



# **National Agency for Food & Drug Administration & Control (NAFDAC)**

## **Registration & Regulatory Affairs (R & R) Directorate**

### **GUIDANCE DOCUMENT FOR SUBMISSION OF APPLICATION IN THE COMMON TECHNICAL DOCUMENT FORMAT - VACCINES FOR HUMAN USE**

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## **Acknowledgments**

This guideline is technically and structurally inspired by Health Canada's Guidance document on Harmonized Requirements for the Licensing of Vaccines and Guidelines for the Preparation of an Application and the World Health Organization (WHO) working document on Vaccine prequalification dossier.

## **1. Introduction**

Vaccines are products of biological origin that exhibit some inherent variability. They are characterized by complex manufacturing processes and are administered to large numbers of healthy children, adolescents and adults.

The responsibility for the quality, safety and efficacy of vaccines lies first and foremost with the manufacturer. The quality of a vaccine cannot be assessed solely by testing the final product alone, NAFDAC has established procedures to ensure that products and manufacturers meet the established regulatory criteria.

### **1.1. Objectives**

The objective of this document is to provide guidance for the preparation of regulatory submission for the Registration of Vaccines for Human Use in Nigeria in line with the widely accepted format and common requirements achieved through the processes of the International Council for Harmonization (ICH) of regulatory requirement for the registration of medicinal products for human use.

In particular, the document seeks to align the Agency's requirement for regulatory submission for the registration of medicines for human use with harmonization drive in the Economic Community of West African States anchored by the West African Health Organization (WAHO).

### **1.2. Scope and Application**

This guidelines document has been developed in pursuance to the NAFDAC act Cap. N1, LFN 2014 and made to provide guidance to applicants on the organization of information to be provided to the agency in seeking marketing authorization for Vaccines for human use. This document applies to all vaccines to be authorized for human use, regardless of where they are manufactured. Applicants are encouraged to read these guidelines document along with the Quality Guidelines for the Registration of Pharmaceutical Products for Human Use in Nigeria and other relevant rules and regulations before preparing their submission and completing application.

## **Module 1 Administrative Information and Prescribing Information**

### 1. Cover letter:

A cover letter should accompany any data being submitted to NAFDAC. The cover letter should clearly state what is being submitted, including reference to the request letter (if applicable) and a brief description of the package.

The cover letter should not contain any scientific information.

Any cross-referenced regulatory document should be clearly stated in the cover letter, and the following information should be included:

- Application type, specify whether new, renewal or variation
- Date of regulatory authorization if applicable.
- Brand name, dosage, presentation, dosage form;
- Manufacturer's name
- Applicant's name
- Number of samples submitted

#### 1.1. Table of contents of the application including Module 1 (Module 1-5)

The Table of Contents (ToC) for the entire regulatory dossier should be placed in this section.

It should list all documents included in Modules 1-5. A module-specific ToC is included with each Module.

#### 1.2. Application information

##### 1.2.1. Application Letter

##### 1.2.2. 1.2.2 Registration Form

##### 1.2.3. 1.2.3 Certificate of Incorporation

##### 1.2.4. 1.2.4 Power of Attorney

##### 1.2.5. 1.2.5 Notarized Declaration of the applicant.

(The applicant should declare that the information submitted is true and correct. Information on the name, position and signature of the applicant, product particulars should be provided in the notarized declaration and should be dated, signed and stamped by a notary public)

##### 1.2.6. Power of Attorney /Contract Manufacturing Agreement

##### 1.2.7. Certificate of Pharmaceutical Product

##### 1.2.8. Certificate of Good Manufacturing Practice

##### 1.2.9. Manufacturing Authorization

##### 1.2.10. Evidence of Trademark Registration

##### 1.2.11. Superintendent Pharmacist's Annual License to Practice

- 1.2.12. Certificate of Registration and Retention of Premises
- 1.2.13. Evidence of Previous Marketing Authorization (If Applicable)
- 1.2.14. Invitation Letter for GMP Inspection
- 1.2.15. Copy of marketing authorizations for all formulations and presentations in the Country of Manufacture and/ or the EMA scientific opinion for article 58products
- 1.2.14 Policy for assignment of date of manufacture of each component as well as the final product and diluents.
- 1.2.15 If the vaccine contains or consists of genetically modified organisms (GMOs), supply a copy of the Environmental Risk Assessment (GMO means an organism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination. Environmental risk assessment means the evaluation of the risk to human health and the environment (which includes plants and animals) connected with the release of GMOs or products containing GMOs.)

### 1.3. **Product Information**

#### 1.3.1 Summary of Product Characteristics (SmPC)

A copy of the Summary of Product Characteristics (SmPC) is to be placed in this section.

When revisions are requested during the course of an evaluation, an annotated version of the revised SmPC is required. The annotations should identify all changes made, either in relation to the last approved SmPC or in response to a request made by the regulatory authority.

#### 1.3.2 Labeling (outer & inner labels)

All container labels, including the inner and outer labels, should be provided in this section. This should include the labels for all strengths, dosage forms and reconstitution diluents.

When additional revisions are requested during the course of the review, an annotated version of the revised label maybe requested, and should be placed in this section.

#### 1.3.3 Package Insert (also known as patient information PIL)

A copy of the Patient Information Leaflet (PIL) is to be placed in this section.

#### 1.3.4 Vaccine temperature stability profile

Additional to stability information in 3.2.P.8, please provide any additional stability data required to support the assignment of VVM type or to support any on-label claim for elevated temperature storage.

#### 1.3.5 Description of immunization /administration devices to be delivered with the vaccine.

- 1.3.6 Post marketing Safety documentation  
Safety data should be submitted both in the case of the initial application for MAH evaluation and for reassessment purposes.
- 1.3.7 Outline of the post-marketing pharmacovigilance plan for the product or Risk Management Plan.
- 1.3.8 Initial evaluation of vaccines that have been in the market for more than five years or reassessment of already prequalified vaccines (The latest PSUR may be provided)
- 1.3.9 Outline of the applicant's procedures for the collection, onward notification and assessment of adverse events.
- 1.3.10 Listing of all reported AEFIs for the vaccine in question in the last five years or since the last reassessment. As far as is possible from the reports received, applicants should list the type of reaction, lot number, date and place of immunization, patients' initials and age and, for immunization series, the dose number. A judgment of seriousness and whether or not the event was expected (in the light of the prescribing to the vaccine made by a clinician and, where relevant, by the applicant company or its independent clinical expert).

1.4. Regional Summaries  
Quality Information Summary (QIS)

1.5. Electronic Review Documents  
Electronic versions of applications are encouraged in searchable Portable Document Format (PDF). This electronic document should be saved to a CD-ROM. All electronic media submitted to support the vaccine regulatory document should be placed in this section

1.6. Samples  
A sample of the product in the same packaging intended for commercial purposes should be submitted along with the application. Please note that mock-up packaging may be used when the final product packaging is not available.

**2. Module 2 Common Technical Document Summaries**

The purpose of this module is to summarize the quality (chemical, pharmaceutical, and biological); nonclinical and clinical information presented in modules 3, 4, and 5 in the licensing application. The experts who draft these summaries should take an objective approach to the decisive points related to the quality of the vaccine; clinical and nonclinical studies performed;

report all pertinent data for the evaluation; and, refer to the corresponding tables included in modules 3, 4, and 5.

Additional information for the preparation of this section can be found in the latest versions of the ICH M4Q, M4S and M4E guidelines.

The information in module 2 should be presented in the following order:

2.1. Common Technical Document Table of Contents (Modules2-5)

The table of contents should be provided

2.2. CTD Introduction

A summary of the type of vaccine, composition, immunological mechanism, and indications proposed for the vaccine.

2.3. Quality Overall Summary

A general summary of the quality of the vaccine should be presented, related to the chemical, pharmaceutical, and biological aspects. This summary should refer exclusively to the information, data, and justifications included in module 3 or in other modules of the submission. For example, if the submission describes more than one drug substance, manufacturer, dosage form, formulation, type of packaging, and/or strength, the applicant should summarize this information in the Quality Overall Summary (QOS) using a similar format as in the Module 3.2 Body of Data.

The format should be as follows:

### **Introduction**

The introduction should include proprietary name, non-proprietary name or common name of the drug substance, company name, dosage form(s), strength(s), route of administration, and proposed indication(s). It is important to note that the Drug Substance refers to the vaccine component or antigen, and the Drug Product refers to the final product.

#### 2.3.S Drug Substance (Name, Manufacturer)

2.3.S.1 General Information (name, manufacturer)

2.3.S.2 Manufacture (name, manufacturer)

2.3.S.3 Characterization (name, manufacturer)

2.3.S.4 Control of Drug Substance (name, manufacturer)

2.3.S.5 Reference Standards or Materials (name, manufacturer)

2.3.S.6 Container Closure System (name, manufacturer)

2.3.S.7 Stability (name, manufacturer)

2.3.P Drug Product (Name, Dosage Form)

2.3.P.1 Description and Composition of the Drug Product (name, dosage form)

2.3.P.2 Pharmaceutical Development (name, dosage form)

2.3.P.3 Manufacture (name, dosage form)

2.3.P.4 Control of Excipients (name, dosage form)

2.3.P.5 Control of Drug Product (name, dosage form)

2.3.P.6 Reference Standards or Materials (name, dosage form)

2.3.P.7 Container Closure System (name, dosage form)

2.3.P.8 Stability (name, dosage form)

2.3.A Appendices

2.3.A.1 Facilities and Equipment (name, manufacturer)

2.3.A.2 Adventitious Agents Safety Evaluation (name, dosage form, manufacturer)

2.3.A.3 Excipients

2.3. R. Regional Information

2.4. Nonclinical Overview

An integrated and critical assessment of the nonclinical evaluation of the vaccine should be provided.

The Nonclinical Overview should be presented in the following sequence:

2.4.1. Overview of the nonclinical testing strategy

2.4.2. Pharmacology

2.4.3. Pharmacokinetics

2.4.4. Toxicology

2.4.5. Integrated overview and conclusions

2.4.6. List of literature references

2.5. Clinical Overview

A succinct discussion and interpretation of the clinical data should be presented. The



Clinical Overview should present the strengths and limitations of the clinical development program and study results, and analyse the benefits and risks of the vaccine in its intended conditions for use.

The format for the Clinical Overview should be as follows:

2.5.1 Product Development Rationale

A discussion of the rationale for the development of the vaccine should be presented.

2.5.2 Overview of Biopharmaceutics

Biopharmaceutical studies are not generally performed for vaccine development. Summary of bioanalytical methods used to assess the immunogenicity of the vaccine in clinical trials should be provided in section 2.5.4.

2.5.3 Overview of Clinical Pharmacology

Pharmacokinetic studies are generally not required for vaccines. However, such studies may be applicable in certain situations, such as the evaluation of vaccine formulations containing new adjuvants. Applicants should seek advice from the regulatory authority.

For vaccines, pharmacodynamics studies generally consist of the immunogenicity studies used to characterize the immune response to the vaccine. A summary of the immunogenicity results should be included in section 2.5.4.

2.5.4 Overview of Efficacy

A critical analysis of the clinical data pertinent to the efficacy of the vaccine in the intended population should be presented. The analyses should consider all relevant data, whether positive or negative, and should explain why and how the data support the proposed indication and prescribing information.

2.5.5 Overview of Safety

A concise critical analysis of the safety data should be presented noting how results support and justify the proposed prescribing information.

2.5.6 Benefits and Risks Conclusions

This section should provide a succinct overall appraisal of the benefit risk assessment by integrating all of the conclusions reached in the previous sections about the safety and efficacy of the vaccine.

## 2.5.7 Literature References

### 2.6. Nonclinical Written and Tabulated Summaries

The format for the Nonclinical Written and Tabulated Summaries should be as follows:

#### 2.6.1 Introduction

An introduction to the vaccine and its proposed clinical use should be presented.

#### 2.6.2 Pharmacology Written Summary

The format should be as follows:

##### 2.6.2.1 Brief Summary

##### 2.6.2.2 Primary Pharmacodynamics

##### 2.6.2.3 Secondary Pharmacodynamics

##### 2.6.2.4 Safety Pharmacology

##### 2.6.2.5 Pharmacodynamic Drug Interactions

##### 2.6.2.6 Discussion and Conclusions

##### 2.6.2.7 Tables and Figures

#### 2.6.3 Pharmacology Tabulated Summary

If applicable, summary tables for the pharmacology studies should be presented.

#### 2.6.4 Pharmacokinetics Written Summary

This type of studies is generally not performed for vaccines. However, bio distribution studies may be applicable to the evaluation of vaccine formulations containing new adjuvants or live recombinant viral/bacterial vectors. The feasibility of such studies should be evaluated on a case-by-case basis. If applicable, the format for the written summary of pharmacokinetic studies should be as follows:

##### 2.6.4.1 Brief Summary

##### 2.6.4.2 Methods of Analysis

##### 2.6.4.3 Absorption

##### 2.6.4.4 Distribution

##### 2.6.4.5 Metabolism

##### 2.6.4.6 Excretion

##### 2.6.4.7 Pharmacokinetic Drug Interactions(nonclinical)

##### 2.6.4.8 Other Pharmacokinetic Studies

##### 2.6.4.9 Discussion and Conclusions

##### 2.6.4.10 Tables and Figures

#### 2.6.5 Pharmacokinetics Tabulated Summary

Pharmacokinetic studies are not generally performed for vaccines. However, for live attenuated vaccines (viral or bacterial including vaccine vectors) there are potential causes of clinically significant infections in the recipient or in contacts. Summaries of studies providing information on shedding, reversion characteristics and transmission to contacts should be provided here.

If applicable, summary tables for the pharmacokinetics studies should be presented.

#### 2.6.6 Toxicology Written Summary

A written summary of toxicology studies should be presented. Refer to guidelines provided for Module 4 below. The format for the Toxicology Written Summary should be as follows:

##### 2.6.6.1 Brief Summary

##### 2.6.6.2 Single-Dose Toxicity

##### 2.6.6.3 Repeat-Dose Toxicity

##### 2.6.6.4 Genotoxicity

##### 2.6.6.5 Carcinogenicity

##### 2.6.6.6 Reproductive and Developmental Toxicity

##### 2.6.6.7 Local Tolerance

##### 2.6.6.8 Other Toxicity Studies

##### 2.6.6.9 Discussion and Conclusions

##### 2.6.6.10 Tables and Figures

#### 2.6.7 Toxicology Tabulated Summary

Summary tables for the toxicology studies should be presented.

#### 2.7. Clinical Summary

A detailed, factual summary of all clinical data should be presented. This includes information provided in clinical study reports, information obtained from any meta-analyses or other cross-study analyses, for which full reports have been included in Module 5; and post-marketing data for vaccines that have been marketed in other regions.

The format for the Clinical Summary should be as follows:

#### 2.7.1 Summary of Biopharmaceutical Studies and Associated Analytical Methods

Biopharmaceutical studies are not generally performed for vaccine development. A summary of the bioanalytical assays used to assess vaccine immunogenicity in clinical trials should be provided in section 2.7.3.

#### 2.7.2 Summary of Clinical Pharmacology Studies

Pharmacokinetic studies are generally not required for vaccines. However, such studies may be applicable in certain situations, such as the evaluation of vaccine formulations containing new adjuvants.

If applicable, the format of the summary should be as follows:

##### 2.7.2.1 Background and Overview

##### 2.7.2.2 Summary of Results of Individual Studies

##### 2.7.2.3 Comparison and Analyses of Results across Studies

##### 2.7.2.4 Special Studies

##### 2.7.2.5 Appendix

#### 2.7.3 Summary of Clinical Efficacy

For vaccines this section should also include a summary of immune response data that supports the selection of dose, dosage schedule, and formulation of the final product.

The format of the Summary of Clinical Efficacy should be as follows:

##### 2.7.3.1 Background and Overview of Clinical Efficacy

This section should present a description of the program of controlled studies and other pertinent studies in the application that evaluated efficacy specific to the indication(s) sought.

For vaccines, immunogenicity studies are usually conducted to characterize the immune response to the vaccine and to support vaccine efficacy. An overview of the scientific rationale, the criteria used for the selection of analytical methods for immunogenicity, and the cut-off / threshold values applied should be provided. In addition, information on the performance characteristics of assays including the validation (e.g. linearity range, sensitivity, specificity) and quality control (e.g. accuracy and precision) should be included.

This section should not include detailed information about individual studies.

#### 2.7.3.2 Summary of Results of Individual Studies

A tabular listing of all studies providing (or designed to provide) information relevant to vaccine efficacy should generally be provided, together with narrative descriptions for important studies. The narrative descriptions should be brief, e.g. similar to an abstract for a journal article, and should describe critical design features and critical results.

#### 2.7.3.3 Comparison and Analyses of Results across Studies

Using text, figures, and tables as appropriate, a summary of all available data that characterize the efficacy of the vaccine should be presented. This summary should include analyses of all data, irrespective of their support for the overall conclusions and should, therefore, discuss the extent to which the results of the relevant studies do or do not reinforce each other. Any major inconsistencies in the data regarding efficacy should be addressed and any areas needing further exploration should be identified. The format of this section is:

2.7.3.3.1 Study Populations

2.7.3.3.2 2.7.3.2.2 Comparison of Efficacy Results of all Studies

2.7.3.3.3 2.7.3.3.3 Comparison of Results in Sub-populations

#### 2.7.3.4 Analysis of Clinical Information Relevant to Dosing Recommendations

#### 2.7.3.5 Persistence of Efficacy and/or Tolerance Effects

#### 2.7.3.6 Appendix

### 2.7.4 Summary of Clinical Safety

A summary of data relevant to safety in the intended vaccine recipient population, integrating the results of individual clinical study reports as well as other relevant reports should be presented. The safety profile of the vaccine, described on the basis of analysis of all clinical safety data, should be outlined in a detailed, clear, and objective manner, with the use of tables and

figures.

The format of the Summary of Clinical Safety should be as follows:

2.7.4.1 Exposure to the Drug

22.7.4.1. Demographic and Other Characteristics of Study Population

2.7.4.2 Adverse Events

2.7.4.2.1 Analysis of Adverse Events

2.7.4.2.2 Narratives

2.7.4.3 Clinical Laboratory Evaluations

2.7.4.4 Vital Signs, Physical Findings, and Other Observations Related to Safety

2.7.4.5 Safety in Special Groups and Situations

2.7.4.6 Post-Marketing Data

2.7.4.7 Appendix

2.7.5 Literature References

A list of references cited in the Clinical Summary should be provided.

2.7.6 Synopses of Individual Studies

This section should include the table entitled Listing of Clinical Studies, described in guidance for Module 5, followed by all individual study synopses organized in the same sequence as the study reports in Module 5.

### 3. **Module 3 Quality**

The Quality information submitted under Module 3 should be up-to-date, comprehensive, appropriately detailed, relevant, and to the extent sufficient to support the approval of a vaccine submission. A properly completed Module 3 will facilitate preparation of the Quality Overall Summary (QOS) and will expedite the submission review process.

The Drug Substance refers to the vaccine component or antigen. For a vaccine containing more than one drug substance, the entire Module 3.2.S Drug Substance for one drug substance should be followed by the entire Module 3.2.S Drug Substance for the next drug substance and then followed by the entire 3.2.P Drug Product. The name of the Drug Substance should be included in the heading of all applicable sections and subsections to clearly distinguish the information for each Drug Substance.

For a vaccine with more than one dosage form or for a vaccine supplied in multiple components, e.g. lyophilized powder with a reconstitution diluent, the entire Module 3.2. P Drug Product for one component or dosage form should be followed by the entire Module 3.2.P Drug Product for the next component or dosage form. The name of the component or dosage form should be included in the headings of the corresponding Module 3 sections.

Additional information for the preparation of this section can be found in ICH M4Q (R1), as well as WHO recommendations for the production and control of specific vaccines and other relevant international regulatory guidelines.

### 3.1 Table of Contents of Module 3.

The table of contents should be provided

### 3.2 Body of Data

#### 3.2.S Drug Substance (Name, Manufacturer)

The information requested under this point should be supplied individually for each antigen in the vaccine.

#### 3.2.S.1 **General Information (name, manufacturer)**

##### 3.2.S.1.1 Nomenclature (name, manufacturer)

Trade and/or non-proprietary name of the drug substance, based on the WHO or Pharmacopoeia requirements, as appropriate.

##### 3.2.S.1.2 Structure (name, manufacturer)

Structural formula, molecular formula, and relative molecular mass (if applicable). The schematic primary sequence such as amino acid sequence indicating glycosylation sites or repeating units of polysaccharide indicating modification sites or other post- translational modifications and relative molecular mass should be provided, if applicable.

##### 3.2.S.1.3 General Properties (name, manufacturer)

A list should be provided of physicochemical and other relevant properties of the drug substance, including immunological characteristics and other biological activity, if applicable.

#### 3.2.S.2 Manufacture (name, manufacturer)

##### 3.2.S.2.1 Manufacturer(s) (name, manufacturer)

Give the name, address, and responsibilities of the manufacturer(s).

3.2.S.2.2 Description of Manufacturing Process and Process Controls (name, manufacturer)

A description of the manufacturing process. Submit a description of the manufacturing process that includes all of the stages. Atypical production process for a vaccine starts with a vial(s) from the respective seed and/or cell bank, including cell cultures, harvest(s), purification, modification reactions (when applicable), filling, storage, and transfer/shipping conditions. Where applicable, include the number of passes.

- Flow chart of manufacturing process showing all of the manufacturing steps, including intermediate processes.
- Batch(es) and Scale Definition: An explanation of the batch numbering system, including information regarding any pooling of harvests or intermediates and batch size or scale should be provided. Since pooling may occur at more than one step, it may be more appropriate to describe the batch size and scale under the respective step(s), both within the flow diagram(s) and in the detailed description.
- Cell culture and harvest: A description of the cell culture, seed culture and harvest from the original inoculum up to the last harvesting operation.
- Description of inactivation or detoxification process. Methods and agents used, parameters controlled, and production stage in which it is performed, when applicable.
- Description of purification process. Method, reagents, and materials used, operating parameters controlled, and specifications. Conditions for the use and reuse of membranes and chromatography columns and the respective validation studies should be provided.
- Description of the conjugation process. Indicate when applicable and/or when a modification of drug substance is performed. Also include information on the origin and quality control of the starting material used to obtain the substance used as a protein carrier.
- Stabilization of the drug substance. Description of the steps performed to stabilize the drug substance, for example, the addition of stabilizers or



other procedures, when applicable.

- Reprocessing. Description of the procedures established for reprocessing the drug substance or any intermediate product; criteria and justification.
- Filling procedure for the active ingredient, in-process controls. Description of the procedure for packaging the drug substance, process controls, acceptance criteria, type of container closure system, type of seal on the container used to store the drug substance, storage and transfer conditions, when applicable.
- Storage and shipping conditions. When applicable, describe the equipment used, areas and buildings (if pertinent) and the shipping and storage conditions for the drug substance.

#### 3.2.S.2.3 Control of Materials (name, manufacturer)

General description of the starting materials. All materials used in the manufacturing of the drug substance are expected to be indicated in this section, along with their control measures. For biologically sourced starting materials, information regarding the source, manufacture and characterization should be provided. For vaccines the following information is also expected to be provided in this section as appropriate:

- Summaries of viral safety information (details to be provided in 3.2.A.2).
- Strain: Information on the origin, number of passes, identification, analysis certificates, processes of attenuation, development or construction and genetic stability, depending on the type of vaccine strain.
- Master/Working/Seed Banks Systems. Origin, identification, characterization, preparation method, analysis certificates, adventitious agents testing, stability, controls, and frequency of the tests, definition of the number of passes should be included. In the case of cell banks, demonstrate that the characteristics of the cells remain unaltered in the passes used in production and successively.
- Embryonated eggs. Information on their origin, identification, quality certificates should be provided.
- General description of the raw materials. Considering the raw materials used in the preparation process from which the drug substance is not directly derived, such as culture media, bovine fetal serum, etc. Submit information

on manufacturer(s), quality certificates, controls performed. In the case of raw materials of animal origin, describe the origin and criteria for selection, shipping, and conservation, and submit a certificate on reduction of the risk of transmission of agents related to animal spongiform encephalopathy.

#### 3.2.S.2.4 Controls of Critical Steps and Intermediates (name, manufacturer)

Identification of critical steps in-process and controls. Selection and justification of critical steps, starting from inoculation up to the production of the drug substance, defining the operational parameters to control during the critical stages, including quality specifications should be included.

Intermediates. Summary of the quality, control, and storage conditions of intermediates isolated during the process should be provided. Stability data supporting storage conditions of intermediates should be provided.

#### 3.2.S.2.5 Process Validation and/or Evaluation (name, manufacturer)

A summary of the process validation and evaluation studies should be provided. The actual validation reports may be requested during the review process. If requested, the reports should be filed in this section.

Information should be sufficient to demonstrate that the manufacturing process (including reprocessing steps) is suitable for its intended purpose and to substantiate the selection of critical process controls (operational parameters and in-process tests) and their limits for critical manufacturing steps (e.g. cell culture, harvesting, purification, and modification). The information provided should support the current manufacturing process proposed for commercial use, and include data to demonstrate consistency in yield and production, and degree of purity. If an adjuvant is added to the drug substance, validation data should be submitted to demonstrate consistency of manufacturing of the drug substance (e.g. dispersion, pre-determined particle size).

Furthermore, for an alum-containing vaccine, study data to demonstrate consistency of adsorption of the drug substance to the adjuvant should

be submitted.

The plan for conducting the study should be described and the results, analysis and conclusions from the executed study (ies) should be provided. The analytical procedures and corresponding validation should be cross-referenced or provided as part of justifying the selection of critical process controls and acceptance criteria.

#### 3.2.S.2.6 Manufacturing Process Development (name, manufacturer)

The developmental history of the manufacturing process should be provided. The description of change(s) made to the manufacture of drug substance batches used in support of the marketing application (e.g. nonclinical or clinical studies) should include, for example, changes to the process or to critical equipment. The reason for the change should be explained. In relation to the change, relevant information on drug substance batches manufactured during development, such as the batch number (and subsequent drug product batch numbers), manufacturing date, scale, and use (e.g. stability, nonclinical, reference material), should be provided.

The significance of the change should be assessed by evaluating its potential to impact the quality (e.g. biological activity, impurity profile) of the drug substance (and/or intermediate, if appropriate). For manufacturing changes that are considered significant, data from comparative analytical testing on relevant drug substance batches should be provided to determine the impact on the quality of the drug substance (see Q6B for additional guidance). A discussion of the data, a justification for selection of the tests and assessment of the results should be included.

Testing used to assess the impact of manufacturing changes on the drug substance(s) and the corresponding drug product(s) can also include nonclinical and clinical studies. A cross-reference to the location of these studies in other sections of Module 3 (e.g. Stability, Control of Drug Substance or Drug Product) and/or in other modules of the submission should be included.

A brief summary of major manufacturing changes made throughout development and conclusions from the assessment used to evaluate product consistency should also be provided.

### 3.2.S3 Characterization (name, manufacturer)

Present data to determine the structure and physicochemical, immunological, and biological characteristics of the drug substance.

#### 3.2.S.3.1 Elucidation of Structure and other Characteristics (name, manufacturer)

For the intended product and product-related substances, details should be provided, if applicable, on primary sequence, secondary and higher-order structure, post-translational forms (e.g. glycoforms), biological activity, purity, and immunochemical/immunogenicity properties. In addition, depending on the type of vaccine, this may include active or passive immunization studies and challenge studies as appropriate.

A summarized description of the intended product and product-related substances and a summary of general properties, characteristic features and characterization data, such as primary and higher order structure and biological activity, should also be provided.

#### 3.2.S.3.2 Impurities (name, manufacturer)

Information on impurities should be provided. All potential impurities, including process related impurities and degradation products for purified vaccines such as polysaccharide/protein or synthetic peptide vaccines, arising from manufacturing, storage or found in stability study batches, should be described regardless of whether they have been detected in any batches.

The actual impurity levels detected (including quantities found in clinical, toxicological, bioavailability, and proposed commercial batches) should be reported, for example, using a summary

table.

The information should also include a discussion of results which are close to or outside limits. A rationale should be provided for the choice of tests used, the proposed limits and their qualification. A rationale for excluding any impurity test(s) from routine release testing due to trace levels should also be provided, where applicable.

3.2.S.4 Control of Drug Substance (name, manufacturer)

3.2.S.4.1 Specification (name, manufacturer)

The specification(s) for the drug substance should be provided. For example, the specifications could be presented using a table with the specification reference number, specification approval date, test parameter(s), method type, method code, source, and acceptance limit(s) at release, at the end of shelf-life or for both.

3.2.S.4.2 Analytical Procedures (name, manufacturer)

Information on the analytical procedures used for testing the drug substance should be provided.

3.2.S.4.3 Validation of Analytical Procedures (name, manufacturer)

Analytical validation information, including experimental data for the analytical procedures used for testing the drug substance, should be provided.

3.2.S.4.4 Batch Analysis (name, manufacturer)

Description of batches and results of batch analyses should be provided. This description should include the batch number, production scale, date of manufacture, production site, manufacturing process and use.

3.2.S.4.5 Justification of Specification (name, manufacturer)

Justification for the drug substance specification(s) should be provided.

3.2.S.5 Reference Standards or Materials (name, manufacturer)

Detailed description of the reference standards or materials used and their quality control testing results. Certificates of analysis should be provided, if

applicable.

3.2.S.6 Container Closure System (name, manufacturer)

Full description of the packaging and container closure system in which the drug substance will be stored until used for preparing the finished product. The information should include identification of all the materials that constitute the packaging container closure system and their specifications.

The suitability of the container closure system should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the drug substance, including adsorption to container and leaching, and/or safety.

3.2.S.7 Stability (name, manufacturer)

3.2.S.7.1 Stability Summary and Conclusions (name, manufacturer)

Should include the study conditions, including all of the storage conditions (temperature, humidity, light) in which the drug substance is evaluated, analytical methods, specifications, summary of results, and conclusions.

3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment

(name, manufacturer)

It refers to the continuation of the stability study, including the number of lots to be included in the study each year and the tests to be performed.

3.2.S.7.3 Stability Data (name, manufacturer)

Should include available data from each batch evaluated during stability studies.

3.2.P Drug Product (Name, Dosage Form)

3.2.P.1 Description and Composition of the Drug Product (name, dosage form)

This should include a description of the drug product, its composition, listing each of the components, drug substance(s), adjuvant, preservatives, stabilizers, and excipients, stating the function of each of them. For lyophilized products, also include a brief description of the diluents and the container closure system employed for the diluents.

3.2.P.2 Pharmaceutical Development (name, dosage form)

Information on the studies performed to establish the dosage form, formulation, manufacturing process, and the container closure system used for the final product. If an adjuvant is added to the drug product, information and data from the adsorption and desorption study should be submitted, if applicable. The studies described in this section are different from the routine quality control tests performed in accordance with the product specifications. The following aspects should be included:

3.2.P.3 Components of the Drug Product (name, dosage form)

Compatibility of the drug substance with the rest of the components in the drug product should be discussed, including adjuvant, preservative, stabilizers, as applicable.

3.2.P.3.1 Drug Product (name, dosage form)

Development of the formulation considering the proposed route of administration. Physicochemical and biological properties of the product, indicating the relevant parameters for developing the drug product should be included. Any changes between the proposed commercial formulation and those formulations used in pivotal clinical trial batches and primary stability batches should be clearly described and the rationale for the changes provided.

3.2.P.3.2 Manufacturing Process Development (name, dosage form)

Description of the selection and optimization of the manufacturing process, particularly for critical aspects. Significant differences between the manufacturing process used to produce batches for pivotal clinical trials or primary stability studies and the proposed commercial manufacturing process should be discussed.

3.2.P.3.3 Container Closure System (name, dosage form)

Full description of the packaging and container closure system. The information should include identification of all the materials that constitute the container closure system and their specifications.

The suitability of the container closure system should be discussed with respect to, for example, choice of materials, protection from

moisture and light, compatibility of the materials of construction with the drug product, including adsorption to container and leaching, and/or safety.

3.2.P.3.4 Microbiological Attributes (name, dosage form)

Where appropriate, the microbiological attributes of the dosage form should be discussed, including, for example, the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. For sterile products, the integrity of the container closure system to prevent microbial contamination should be addressed.

3.2.P.3.5 Compatibility (name, dosage form)

The compatibility of the drug product with reconstitution diluents (e.g. precipitation, stability) should be addressed to provide appropriate and supportive information for the labelling. This information should cover the recommended in-use shelf life at the recommended storage temperature and at the likely extremes of concentration.

3.2.P.4 Manufacture (name, dosage form)

3.2.P.4.1 Manufacturer(s) (name, dosage form)

Name, address, and responsibilities of each manufacturer involved, including contract manufacturers for production and quality control.

3.2.P.4.2 Batch Formula (name, dosage form)

Provide the formula of the production lot, including a list of all components.

3.2.P.4.3 Description of Manufacturing Process and Process Controls (name, Dosage form)

- Flow chart of manufacturing process. Showing all of the steps in the process and indicating the points at which the material enters the process, identifying the critical steps and control points in the process, intermediate products, and final product.
- Batch and Scale Definition. An explanation of the batch numbering system and scale at each stage of manufacture (e.g. filling, lyophilisation, and packaging).



- Formulation process. Description of the formulation process, the in-process controls, acceptance criteria and the critical steps identified. Information regarding any pooling of bulks or intermediates should be provided.
- Filling process. Description of the filling process, the process controls, acceptance criteria, and the critical steps identified.
- Reprocessing. Description of the procedures established for reprocessing the drug product or any intermediate product; criteria and justification.
- Storage and shipping conditions. When applicable, identify the type and working capacity of the equipment used, areas and buildings (if pertinent), and describe the shipping and storage conditions for the drug product. Additional information should be provided in 3.2.A.1.

#### 3.2.P.4.4 Control of Critical Steps and Intermediates (name, dosage form)

Identification of critical steps in the process and controls. The selection and justification of critical steps in the drug product manufacturing process should be included. Tests and acceptance criteria developed to identify the critical steps in the manufacturing process and how they were controlled should be described.

Intermediates. Information on the quality and control of intermediates isolated during the process should be provided.

#### 3.2.P.4.5 Process Validation and/or Evaluation (name, dosage form)

A summary of the process validation and evaluation studies should be provided.

***NAFDAC may request for the validation reports may during the review process. If requested, the reports should be filed within this section.***

The information provided should support the current manufacturing process proposed for commercial use, including in-process test results and data from relevant manufacturing batches to demonstrate consistency in yield and production, and degree of purity. A summary of the validation study for the extent of reuse and integrity of membranes should be provided, including

data to demonstrate consistency in the quality and safety of the drug product.

The suitability of any proposed reprocessing procedures and the criteria for the reprocessing of any intermediate or the drug product should be discussed.

It is also necessary to provide information on the viral safety of the product, when applicable (e.g. products derived from cell lines of human or animal origin).

### 3.2.P5 Control of Excipients (name, dosage form)

#### 3.2.P.5.1 Specifications (name, dosage form)

Provide information on the specifications for all of the substances employed in the formulation of the drug product that are different from the drug substance.

#### 3.2.P.5.2 Analytical Procedures (name, dosage form)

Description or literature of reference of the methods used to control these substances.

#### 3.2.P.5.3 Validation of Analytical Procedures (name, dosage form)

Include the procedures used to control substances employed in formulating the final product.

#### 3.2.P.5.4 Justification of Specifications (name, dosage form)

Include information about all substances used in formulating the final product.

#### 3.2.P.5.5 Excipients of Human or Animal Origin (name, dosage form)

Provide information on the source, origin, description of the quality tests performed, specifications, determination of adventitious agents, and viral safety data.

#### 3.2.P.5.6 Novel Excipients (name, dosage form)

For any novel excipient, including adjuvants, preservatives and stabilizers, used for the first time in a vaccine for human use or for a new route of administration, all information on the manufacture, characterization, and control should be submitted under 3.2.A.3 according to the drug substance and/or drug product CTD format, with a cross-reference to 3.2.A.3 under this section. Cross-references to nonclinical studies (Module 4) and clinical studies (Module 5)

supporting the safety of a novel excipient should also be provided under this section.

- 32P6 Control of Drug Product (name, dosage form)
- 3.2.P.6.1 Specification(s) (name, dosage form)  
Indicate the specifications for the drug product.
- 3.2.P.6.2 Analytical Procedures (name, dosage form)  
Information on the analytical procedures used for quality control of the drug product. Non-pharmacopeia methods, summaries or references may be accepted (e.g. when pharmacopeia methods are unavailable or inappropriate and appropriately validated in-house methods are used). Additional information could be requested.
- 3.2.P.6.3 Validation of Analytical Procedures (name, dosage form)  
Include information on the validation of the analytical procedures for the drug product, including experimental data.
- 3.2.P.6.4 Batch Analyses (name, dosage form)  
Description of batches and results of batch analyses should be provided. This description should include the batch number, production scale, date of manufacture, production site, manufacturing process and use.
- 3.2.P.6.5 Characterization of Impurities (name, dosage form)  
As applicable, depending on the method used to manufacture the vaccine submitted for licensing.
- 3.2.P.6.6 Justification of Specification(s) (name, dosage form)  
Provide justification of the specifications proposed for the drug product.
- 32P7 Reference Standards or Materials (name, dosage form)  
Provide information on the reference standards and/or materials used in the tests to control the drug product.
- 32P8 Container Closure System (name, dosage form)  
Describe in detail the type and form of container closure systems of the drug product, including the materials of which they are made and quality specifications.

3.2.P9 Stability (name, dosage form)

3.2.P.9.1 Stability Summary and Conclusion (name, dosage form)

Submit the stability study that complies with each country's legislation, including the study protocol, specifications, analytical methods, detailed description of the container closure system for the product evaluated, storage conditions (such as temperature and relative humidity), summary of results for at least three lots of drug product prepared from different lots of drug substance, conclusions, and proposed shelf-life.

It is important to provide additional studies on the stability of the vaccine in intermediate stages in the manufacturing process that require different temperatures from the storage temperature, studies of challenge temperatures, photosensitivity or other specifications, depending on the type of vaccine, evaluated for at least three lots.

3.2.P.9.2 Post-approval Stability Protocol and Stability Commitment (name, Dosage form)

Include the stability program or stability commitment to be carried out once the vaccine is on the market, including the number of lots to be included in the study each year and the tests to be performed. These results should be submitted periodically to update the information on the stability of the vaccine evaluated.

3.2.P.9.3 Stability Data (name, dosage form)

Include the complete results of each lot evaluated during stability studies.

***If applicable, forced degradation studies should be filed within this section.***

3.2.A Appendices

3.2.A.1 Facilities and Equipment (name, manufacturer)

A diagram illustrating the production flow, including materials, personnel, waste, and intermediate products in relation to the manufacturing areas; information on adjacent areas related to

protection and maintenance of the integrity of the vaccine should be provided. Also, submit information on all of the products prepared and/or handled in the same areas as the product submitted for licensing. Describe the procedures to avoid cross-contamination of areas and equipment.

3.2.A.2. Adventitious Agents Safety Evaluation (name, dosage form, manufacturer)

Additional, detailed information on evaluation of the safety of the product in relation to adventitious agents of both viral and non-viral origin should be submitted.

3.2.A.3 Excipients

This appendix is *required* where applicable.

Novel Excipients - For any novel excipient, including adjuvants, preservatives and stabilizers, used for the first time in a vaccine for human use or for a new route of administration, information to support the quality, safety, and suitability for use should be provided in this appendix. This section should be submitted according to the drug substance and/or drug product CTD format described in this document along with cross- references to nonclinical studies (Module 4) and clinical studies (Module5) supporting the safety of a novel excipient.

Other Excipients - Any extensive drug substance and/or drug product information which is necessary to support the quality, safety, suitability for use, and 'approvability' of any (non-novel) non-compendia excipient, and/or any excipient of human or animal origin, should also be provided in this section.

3.2.R Regional Information

3.2.R.1 Production Documentation

3.2.R.1.1 Executed Batch Records (name, dosage form, manufacturer)

Executed batch records for 3-5 consecutively manufactured or consistency drug product lots from each production site or facility should be provided.

3.2.R.2 Medical Devices (name, dosage form)

For a vaccine supplied with a medical device, a description of the device(s),

including its application, manufacturer, and confirmation that it has been notified or approved for use by NAFDAC should be provided.

#### 3.2.R.3 Lot Release Documentation (name, dosage form)

The proposed test protocol format for the release package, including Certificate of Analysis for the drug substance or drug product, and safety certification for any biological excipient used, if applicable (e.g. a Plasma Certificate), should be provided. The documentation should include the name and title of the delegate with signing authority for lot release.

#### 3.2.R.4 Site master file

### 3.3 Literature References

## 4. Module 4. Nonclinical Study Reports

Nonclinical studies should comply with the WHO's *Guidelines on Nonclinical Evaluation of Vaccines*, WHO Technical Report Series No. 927, 2005, or the most recent version. In addition, vaccines containing adjuvants should comply with the WHO *Guidelines on the Nonclinical Evaluation of Vaccine Adjuvants and Adjuvanted Vaccines*. Additional information for the preparation of this section can be found in ICH M4S(R2).

### 4.1 Table of Contents of Module4.

The table of contents should be provided.

### 4.2 Study Reports

#### 4.2.1 Pharmacology

##### 4.2.1.1. Primary Pharmacodynamics

A pharmacodynamics study for a vaccine product is generally conducted to evaluate the immunogenicity of the vaccine or, when animal models are available, the capacity of a vaccine to confer protection. In addition, a pharmacodynamics study may also extend to include the pharmacology of an adjuvanted vaccine to provide evidence for the need for the adjuvant.

##### 4.2.1.2. Secondary Pharmacodynamics Generally not performed for vaccines

##### 4.2.1.3. Safety Pharmacology

The purpose of a safety pharmacology study is to investigate the effects of the candidate vaccine on vital functions. Although not usually required for vaccines, safety pharmacology studies may be

recommended by the NAFDAC in some cases. For example, if data from nonclinical and/or human clinical studies suggest that the adjuvanted vaccine may affect physiological functions (e.g. central nervous, respiratory, and cardiovascular systems, renal functions and body temperature) other than the immune system, safety pharmacology studies should be incorporated into the safety assessment program.<sup>1</sup>

4.2.1.4. Pharmacodynamic Drug Interactions Generally not performed for vaccines

#### 4.2.2 Pharmacokinetics

Generally not performed for vaccines; however, bio distribution studies may be applicable to the evaluation of vaccine formulations containing new adjuvants or live recombinant viral/bacterial vectors. The feasibility of such studies should be evaluated on a case-by-case basis.

Where pharmacokinetic studies have been performed, the study reports should be provided in the relevant sections below:

4.2.2.1. Analytical Methods and Validation Reports (if separate reports are available)

4.2.2.2. Absorption

4.2.2.3. Distribution

4.2.2.4. Metabolism

4.2.2.5. Excretion

4.2.2.6. Pharmacokinetic Drug Interactions(nonclinical)

4.2.2.7. Other PharmacokineticStudies

#### 4.2.3 Toxicology

##### 4.2.4 Single-Dose Toxicity

Single dose toxicity studies on the final formulated vaccine product, which are applicable to small molecule chemical drugs, are usually not needed for vaccines. Acute effects of administering the vaccine can also be monitored in repeated dose toxicity studies if they are adequately designed (e.g. evaluation is conducted after administration of the first dose). Alternatively, acute effects can be assessed in a single dose design as part of a local tolerance study.

4.2.4.1. Repeat-Dose Toxicity

Information should be included to justify the study design (e.g. number of animals per group), animal model used (e.g. animal species, age, dose, route of administration) and the parameters monitored.

4.2.4.2. Genotoxicity

Generally not performed for vaccines

However, it may be required if there is a component of the vaccine formulation such as a new adjuvant with a new chemical entity.

Where genotoxicity studies have been performed, the reports should be provided in the relevant sections below:

4.2.4.3. Invitro

4.2.4.4. In vivo (supportive toxicokinetics evaluations)

4.2.4.5. Carcinogenicity (including toxicokinetics) Generally not performed for vaccines

However, it may be required if there is a component of the vaccine formulation such as a new adjuvant with a new chemical entity.

Where carcinogenicity studies have been performed, the reports should be provided in the relevant sections below:

4.2.4.6. Long-term studies (not included in repeat-dose toxicity or pharmacokinetics)

4.2.4.7. Short- or medium-term studies (not included under repeat-dose toxicity or pharmacokinetics)

4.2.4.8. Other studies

4.2.4.9. Reproductive and Developmental Toxicity

Developmental toxicity studies are usually not necessary for vaccines indicated for immunization during childhood. However, if the target population for the vaccine includes pregnant women and women of child-bearing potential, developmental toxicity studies should be considered unless a scientific and clinically sound argument is put forward by the manufacturer to show that conducting such studies is unnecessary.

Where reproductive and developmental toxicity studies have been performed, the reports should be provided in the relevant sections below:

4.2.4.10. Fertility and early embryonic development

4.2.4.11. Embryo-fetal development

4.2.4.12. Prenatal and postnatal development, including maternal function

4.2.4.13. Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

4.2.4.14. Local Tolerance



The evaluation of local tolerance should be conducted either as a part of the repeated dose toxicity study or as a stand-alone study.

4.2.4.15. Other Toxicity Studies (if available)

Where other toxicity studies have been performed the reports should be provided in the relevant sections below:

4.2.4.16. Antigenicity

4.2.4.17. Immunotoxicity

4.2.4.18. Mechanistic studies (if not included elsewhere)

4.2.4.19. Dependence

4.2.4.20. Metabolites

4.2.4.21. Impurities

4.2.4.22. Other studies

### 4.3 Literature References

## 5. Module 5. Clinical Study Reports

Applicants may refer to the most up to date version of the WHO *Guidelines on Clinical Evaluation of Vaccines: Regulatory Expectations*. The WHO recommendations applicable to the specific vaccine should also be considered as well as other national and international regulatory guidelines. Additional information for the preparation of this section can be found in ICH M4E.

Clinical trials in humans are generally classified into three Phases: Phase I, Phase II and Phase III and, formal regulatory approval is required to undertake any of these studies. This is in addition to ethical clearance which is required for clinical trials. All studies of human subjects require proper ethical review, in accordance with the Declaration of Helsinki.

*A Clinical Trial Application (CTA) is required for studies conducted in Nigeria. Applicants should refer to appropriate NAFADC Guidelines for Clinical Trial Applications for more information.*

Phase I studies are primarily concerned with safety. The Phase I clinical studies carry out initial testing of a vaccine in small numbers (e.g. 20) of healthy adults to test the safety of a vaccine, its tolerability, and, if appropriate, clinical laboratory and immunological parameters.

Phase II studies involve larger numbers of subjects and are intended to provide preliminary information about a vaccine's ability to produce its desired effect (usually a specific immune response) in the target population and its general safety.

To fully assess the protective efficacy and safety of a vaccine, extensive Phase III trials are required. Phase III clinical trials are the pivotal studies on which the decision on whether to grant the licence is based and sufficient data has to be obtained to demonstrate that a new product is safe and effective for the purpose intended.

Ideally, by the beginning of the Phase III stage of development, a vaccine should have been fully characterized and the final manufacturing process, specifications and batch release testing procedures should have been established. Additional information may be required to support quality changes made post-Phase III studies.

An application for licensing may be submitted to NAFDAC on the basis of the data from Phase III testing and, if approved, the vaccine then becomes commercially available in Nigeria.

The structure of the clinical development programme must be tailored to the type of vaccine and the antigenic content. For example, the clinical evaluation of a vaccine that contains only novel antigen(s) may of necessity be very different from that of a vaccine that contains one or more previously evaluated antigens. Such factors also influence whether clinical protection trials will be required, whether or not they are feasible, or whether an approval may reasonably be based on immunogenicity data only. In all instances, it is the obligation of the applicant to justify the content and structure of the clinical development programme. Pre-submission meetings with regulatory authorities may assist in ensuring that the content of the final data package is likely to be acceptable.

#### 5.1 Table of Contents of Module5.

The table of contents is required.

#### 5.2 Tabular Listing of All Clinical Studies

A tabular listing of all clinical studies and related information should be provided (e.g. type of study, study identifier, location of study report in the application, study objectives, study design and type of control, dosage regimen, route of administration, number and type of subjects, study status). The sequence in which the studies are listed should follow the sequence described in section 5.3 below.

### 5.3 Clinical Study Reports

Clinical study reports should be provided in the relevant sections below. Additional information on the structure and content of the Clinical Study Report can be found in the ICH E3 Guideline.

#### 5.3.1. Reports of Biopharmaceutical Studies

Biopharmaceutical studies are not generally performed for vaccines. When immunogenicity studies are conducted, reports of bioanalytical assays results should be provided in section 5.3.5.

#### 5.3.2. Bioavailability Study Reports

#### 5.3.3. Comparative Bioavailability and Bioequivalence Study Reports

#### 5.3.4. In vitro - In vivo Correlation Study Reports

#### 5.3.5. Reports of Bioanalytical and Analytical Methods for Human Studies

#### 5.3.6. Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials Not generally performed for vaccines.

#### 5.3.7. Plasma Protein Binding Study Reports

#### 5.3.8. Reports of Hepatic Metabolism and Drug Interaction Studies

#### 5.3.9. Reports of Studies Using Other Human Biomaterials

#### 5.3.10. Reports of Human Pharmacokinetic (PK) Studies Not generally performed for vaccines.

#### 5.3.11. Healthy Subject PK and Initial Tolerability Study Reports

#### 5.3.12. Patient PK and Initial Tolerability Study Reports

#### 5.3.13. Intrinsic Factor PK Study Reports

#### 5.3.14. Extrinsic Factor PK Study Reports

#### 5.3.15. Population PK Study Reports

#### 5.3.16. Reports of Human Pharmacodynamic Studies

For vaccines, the immunogenicity studies are usually conducted to support the selection of dose, dosage schedule, and formulation of the final product, and the study reports should be provided in Section 5.3.5.

#### 5.3.17. Healthy Subject PD and PK/PD Study Reports

#### 5.3.18. Patient PD and PK/PD Study Reports

#### 5.3.19. Reports of Efficacy and Safety Studies

Reports of all clinical studies designed to assess the efficacy and safety of the vaccine conducted by the sponsor (or otherwise available), including all completed and all ongoing studies of the vaccine in proposed and non-proposed indications, should be provided in the relevant sections below. This should include the reports of the immunogenicity studies conducted to support the selection of dose, dosage schedule, and formulation of the final product.

For live attenuated vaccines (viral or bacterial, including vaccine vectors), there is a risk of clinically significant infections in the recipient or in contacts. Clinical study reports providing information on shedding, reversion characteristics, and transmission to contacts should be provided in this section.

#### 5.3.20. Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

Controlled clinical study reports should be sequenced by type of control in the following order:

- Placebo control (could include other control groups, such as an active comparator or other doses)
- No-treatment control (not generally performed for vaccines)
- Dose-response (without placebo)
- Active control (without placebo)
- External (Historical) control, regardless of the control treatment

#### 5.3.21. Study Reports of Uncontrolled Clinical Studies

Study reports of uncontrolled clinical studies, e.g. reports of open label safety studies.

#### 5.3.22. Reports of Analyses of Data from More than One Study

Reports of formal integrated analyses, meta-analyses and bridging analyses.

#### 5.3.23. Other Study Reports

This section can include the following:

- Reports of interim analyses of studies pertinent to the claimed indications
- Reports of controlled safety studies not reported elsewhere
- Reports of controlled or uncontrolled studies not related to the claimed indication
- Reports of ongoing studies
- Development Safety Update Reports

#### 5.3.24. Reports of Post-Marketing Experience

Relevant post-marketing studies or information (including all significant safety observations) should be included here.

(The latest PSUR maybe be provided).

#### 5.3.25. Case Report Forms and Individual Patient Listings (when submitted)

Case report forms and individual patient data listings that are described in appendices

16.3 and 16.4 in the ICH E3 guideline should be placed in this section, when submitted. They should be presented in the same order as the clinical study reports and indexed by study.

#### **5.4 Literature References**

This section should include copies of all references cited in the Clinical Overview and copies of important references cited in the Clinical Summary or in the individual technical reports that were provided in Module 5, section 5.3. Only one copy of each reference should be provided. Copies of references that are not included here should be immediately available on request.

## **ANNEX A: PRODUCT LABELLING GUIDANCE**

The product labelling shall be based on the NAFDAC guidance for product labelling.

### **Module 1.3.1 Summary of Product Characteristics (SmPC)**

The format of the SmPC document is to be consistent with the NAFDAC SmPC Template. The information should be provided in English language.

Refer to NAFDAC SmPC Guidance

Use NAFDAC SmPC Template

### **Module 1.3.2 Patient Information Leaflet**

The format of the PIL is to be consistent with the NAFDAC PIL template. The information should be provided in the English Language

Refer to NAFDAC PIL Guidance

Use NAFDAC PIL Template

### **Module 1.3.3 Container Labelling (Inner and Outer Labels)**

The primary and secondary packaging must include the following information in a legible, understandable and indelible manner. The information should be provided in English.

The Container Labelling is to be consistent with the NAFDAC labelling guideline.

Refer to NAFDAC Label Guidance

## **Annex B: Management of Applications And Standard Operating Procedures**

1.0. For vaccines that have been prequalified by the World Health Organization, registration will be via the Collaborative Procedure for the Accelerated Registration of WHO Prequalified medicines and vaccines.

### 2.0. General Policies on Applications

A separate application is required for each product. For purposes of clarification, one application could be submitted for products containing the same active ingredients and the same strength made by the same manufacturer at the same manufacturing site, to the same specifications and dosage form, but differing only in packing or pack sizes. On the other hand, separate applications shall be submitted for products that contain the same active ingredient(s) but of different dosage forms, different volumes, and proprietary or brand name.

### 2.1. Classes of Applications

Applications shall be classified into three (3)

- New Applications
- Renewal of applications (i.e., registration)
- Variation of Applications (i.e., of a registered product)

#### 2.1.1. New Applications

Applications for the registration of a pharmaceutical product either submitted to the Director General NAFDAC and copy the Director Registration and Regulatory Affairs Directorate for the granting of market authorization. In addition to the dossier submitted, the applicant shall provide a site master file of the plant in which the product was manufactured. (Submitted in Module 3).

#### 2.1.2. Applications for Renewal of Registration

Applications for renewal of registration shall be made at least 3 months before the expiry of existing registration and shall follow the "Guidelines for the Renewal of Marketing Authorization Licence for a Pharmaceutical Product".

#### 2.1.3. Application for Variation of a registered product

Applications for variation to a registered product shall be made according to requirements "NAFDAC Variation Guidelines"

3.0. Submission of Application

Applications for the registration of products for market authorization shall be made to the Director General of NAFDAC and copy Director Registration and Regulatory Affairs NAFDAC in accordance with the approved format.

4.0. Application Fees

Application fees shall be paid for each application submitted. -This shall be as per the approved NAFDAC tariff.

5.0. Timelines

Post Approval Variation and Renewal of registration will be processed within 90 working days of receiving the applications. Complete new applications will be processed within 12 months of receipt of the application. The applicant will be required to provide any requested additional data within 6 months.

In case additional time is required, a formal request must be submitted.

6.0. Withdrawal of an Application

When the applicant fails to submit written responses to queries within 6 months from the date of their issuance, it will be deemed that the applicant has withdrawn the application or if the queries have been reissued for a second time and the applicant provides unsatisfactory responses, the product will be disqualified and the application will be rejected. The applicant will be required to apply afresh.

7.0. Validity Of Registration

The registration of a pharmaceutical product shall be valid for five (5) years unless otherwise suspended or revoked by NAFDAC, or withdrawn by applicant.

8.0. Appeals

Any person aggrieved by a decision in relation to any application for marketing authorization of a vaccine should please refer to the guidelines for complaints for guidance.

[https://www.nafdac.gov.ng/wpcontent/uploads/Files/Complaints/Guidelines-for-complaints\\_appeal-QMS-GLD-001-00.pdf](https://www.nafdac.gov.ng/wpcontent/uploads/Files/Complaints/Guidelines-for-complaints_appeal-QMS-GLD-001-00.pdf)