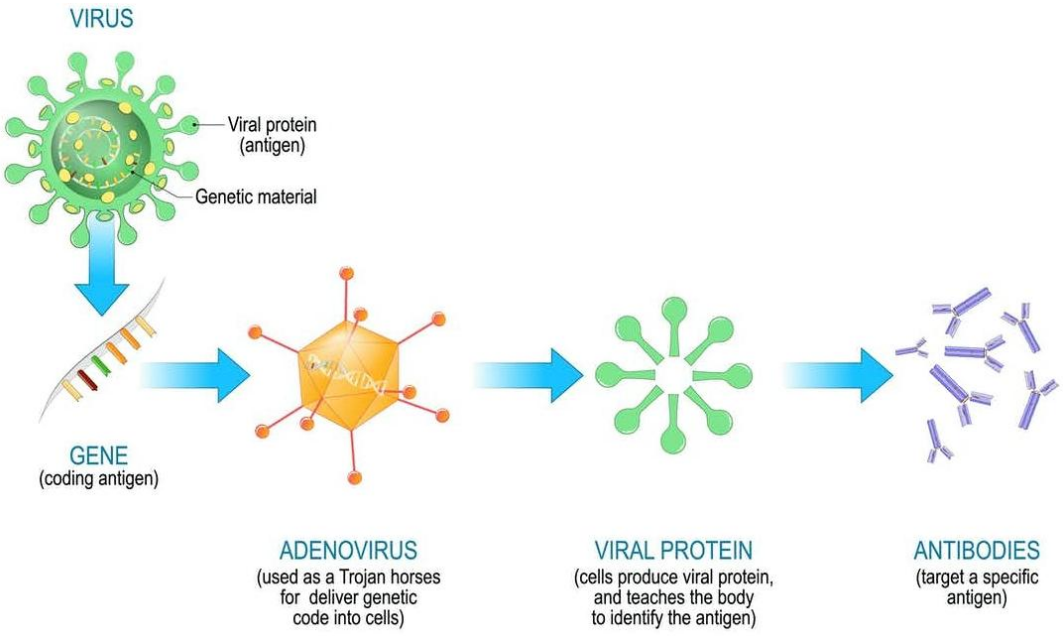
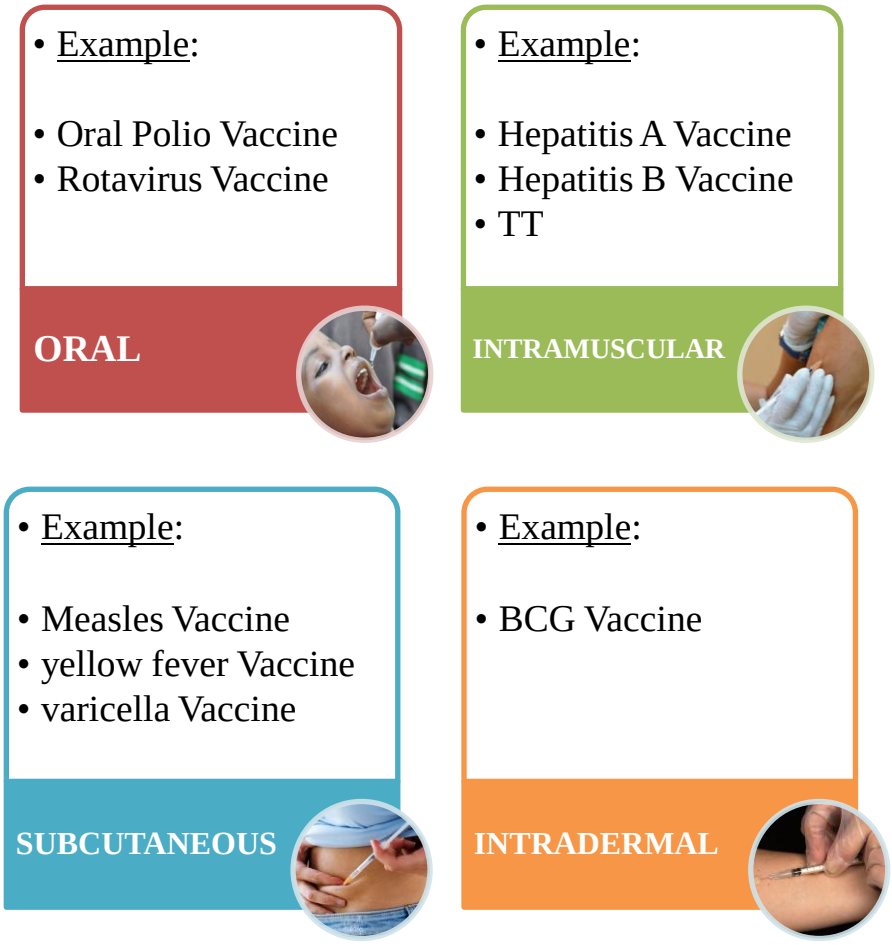


Fig. 6. MOA of viral vector vaccines [12]

2. DISCUSSION

2.1 Types of Routes of Administration of Vaccines



2.2 How Do Vaccines Work

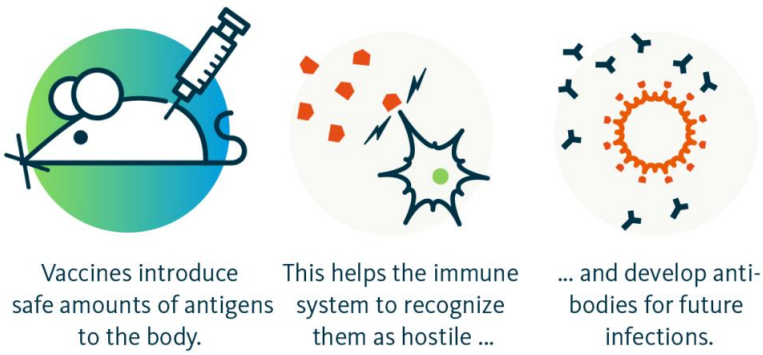


Fig. 7. Process of development of immunity against viruses [15]

Step 1: A disease that has been weakened or killed is injected into the body [13].
Step 2: Antibodies are produced by the body to fight infections [14].
Step 3: If the body is ever attacked by disease germs, the antibodies will return to eliminate them [16].

2.3 Formulation & Process Development

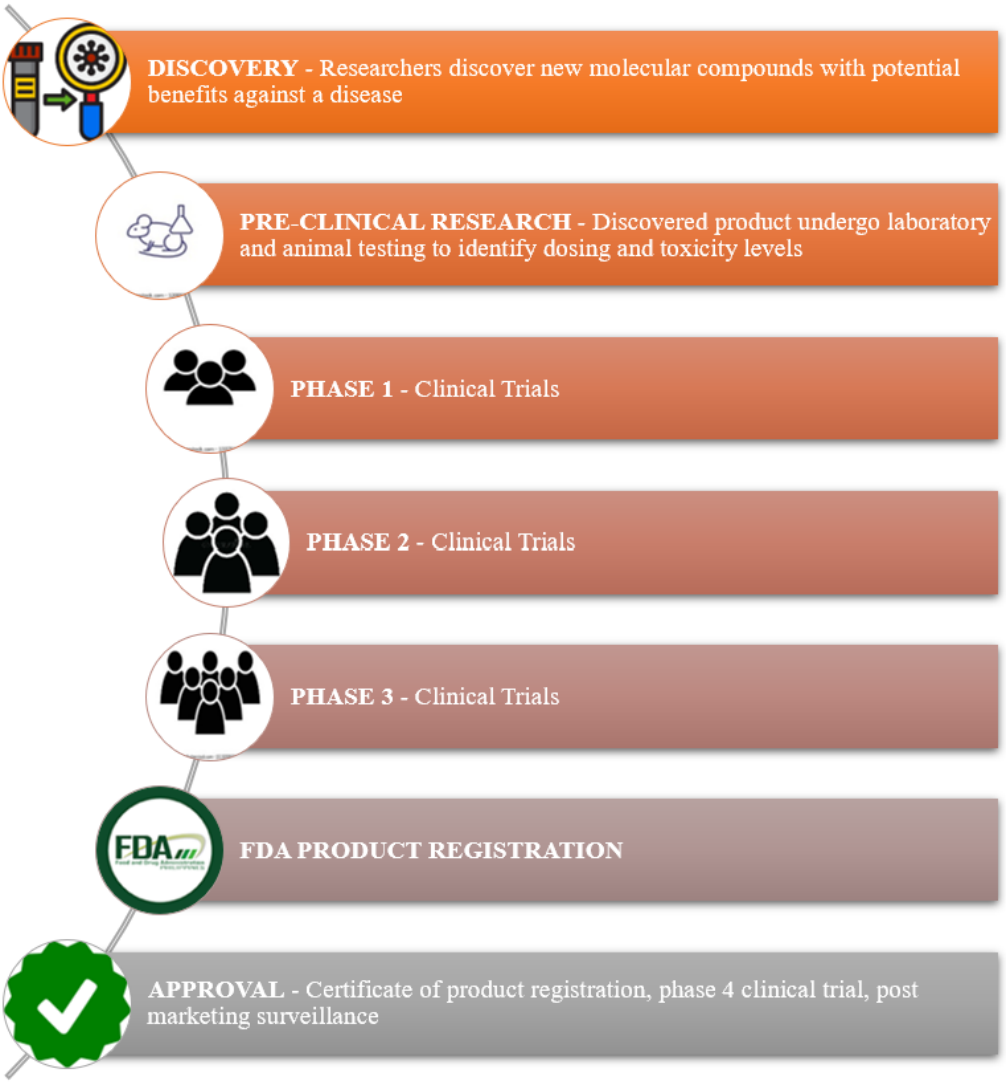


Fig. 8. Formulation and process development stages of vaccine in philippines [17-19]

2.4 Good Manufacturing Practice (GMP)

GMP Inspection Process:

A. Inspection Team

A team of inspectors must include at least two members, with one designated as the lead. When appropriate, a subject matter expert (SME) from a roster of approved Specialists chosen based on qualification and competency may be summoned.

B. Frequency

The frequency of inspection is determined using a risk-based methodology based on the inherent risk associated with the product and manufacturing process, as well as the manufacturer's compliance history.

Table 1. Good manufacturing practice for vaccine development in philippines [20]

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		

C. Manner of Inspection

Inspection can either be:

I. Announced Inspection-
II. Unannounced 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.

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.

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.

G. Compliance Period

Following the examination, the manufacturer receives a post-inspection letter summarising the problems detected. The establishment receives two submissions of the CAPA plan for all inadequacies.

2.5 Good Laboratory Practice & Good Clinical Practice

2.5.1 GLP

Good Laboratory Practice is defined as "an organisational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, documented, archived, and reported" by the OECD Principles [21,22].

Table 2. Good laboratory practice requirement for vaccines in the philippines

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 3. Good clinical practice requirement for vaccines in philippines [22 and 23]

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

2.5.2 GCP

GCP is an international ethical and scientific quality standard for planning, executing, documenting, and reporting human subject experiments.

2.6 Requirements for Clinical Trials

Regulations Governing the Conduct of Clinical Trials for Investigational Drugs:

Table 4. Clinical trial requirement for vaccines in philippines [23]

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	

2.6.1 Clinical trial approval process flow chart

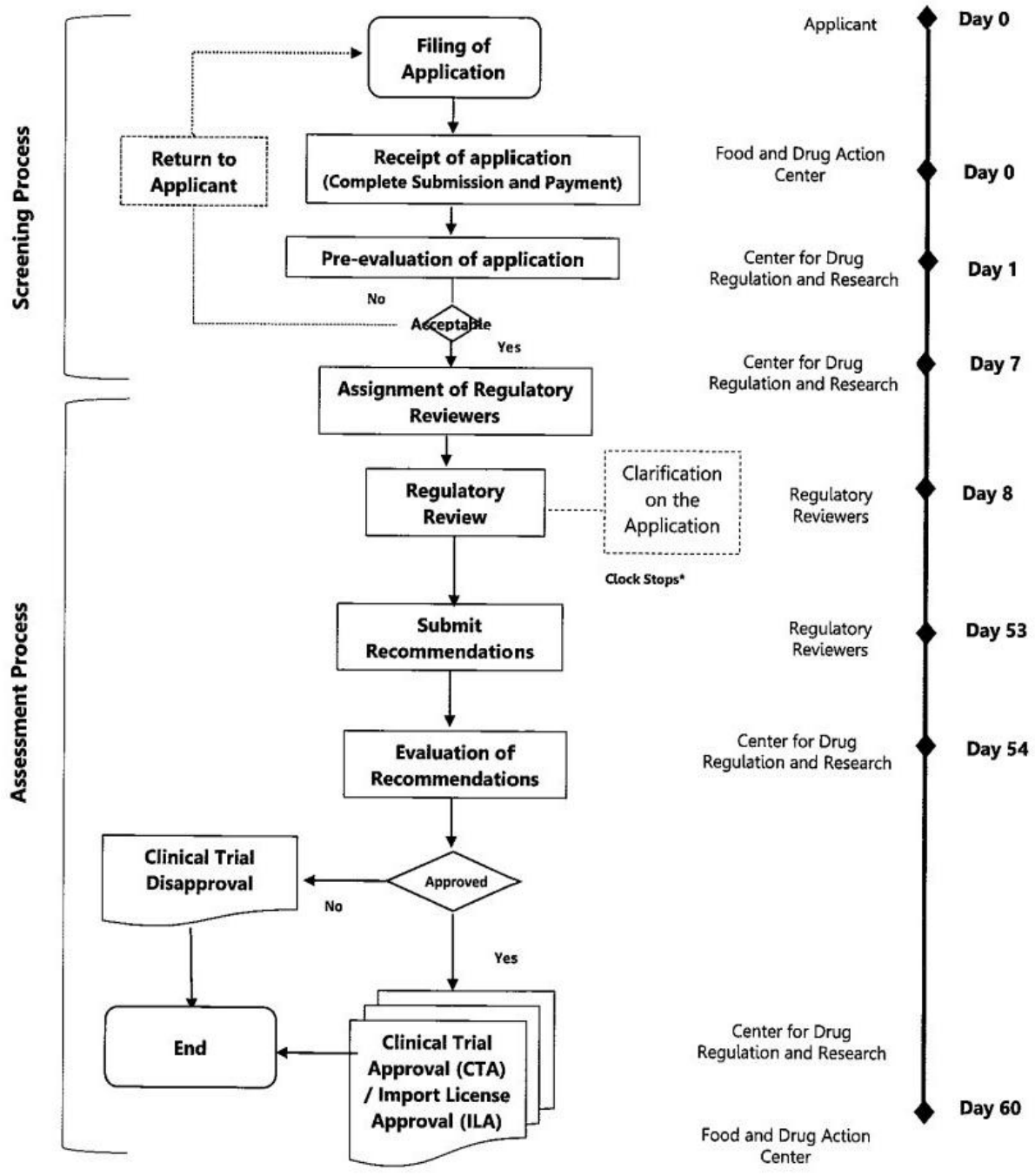


Fig. 9. Clinical trial approval process in philippines [23]

2.7 Stability Studies: Development & Ongoing

ICH Guideline - Q5C is adopted by FDA Philippines.

Table 5. Requirements for stability studies on vaccines in philippines [24]

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]

2.8 Product Dossier Requirements

2.8.1 Asian Common Technical Document (ACTD)

Part I: Table of Content

Part I begins with the ACTD's overarching Table of Contents, which offers a basic summary of the material available.

Part II. Quality Document

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

Part III. Nonclinical Document

Part III should begin with a nonclinical overview and end with a nonclinical discussion. Written summaries are nonclinical tabulated summaries.

Part IV. Clinical Document

Part IV should provide both a clinical overview and a clinical summary.

3. 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.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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