FOOD AND DRUGS AUTHORITY

GUIDELINES FOR REGISTRATION OF

VACCINES

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1.0 INTRODUCTION

Vaccines manufactured in its manufacturing facility. The Food and Drugs Authority's (FDA) guidelines for the registration of human vaccines provide guidance to applicants intending to register their product in Ghana. In addition, the guidelines publish the required format and content for submitting a veterinary vaccine registration application to the FDA, and provide guidance that ensure that products and manufacturers meets the minimum established regulatory requirements to do business in Ghana.

Human vaccines are products of biological origin, which exhibit some intrinsic variability. They are characterized by complex manufacturing processes and are administered to large numbers of healthy infants, children, adolescents, and adults. Solely testing the final product alone cannot assess their quality; hence, a complete product development dossier, in addition, to a satisfactory current Good Manufacturing Practice (cGMP) audit of the manufacturing facility shall be required to make a regulatory decision.

The FDA fully evaluates all data and information submitted on the quality, safety and efficacy profiles of human vaccines application for completeness, and in line with requirements contained in these guidelines. The FDA shall register the vaccine and grant marketing authorization following satisfactory evaluation outcome.

These guidelines provide guidance on the requisite data and information that is needed in an application dossier, and evidence to show that the product development pathway contains information on the various stages of development; research, product development, production, quality control, non-clinal and clinical studies, and guarantees that the quality, safety and efficacy required of the vaccine to be used in humans has been established.

1.1 SCOPE

The FDA guidance document applies to all registration application for vaccines intended for use in humans, regardless of where they were manufactured, whether they are licensed in the country of origin or not. The guidance document consisted of five modules (i.e. Module 1- Module 5) and it is in Common Technical Document format.

2.0 GLOSAARY

The definitions herein apply to the harmonized requirements for the registration applications of vaccines and its guideline for preparation of application are included in this glossary in alphabetical order.

- **Active ingredient of the vaccine:** the antigenic substances (or compounds thereof) that can induce specific responses in humans against an infectious agent, its antigens or toxins.
- **Batch or lot:** set of final packages of finished vaccine, hermetically sealed, that is homogeneous with respect to the risk of cross-contamination during the packing and freeze-drying processes. Therefore, all final packages must have been filled from a single set of ingredients in a single working session and, if applicable, freeze-dried in standardized conditions in the same room.
- **Carrier protein:** a protein used mainly in conjugated polysaccharide vaccines to which the polysaccharide antigen is linked in order to improve both the magnitude and type of the immune response.
- **Clinical particulars**: These are indications for use, contra-indications, undesirable effects (with reference to frequency and seriousness), precautions for use, dosage and method of administration, overdose, special warnings, major and minor incompatibilities (If appropriate), special precautions during administration of the product, first aid and safety directions.
- **Country of origin:** it corresponds to the country where the legal certifications of the product are generated.
- **Dosage form:** the physical form in which a product is prepared for administration to the recipient.
- **Shelf life:** it is the date before which the quality of the vaccine remains acceptable for its intended use as outlined in the market authorization. It is established based on stability studies.
- **Final bulk product:** any product that has gone through all stages of processing, including formulation but not final packaging.
- **Finished product**: final pharmaceutical form that has gone through all steps of the manufacturing process, including final packaging.

- **Good Manufacturing Practices (GMP):** set of procedures and practices to ensure consistent controlled production of batches of pharmaceutical products, according to proper quality standards for the intended use thereof and the conditions required for their sale.
- **Immunological properties:** These are the diseases and/or conditions that the product is designed to treat, prevent or detect and the type of immune response and correlation with protection. If the type of response has not been determined, a general summary of what is known about the infectious agent and the type of responses that are likely to be effective in conferring protection must be provided. Information on efficacy, claims and the duration of immunity must also be provided.
- **Lot release:** process for the evaluation of each individual lot of vaccine submitted be used in the market; this means independent control of each lot to guarantee that all the lots produced and used in a country are in compliance with the established quality specifications. This process can be performed by detailed review of Summary Protocols of Production and Quality Control, and includes laboratory testing when it is considered necessary.
- **License:** in some countries it is called registration. Procedure whereby the National Regulatory Authority grants permission for the product in question to be sold and distributed in the country.
- **Master cell bank:** culture of specific cells of known origin that are distributed in a container or packages in a single operation to ensure uniformity and stability in storage. The master bank is usually kept at a temperature of -70°C or less. In some countries, it is called the primary bank.
- **Product development:** all studies to show that the dose, formulation, manufacturing process and packaging system, as well as the microbiological properties, are appropriate for the proposed purpose.
- **Product to be licensed:** both, the document outlining the harmonized requirements for the licensing of vaccines in the Americas and its guidelines for preparation of application, apply to the registration of vaccines in the Americas. The vaccine may be also referred as the product.

- **Raw materials:** any substance used to make or extract the active ingredient but from which the active ingredient is not directly derived. For example, culture media, fetal bovine serum, etc.
- **Starting materials:** any substance of biological origin, such as microorganisms, organs and tissues of plant or animal origin, including cells or fluids of human or animal origin and recombinant cell substrates.
- **Validation:** series of documented procedures or actions, consistent with good manufacturing practices, demonstrating that the processes, equipment, materials, activities and/or systems satisfy the predetermined specifications and quality attributes.
- **Working cell bank:** culture of cells derived from a master cell bank and intended to prepare production cultures. The working cell bank is usually kept at a temperature of -70°C or less. In some countries, it is called the secondary bank.

3.0 ADMINISTRATIVE REQUIREMENTS

The legal information accompanying the dossier should be duly certified and authenticated under the procedure in effect in the country of origin, and issued by the appropriate entity.

- **Qualified person responsible for the product release** (under the country's legislation). Submit a document issued by the manufacture on the individuals responsible for the vaccine release. The information should include the identity and designation of the authorized person in charge of regulatory activities.
- **Certificate of Pharmaceutical Product**

  Using the World Health Organisation (WHO) model, this certificate includes information on compliance with good manufacturing practices (GMP). A free sale certificate where applicable should be submitted in addition to the GMP certificate.
- **Certificate of good manufacturing practices of other manufacturers involved in the production of the vaccine**

  This should include manufacturers that are involved in any stage of the production process, for example manufacturer(s) of the active ingredient(s),

the diluents, and those responsible for labelling and packaging of the finished product. It is important that the certificate indicates the procedures that the establishment is authorized to perform.

- **Trademark certificate** (optional)
- **Proposed brand name and art work for primary and secondary labels**

  These should be submitted for approval by FDA prior to submission of application, dossier and samples for registration.
- **Invention patent certificate** (based on the country of origin's legislation)
- **Batch release certificate**

  Refers to the batch release certificate issued by the regulatory authority of the country of origin of the product or the regional regulatory authority responsible for its release. The certificate should correspond to those samples submitted with the application for registration. Please refer to the FDA website for the minimum requirements (batch release document).
- **Lot release certificate**

  Refers to the lot release certificate issued by the regulatory authority of the country of origin of the product or the regional regulatory authority responsible for its release. The certificate should correspond to those samples submitted with the application for registration.
- **Manufacturer's declaration**

  A document should be presented certifying that the information provided is the information corresponding to all the studies performed, regardless of their results. This should include all the pertinent information regarding all toxicological and/or clinical tests or trials of the biological product that are incomplete or have been abandoned and/or completed tests related to indications not covered by the application.

3.1 Specific Requirements

- The presentation of the vaccine shall not have any resemblance in spelling and pronunciation of name, or packaging to another vaccine, that has been previously registered by the Authority.
- All samples submitted should conform to existing labelling regulations as specified in page 13 of these guidelines.

All documentation submitted shall be in English, and must be legibly printed and not handwritten.

- Four (4) copies of the labels and leaflet inserts, conforming to existing labelling regulations in Ghana (see page 17 of these guidelines).
- If the product is produced on contract manufacture, evidence of the contract agreement shall be produced in the documentation submitted.
- Products submitted for registration shall have at least 60% of its shelf-life remaining. This notwithstanding, products with shelf-life less than 24months shall have at least 80% of its shelf-life remaining at the time of submission.
- The use of an International Non-proprietary Name (INN) as a brand name shall not be permitted.
- The packages of all products submitted for registration shall include package inserts/patient information leaflet (where applicable)

3.2 **New Registration**

- An applicant for the registration of a biological vaccine, either locally manufactured or imported, shall be made in writing.
- An application form shall be completed in accordance with the sequence of appendices and shall be dated, signed and stamped by the applicant/license holder.
- If the applicant is a foreign company, it shall appoint a local agent through whom the application shall be submitted.
- The local agent shall be a registered pharmaceutical wholesale company or an accredited manufacturer's representative registered as a pharmacist in Ghana.\
- Applications shall be accompanied by:
    - A duly signed covering letter
    - Two (2) soft copies (one CD-ROM and a DUPLICATE CD-ROM) of completed application forms and the dossier in the Common Technical Document (CTD) format
    - Samples of the product in the final package as specified in the Authority"s sample schedule. Refer to www.fdaghana.gov.gh
    - Reference /working standards for Active Pharmaceutical Ingredients (API) and related impurities where necessary.

- All supporting documents as specified on the application form
- Clinical trial certificate where applicable
- Non-refundable application fee as specified in the Authority's fee schedule.

- All documentation submitted shall be in English, and must be legibly printed and not hand written. These guidelines should be read in conjunction with other guidelines on the Authority's website www.fdaghana.gov.gh. Those documents provide specific guidance on the batch release requirements.
- The Authority generally accepts data generated by tests which have been conducted according to monographs in the most recent editions of the reference Pharmacopeia as stated in the Public Health Act (ACT 851, 2012, Section 112).
- The original certificate of analysis for the batch of the vaccine being submitted for registration and issued by a recognized public analyst shall be submitted.
- The Authority shall approve the application before any importation of the vaccine is made into the country other than those used as samples for the purpose of this application.

3.2 Registration Variation

- An application for the variation of registration of a vaccine prior to re-registration shall be made to the Authority. This variation shall be approved by the Authority before any importation of the product shall be made into the country.
- The application shall be accompanied by:
  - A duly signed covering letter
  - Documentation in support of the variation. Refer to Guidelines for reporting variation to a registered Biological Product in Ghana (FDA/SMC/BPD/GL-VAR/2015/07) for the necessary documentation
  - Samples reflecting the variation as specified in the Authority's samples schedule.
  - Non-refundable variation fee as specified in Authority's approved fees Schedule.

- This variation shall be approved by the Authority before any importation of the varied product is made into the country, other than those used as samples for the purpose of this application.

3.3 Registration Renewal

3.3.1 An application for the re-registration of a biological product shall be made three (3) months before expiration of the last registration.

3.3.2 The application shall be accompanied by:

3.3.2.1 A covering letter

3.3.2.2 Supporting documentation for any variations since the biological product was last registered

3.3.2.3 Samples of the biological product in the final package as specified in the Authority's samples schedule

3.3.2.4 Non-refundable application fee as specified in Authority's approved fees schedule.

3.3.2.5 Certificate of Analysis (CoA) of the finished product

3.3.2.6 Certificate of Pharmaceutical Product (CoPP) issued by the statutory national drug regulatory authority, in accordance with the World Health Organization (WHO) Certificate Scheme for Pharmaceutical Products moving into International Commerce.

3.3.2.7 Long-term/Real-time, real condition stability studies for three production batches (Protocol and Report)

3.3.2.8 Method of analysis (Protocol and Report) Analytical Method

3.3.2.9 Validation (Protocol and Report)

3.3.2.10 Batch release documents.

3.3.2.11 Reference Standard/ Reference Product

3.3.2.12 Certificate of Analysis of the reference standard/Reference Product

3.3.2.13 Risk management plan and pharmacovigilance/data on post market surveillance (refer to www.fdaghana.gov.gh).

3.3.3 The re-registration shall be approved by the Authority before any importation of the product is made into the country, other than those used as samples for the purpose of this registration.

3.4 Summary of the characteristics of the vaccine

A summary of the characteristics of the vaccine should be provided. The summary should contain all analytical testing performed to characterize the biological API with respect to identity, potency and stability. Results of analysis may be presented in a tabular form, with copies of chromatograms or spectra, photographs of gels or immunoblots, actual histograms of cytometric analysis contained in another section.

Note: Results for quantitative assays should be presented as actual data not generally as “Pass” or “Fail”.

For biological activity tests, further characterization may include; specific identity testing, cytometric analysis, neurovirulence testing (when appropriate), serotyping, electrophoretic typing, inactivation studies, neutralization assay and titrations and pathogenecity assays (if product is a live vaccine)

Results of all important in vivo and in vitro bioassays performed on the manufacturer’s reference standard lot to demonstrate potency and activity of the vaccine API should be provided.

A complete description of the protocol used for each bioassay, the control standard reference number used, the validation of the inherent variability of the test and the established acceptance limits for each assay should be included. The characteristics of specific antibodies used in the immunochemical or serological assays should also be included

3.5 Monograph for health professionals

Submit the proposed monograph on the product which will be distributed to health professionals

3.6 Imported vaccines

Applicant should obtain clearance from the FDA prior to the importation of vaccines for either retail or registration. Issuance of import permit for registration samples of the vaccine shall no guarantee automatic registration of the product.

Subsequent importation of vaccine shall be accompanied by the Batch release document, and the corresponding batch release certificate. Note that import permit application submitted through the GC-NET shall be processed only if the necessary release documents have been submitted to the Authority in advance (five working days prior to issuance of GC-NET import permit).

3.6 Expert reports

Applicants may provide an expert report if the applicants consider that such reports may assist in interpretation of data and evaluation of the application. A brief résumé for each expert must be provided and their professional relationship to the applicant must be stated.

The Executive Summary within the Overview must include the reasons for the application. For a new product, this should include whether the product contains a new active constituent and scientific argument for registration of the product. The argument should outline the importance, prevalence and (if applicable) the regional distribution of the disease the vaccine is intended to control.

3.7 Registration status in other countries

Details of any known current or previous applications or approvals in other countries for products containing the same formulation must be provided. In all cases the details of any current or previous application or approvals for this formulation overseas must be provided.

3.8 Requirements for registration/marketing authorization reliance

Regarding products that have already been approved by a well-resourced NRA, the FDA shall activate the reliance pathway to facilitate regulatory decisions either on a case-by-case basis or at the explicit request of the Applicant. The Applicant shall submit to the FDA, the full CTD dossier and the full assessment report(s) of the registration/marketing authorization submission made to the well-resourced NRA or the WHO. The application shall be identical to that submitted, evaluated and approved by the well-resourced or reference NRA or the WHO.

3.9 Appealing a rejected registration application

The FDA makes the final decision on an application made under the section 118 of Public Health Act 2012 Act 851 for the registration and re-registration.

The FDA during the registration process can reject an application when it is not part of a treatment regimen for a Programme under the Ministry of Health, for Safety or Quality reasons.

An Applicant may appeal a decision made by the FDA as indicated in Section 118 subsection 6 of the Public Health Act 2012, Act 851 within sixty days after the date of the notification of rejection.

The appeal representation shall be made in writing to the Authority addressed to:

The Chief Executive Officer

Food and Drugs Authority

P. O. Box CT 2783

Cantonments

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On receipt of the intention to appeal, the FDA will subject the notice of appeal to its internal appeal processes.

Where the FDA is satisfied with the representations submitted, the FDA may approve the registration of the medicinal product or if the FDA is still not satisfied, it shall reject the application.

3.10 DATA REQUIREMENTS AND GUIDELINES FOR IMPLEMENTATION

This section sets out the data requirements and guidelines. Data must be provided for each of the elements described below. The FDA may accept valid scientific argument that data need not be submitted for one or more of the data elements.

3.11 RECCOMENDED FORMAT FOR DOSSIER SUBMISSION

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1.2.2 Non-proprietary name or common name of vaccine

1.2.3 Concentration

1.2.4 Dosage Form

1.2.5 Senior Executive Officer / Senior Medical or Scientific Officer

1.2.6 Legal Representative in Country

1.2.7 Vaccine proprietary

1.2.8 Manufacturer of active ingredient(s)

1.2.9 Manufacturer of the finished product

1.2.10 Other manufacturers involved in the production process

1.2.11 Officials responsible for releasing batches of finished product

1.2.12 Commercial presentation of vaccine

1.2.13 Route of administration

1.2.14 Storage conditions

1.2.16 Strength of each unit of dose

1.2.16 Legal documents on the product:

- Document recognizing the technical director or technical professional responsible for the product
- Authorization of representative
- Certificate of Pharmaceutical Product (CPP)
- Certificate of Good Manufacturing Practices (GMP)
- Trademark certificate (optional)
- Patent certificate (under national legislation)
- Batch release certificate issued by NRA (imported products)
- Manufacturer's statement that all relevant information has been included and is accurate

1.3 SUMMARY OF PRODUCT CHARACTERISTICS AND PRODUCT LABELING

1.3.1 Summary of product characteristics

1.3.2 Product Labeling

1.3.2.1 Primary package label

1.3.2.2 Secondary packaged label

1.3.2.3 Package insert

1.3.2.4 Final packaging

1.3.2.5 Monograph for health professionals or information for prescription in extended or reduced form

1.3.3 Samples

1.3.3.1 Samples of finished product (in accordance with FDA samples schedule)

1.3.3.2 Summary protocol of batch production and control

1.4 LIST OF COUNTRIES WHERE THE PRODUCT HAS BEEN LICENSED AND SUMMARY OF APPROVAL CONDITIONS

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2.5.2 Overview of immunogenicity

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2.5.5 Overview of safety

2.5.6 Conclusions on risk-benefit balance

2.5.7 Literature References

2.6 NON-CLINICAL SUMMARY

2.6.1 Introduction

2.6.2 Written pharmacological summary

2.6.3 Tabulated pharmacological summary

2.6.4 Written pharmacokinetic summary (when appropriate)

2.6.5 Tabulated pharmacokinetic summary (when appropriate)

2.6.6 Written toxicological summary

2.6.7 Tabulated toxicological summary

2.7 CLINICAL SUMMARY

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2.7.2 Summary of the clinical immunogenicity studies

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2.7.5 Literature Reference

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3. 2. S. 1. 2 Structural formula, molecular formula and relative molecular weight (if applicable)

3. 2. S. 1. 3 Description and characterization of active ingredient

3. 2. S. 1. 4 General description of the starting materials

- Strain
- Master / Working Seed System Banks
- Embrocated eggs

3. 2. S. 1. 5 General description of the raw materials

3. 2. S. 1. 6 Analytical certificates signed by the manufacturer and the applicant for licensing

3. 2. S. 2 MANUFACTURING PROCESS FOR THE ACTIVE INGREDIENT

3. 2. S. 2. 1 Manufacturer(s)

3. 2. S. 2. 2 Description of manufacturing process

- active ingredient, in-process controls

3.2.S.2.3 Material control

3.2.S.2.4 Identification of critical steps in process and controls. Selection and justification of critical steps

3.2.S.2.5 Validation of manufacturing process. Description of changes

3.2.S.3 CHARACTERIZATION OF ACTIVE INGREDIENT

3.2.S.4 QUALITY CONTROL OF ACTIVE INGREDIENT

3.2.S.4.1 Specifications

3.2.S.4.2 Description of analytical procedures, validation and justification of specifications

3.2.S.4.3 Validation of analytical procedures

3.2.S.4.4 Batch analysis and consistency results

3.2.S.4.5 Justification of specifications

3.2.S.5 REFERENCE STANDARDS OR MATERIALS

3.2.S.6 PACKAGING/CONTAINER CLOSURE SYSTEM

3.2.S.7 STABILITY OF ACTIVE INGREDIENT

3.2.S.7.1 Protocol of stability study, summary and conclusions

3.2.S.7.2 Post-approval stability program

3.2.S.7.3 Stability data

3.2.S.7.4 Storage and shipping conditions of active ingredient

3.2.S.8 CONSISTENCY OF PRODUCTION OF ACTIVE BIOLOGICAL SUBSTANCE

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3.2.P.1 DESCRIPTION AND COMPOSITION OF FINISHED PRODUCT

3.2.P.2 PHARMACEUTICAL DEVELOPMENT

3.2.P.2.1 Active ingredient

3.2.P.2.2 Finished product

3.2.P.2.3 Manufacturing process

3.2.P.2.4 Packaging/container closure system, compatibility

3.2.P.2.7 Justification of final qualitative/quantitative formula

3.2.P.3 MANUFACTURE OF FINISHED PRODUCT

3.2.P.3.1 Manufacturer

3.2.P.3.2 Batch formula

3.2.P.3.3 Description of manufacturing process

3.2.P.3.4 Control of critical and intermediate steps

3.2.P.3.5 Validation and/or evaluation process

3.2.P.3.6 Description of batch identification system

3.2.P.4 CONTROL OF ADJUVANT, PRESERVATIVE, STABILIZERS AND EXCIPIENTS

3.2.P.4.1 Specifications

3.2.P.4.2 Analytical procedures

3.2.P.4.3 Validation of analytical procedures

3.2.P.4.4 Justification of specifications

3.2.P.4.5 Substances of human or animal origin

3.2.P.4.6 Use of new adjuvant, preservatives, stabilizers and excipients

3.2.P.5 CONTROL OF FINISHED PRODUCT

3.2.P.5.1 Specifications

3.2.P.5.2 Analytical procedures

3.2.P.5.3 Validation of analytical procedures

3.2.P.5.4 Batch analysis and consistency results

3.2.P.5.5 Determination and characterization of impurities

3.2.P.5.6 Justification of specifications

3.2.P.5.7 Analytical certificates signed by manufacturer and applicant for licensing

3.2.P.6 REFERENCE STANDARDS OR MATERIALS

3.2.P.7 PACKAGING/CONTAINER CLOSURE SYSTEM

- Specifications of primary and secondary packaging
- Test and evaluation of packaging materials

3.2.P.8 STABILITY

3.2.P.8.1 Protocol of stability study, summary and conclusions:

- For freeze-dried products, include stability study of freeze-dried material, diluents and reconstituted product
- Thermostability (where applicable)

3.2.P.8.2 Post-approval stability program

3.2.P.8.3 Stability data

3.2.P.8.4 Description of procedures to guarantee cold chain

3.2.A APPENDIX

Include the following information in the appendix of Module3:

3.2.A.1 Equipment and facilities

3.2.A.2 Safety evaluation of adventitious agents

3.3 LITERATURE REFERENCES

MODULE 4

NON CLINICAL INFORMATION

The non-clinical studies should follow the guidelines of the WHO Guide on non-clinical evaluation of vaccines, Technical Report Series No. 927, WHO, 2005, or the current edition thereof.

4.1 TABLE OF CONTENTS OF MODULE 4

4.2 REPORT ON STUDIES

4.2.1 PHARMACOLOGY

4.2.1.1 Pharmacodynamic studies (immunogenicity of the vaccine)

4.2.1.2 Pharmacodynamic studies of adjuvant (if applicable)

4.2.2 PHARMACOKINETICS

4.2.2.1 Pharmacokinetics studies

4.2.3 TOXICOLOGY

4.2.3.1 General toxicology - information on:

- Design of study and justification of animal model
- Animal species used, age and size of groups
- Dose, route of administration and control groups
- Parameters monitored
- Local tolerance

4.2.3.2 Special toxicology (for vaccines to which it applies):

- Special immunological investigations
- Toxicity studies in special populations
- Genotoxicity and carcinogenicity studies
- Reproductive toxicity studies

4.2.3.3 Toxicity of new substances used in formulation (new adjuvant, stabilizers, and additives)

4.2.4 SPECIAL CONSIDERATIONS

4.2.4.1 For attenuated vaccines an evaluation of possibility of microorganism shedding through natural avenues of excretion

4.3 LITERATURE REFERENCES

MODULE 5

CLINICAL INFORMATION

The information should be consistent with the WHO Guidelines on Clinical Evaluation of Vaccines: Regulatory Expectations (WHO Technical Report Series, 924, 2005, or latest edition) and regulatory guidelines in each country.

5.1 TABLE OF CONTENTS FOR MODULE

5.2 CONTENTS: REPORTS OF CLINICAL STUDIES

- Phase I studies
- Phase II studies
- Phase III studies
- Special considerations

- Adjuvant
- Non-inferiority studies (for combined vaccines, or approved vaccines prepared by new manufacturers)
- Combined vaccines or vaccines made by new

5.3 CLINICAL STUDY REPORTS

5.3.6 PHASE IV STUDIES AND/OR PHARMACOVIGILANCE PLAN (IF APPLICABLE)

5.4 LITERATURE REFERENCES

CHARPTER 2

GUIDELINES FOR THE PREPARATION OF THE APPLICATION INTRODUCTION

This document is intended to provide additional guidance to the applicant for the preparation of submissions in Chapter 1 of this document, and also to offer complementary information.

Because of their special characteristics, vaccines are mostly considered as new products for licensing purposes.

MODULE 1

ADMINISTRATIVE – LEGAL INFORMATION

The requirements include:

1.1 TABLE OF CONTENTS (MODULES 1 TO 5).

The application to license vaccines should include an index of the information contained in each module.

1.2 APPLICATION FORM

GHFDA minimum requirement:

1.2.1 Proprietary, commercial or trade name of vaccine. It corresponds to the name under which the vaccine will be registered.

1.2.2 Non-proprietary name or common name of vaccine. The name adopted by the World Health Organization, the common international name, or the name contained in official pharmacopeias recognized in the country.

1.2.3 Concentration. State the concentration of the active ingredient(s) contained in the vaccine.

1.2.4 Dosage Form. Indicate the dosage form of the vaccine, for example, injectable solution, and lyophilized power for injectable suspension.

1.2.5 Senior Executive Officer / Senior Medical or Scientific Officer. The professional responsible for the product in the country where licensing is applied for. Give the full name, address, telephone, fax, e- mail, professional license number, and the registration number of his/her degree, as per the country's legislation.

1.2.6 Legal Representative in Country. Refers to the company that represents the product, which will be responsible for marketing it in the country. Give the full name, address, telephone, fax, and e-mail. Some countries in the Region do not require legal representatives' resident in the country to obtain the licensing of a product.

1.2.7 Vaccine proprietary. Give the full name of the market authorization holder of the vaccine if licensed in the country of origin, also address, telephone, fax, and e-mail.

1.2.8 Manufacturer of active ingredient(s). Give the name, address, telephone, fax, and e-mail of the manufacturer(s) involved in the production of the active ingredient(s) in the vaccine.

1.2.9 Manufacturer of the finished product. Give the name, address, telephone, fax, and e-mail of the manufacturer(s) involved in the production of the finished product.

1.2.10 Other manufacturer(s) involved in the production process of the vaccines. In the event that some parts of the manufacturing process are performed by a different company, give name, address, telephone, fax, and e-mail. For lyophilized vaccines, include the name, address, telephone, fax, and e-mail of the producer of the diluents.

1.2.11 Official responsible for batch release of finished product. Give the name and position of the person responsible for the release of the lots of vaccine.

1.2.12 Commercial presentation of vaccine. Indicate whether the vaccine is offered for sale in single or multiple doses presentation and whether it will be distributed in a single package or in a multi - unit package and whether it contains any additional accessories, for example a transfer device.

1.2.13 Route of administration. Indicate the route of administration of the vaccine.

1.2.14 Storage conditions. Indicate the storage temperature for the vaccine and any other storage conditions, for example: protect from light, do not freeze.

1.2.15 Strength of each unit of dose.

1.2.16 Legal documents on the product. The legal information should be duly certified, authenticated under the procedure in effect in the country of origin, and issued by the appropriate entity. The certified documents may be presented during the license process and they will not constitute a limitation for the dossier submission.

- Document recognizing the technical director or technical professional responsible for the product. Required based on country's legislation. Submit a document issued by the manufacturer of the vaccine giving information regarding the individuals responsible for the product in the country indicating who is authorized to perform the related regulatory activities, including application for the
- vaccine licensing.
- Authorization of representative. Document issued by the applicant/manufacturer of the vaccine authorizing the company to represent it and market the vaccine in the country.
- Certificate of Pharmaceutical Product (CPP). Using WHO model. Required for imported vaccines since it is the certificate issued by the regulatory authority that grants the license in the country of origin. This certificate includes information on compliance with GMP. Some countries issue a Free Sales Certificate (FSC); this should be submitted in addition to the GMP certificate.
- Certificate of Good Manufacturing Practices of all manufacturer(s) involved in the vaccine production process. This should include manufacturers that are involved in any stage of the production process, for example manufacturer(s) of the
- active ingredient(s), the diluents, and those responsible for labeling and packaging the finished product. It is important that the certificate indicates the procedures that the establishment is authorized to perform.
- Trademark certificate (optional)
- Patent certificate (under national legislation)
- Batch release certificate issued by NRA (imported product). Refers to the lot release certificate issued by the regulatory authority of the country of origin of the product or the regional regulatory authority responsible for its release. The certificate should correspond to those samples submitted with the application for licensing, as applicable.
- Manufacturer's statement that all relevant information has been included and is accurate. A document should be presented certifying that the information provided is the information corresponding to all the studies

performed, regardless of their results. These include all the pertinent information regarding all toxicological and/or clinical tests or trials of the vaccine that are incomplete or have been abandoned and/or completed tests related to indications not covered by the application

1.3 SUMMARY OF PRODUCT CHARACTERISTICS AND PRODUCT LABELING

1.3.1 Summary of product characteristics. A summary should be submitted of the characteristics of the vaccine under evaluation.

1.3.2 Product labeling. The text proposed for the primary label, the secondary label or exterior packaging, and the package insert should be included.

1.3.2.1 Primary package label. Submit the label proposed for the vaccine's primary package or container, which should provide the following information as a minimum:

- Proprietary, commercial or trade name
- Non-proprietary name or common name
- Dosage form
- Concentration, potency, or viral titer
- Content/volume
- Volume/dose
- Number of doses per vial (for multidose presentations)
- Route of administration
- Storage temperature (if the size of the package so permits)
- Warnings
- Lot number
- Expiry date
- Manufacturer
- Registration number

1.3.2.2 Secondary packaged label. Include the text proposed for the vaccine's secondary packaging, also known as the packaging that protects the primary vaccine container, which should provide the following information as a minimum:

- Proprietary, commercial or trade name
- Non-proprietary name or common name

- Dosage form
- Concentration, potency, or viral titer
- Content/Volume
- Volume/dose
- Number of doses per vial (for multidose presentations)
- Composition
- Excipients
- Product storage
- Route of administration
- Instructions for preparation
- Mode of use
- Warnings
- Identification marks (some countries require that an identification mark indicating the type of product be included, for example a yellow band for pediatric products)
- Lot number
- Date of expiry
- Name and address of the manufacturer of the finished product
- Name and address of the company responsible for packaging
- Name and address of the owner, representative, or distributor
- Name of the professional in charge
- Registration number

1.3.2.3 Package insert. Include the text proposed for the package insert, which should contain the following information as a minimum:

- Proprietary, commercial or trade name
- Non-proprietary or common name
- Pharmaceutical form
- Concentration, potency, or viral titer
- Content/Volume
- Volume/dose
- Number of doses per vial (for multidose presentations)
- Composition

- Excipients
- Cell substrate
- Route of administration
- Indications
- Immunization plan
- Proper use
- Precautions
- Warnings
- Adverse events allegedly associated with vaccination and immunization
- Contraindications
- Use during pregnancy and breast feeding
- Storage of the product/storage conditions
- Name and address of the manufacturer of the finished product
- Name and address of the company responsible for packaging

1.3.2.4 Final packaging. Samples, or alternatively labels and cartons, of the primary and secondary packaging of the vaccine, including the package insert and accessories should be submitted. The purpose of this is to provide an example of the vaccine, including accessories, if any, to verify that they correspond to what is described for the characteristics of the vaccine under evaluation.

1.3.2.5 Monograph for health professionals or information for prescription in extended or

reduced form. Submit the proposed monograph on the vaccine to be distributed to health professionals.

1.3.3 Samples

1.3.3.1 Samples of finished product (in accordance with legislation of each country). Samples must be sent for the corresponding analytical evaluation.

1.3.3.2 Summary protocol of batch production and control. This protocol should follow the format recommended by the WHO in the specific requirements for the production and control of the specific vaccine submitted for market authorization. These protocols are published in the WHO's Technical Report Series. For novel vaccines for which there are no specific WHO recommendations, submit a template of the protocol proposed for its

evaluation or a protocol that has been approved by the regulatory authority of the country of origin.

1.4 LIST OF COUNTRIES WHERE THE PRODUCT HAS BEEN LICENSED AND SUMMARY OF APPROVAL CONDITIONS.

The list of countries where the vaccine is registered at the time the application for registration is submitted or, if there are none, the countries where registration is being processed. In the event the product has been registered in other countries, attach the summary of the conditions under which the market authorization was granted by that regulatory authority.

1.5 INFORMATION REGARDING EXPERTS.

A declaration should be sent signed by each of the experts who performed the product evaluation from the standpoint of quality, nonclinical studies and clinical studies. Attach a summary of their academic records and employment experience and state the professional relationship between the experts and the applicant of market authorization.

1.6 ***ENVIRONMENTAL RISK ASSESSMENT*****.** Include an evaluation of the possible Environmental risks posed by the use and/or disposal of the vaccine and give proposals in that regard and the indications or warnings to be included on the product label.

MODULE 2. 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 market authorization 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. The information in module 2 should be presented in the following order:

2.1 GENERAL TABLE OF CONTENTS.

A general index should be included of the scientific information contained in modules 2 to 5.

2.2 INTRODUCTION.

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

2.3 OVERALL QUALITY 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 registration document. The format to be followed is:

INTRODUCTION

2.3.S Summary of active ingredient

2.3.P Summary of final product

2.4 OVERVIEW OF NON-CLINICAL STUDIES.

A comprehensive and critical assessment of the results of the evaluation of the vaccine in animals and in vitro testing should be presented and the safety characteristics of the vaccine for use in humans should be defined. The data should be presented as a written and tabulated summary, in the following order:

- Introduction
- Written pharmacological summary
- Tabulated pharmacological summary

- Written pharmacokinetic summary (when appropriate)
- Tabulated pharmacokinetic summary (when appropriate)
- Written toxicological summary
- Tabulated toxicological summary

2.5 OVERVIEW OF CLINICAL STUDIES.

Should present a critical analysis of the clinical results included in the clinical summary and in module 5. Include a summary of the clinical development of the vaccine, the design of the pivotal studies, and the decisions related to the clinical studies and their performance, and also an overview of the clinical conclusions and an evaluation of the risks/benefit in relation to the results of the clinical studies and justification of proposed doses should be included. All the data related to efficacy and safety assessed through the development of the vaccine will be presented, as well as any outstanding problems. The data should be presented in a written and tabulated summary in the following order:

INTRODUCTION

TABLE OF CONTENTS

2.5.1 Detailed discussion of product development
2.5.2 Overview of immunogenicity
2.5.4 Overview of efficacy
2.5.5 Overview of safety
2.5.6 Conclusions on risk-benefit balance
2.5.7 Literature References

2.6 NON-CLINICAL SUMMARY.

A summary of the results of the pharmacological, pharmacokinetic, and toxicological tests on animals and/or “in vitro” should be included. An objective written and tabulated summary should be presented in the following order:

2.6.1 Introduction
2.6.2 Written pharmacological summary
2.6.3 Tabulated pharmacological summary
2.6.4 Written pharmacokinetic summary (when appropriate)

2.6.5 Tabulated pharmacokinetic summary (when appropriate)

2.6.6 Written toxicological summary

2.6.7 Tabulated toxicological summary

2.7 CLINICAL SUMMARY.

A critical summary of the results submitted in module 5. This summary should include of all the clinical studies performed. It should also present a synopsis of each study. The summary of clinical information should be in the following order:

INTRODUCTION

TABLE OF CONTENTS

2.7.2 Summary of the clinical immunogenicity studies

2.7.3 Summary of the clinical efficacy studies

2.7.4 Summary of the clinical safety studies

2.7.5 Literature References

MODULE 3

QUALITY INFORMATION (CHEMISTRY, MANUFACTURE AND CONTROL)

3.1 TABLE OF CONTENTS OF MODULE 3.

In accordance with the general plan agreed internationally for registration of vaccines.

3.2 CONTENTS.

Corresponds to the basic principles and requirements of the active ingredient(s) and finished product. This includes the chemical, pharmaceutical, biological data on development, the manufacturing process, certificates of analysis, characterization and properties, quality control, specifications and stability of each of the active ingredients and finished product as indicated below.

3.2. S ACTIVE BIOLOGICAL SUBSTANCE.

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

3.2.S.1 GENERAL INFORMATION, STARTING MATERIALS AND RAW MATERIALS

3.2. S.1.1

Trade and/or non-proprietary name(s) of active(s) ingredient(s). Based on the WHO or Pharmacopoeia requirements, as appropriate.

3.2.S.1.2

Structural formula, molecular formula and relative molecular weight (if applicable). For example, in synthetic vaccines containing polysaccharides or proteins include the schematic amino acid sequence, indicating the glycosylation sites or other modifications and relative molecular mass.

3.2. S.1.3

Description and characterization of active ingredient. Including physicochemical properties and biological activity.

3.2. S.1.4

General description of the starting materials. For each biological starting material used to obtain or extract the active ingredient, include a summary of viral safety of the material:

- 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, determination of foreign agents, stability, controls, and frequency of the tests, definition of the number of passes. 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.

3.2. S.1.5

General description of the raw materials. Considering the raw materials used in the preparation process from which the active ingredient 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.1.6

Analytical certificates signed by the manufacturer and the applicant for licensing.

3.2. S.2 MANUFACTURING PROCESS FOR ACTIVE INGREDIENT.

3.2. S.2.1

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

3.2. S.2.2

Description of manufacturing process. Submit a description of the manufacturing process that includes all the stages. A typical 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 conditions. Where applicable, include the number of passes.

- Flow chart of manufacturing process. Showing all the manufacturing steps, including intermediate processes.

- Description of batch identification system. Identification of the lot in each stage of the process, including when mixtures are made. Also submit information on the manufacturing scale and lot size.
- 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 re-use of membranes and chromatography columns and the respective validation studies.
- Description of conjugation process. Indicate when applicable and/or when a modification of active ingredient is done. Also include information on the origin and quality control of the starting material used to obtain the substance used as protein carrier.
- Stabilization of active ingredient. Description of the steps performed to stabilize the active ingredient, for example, the addition of stabilizers or other procedures, when applicable.
- Reprocessing. Description of the procedures established for reprocessing the active ingredient or any intermediate product; criteria and justification.
- Filling procedure for the active ingredient, in-process controls. Description of the procedure for packaging the active ingredient, process controls, acceptance criteria, type of container closure system, type of seal on the container used to store the active ingredient, storage and transfer conditions, when applicable.

3.2. S.2.3 Material controls

3.2. S.2.4

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

3.2. S.2.5

Validation of manufacturing process. Description of changes. Information on validation procedures and/or evaluation of the manufacturing procedures, including

reprocessing, establishment of critical steps, and criteria for establishing the control limits on the critical steps.

3.2. S.3 CHARACTERIZATION OF ACTIVE BIOLOGICAL SUBSTANCE.

Present data to determine the structure and physicochemical, immunological, and biological characteristics of the active ingredient.

3.2. S.4 QUALITY CONTROL OF ACTIVE BIOLOGICAL SUBSTANCE

3.2. S.4.1 Specifications

3.2. S.4.2 Analytical procedures

3.2. S.4.3 Validation of analytical procedures

3.2. S.4.4 Batch analysis and consistency results

3.2. S.4.5 Justification of specifications

3.2. S.5 REFERENCE STANDARDS OR MATERIALS.

Detailed description of the reference standards or materials used and analysis certificates.

3.2.S.6 PACKAGING/CONTAINER CLOSURE SYSTEM.

Full description of the packaging and container closure system in which the active ingredient 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. When applicable, discuss the types of materials selected with respect to protection of the active ingredient against humidity and light.

3.2. S.7 STABILITY OF ACTIVE INGREDIENT

3.2. S.7.1 PROTOCOL OF STABILITY STUDY, SUMMARY AND CONCLUSIONS.

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

3.2. S.7.2 POST-APPROVAL STABILITY PROGRAM.

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.

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

3.2. S.7.4 STORAGE AND SHIPPING CONDITIONS OF ACTIVE INGREDIENT.

When applicable, describe the equipment used, areas, and buildings (if pertinent) and the shipping and storage conditions.

3.2. S.8 CONSISTENCY OF PRODUCTION OF ACTIVE INGREDIENT.

Summary protocol of the production and control of three consecutive lots of active ingredient, analysis certificates in the event this information is not included in the summary protocol for the finished product, an analysis of the results of these lots in terms of production consistency.

3.2. P FINISHED PRODUCT

3.2. P.1 DESCRIPTION AND COMPOSITION OF FINISHED PRODUCT.

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

3.2. P.2 PHARMACEUTICAL DEVELOPMENT.

Information on the studies performed to establish the dosage form, formulation, manufacturing process, and the container closure system used for final product. The studies described in this

points are different from the routine quality control tests performed in accordance with the product specifications. Include the following aspects:

3.2. P.2.1 ACTIVE INGREDIENT.

Compatibility employed in the manufacturing process. It is also necessary to provide information on the viral safety of the product, when applicable.

3.2. P.3.6 DESCRIPTION OF BATCH IDENTIFICATION SYSTEM.

Define the lot in the stages of filling, lyophilization (if it applies) and packaging.

3.2.P.4 CONTROL OF ADJUVANT, PRESERVATIVE, STABILIZERS AND EXCIPIENTS

3.2. P.4.1 SPE IFICATIONS.

Provide information on the specifications for all the substances employed in the formulation of the finished product that are different from the active ingredient.

3.2. P.4.2 ANALYTICAL PROCEDURES.

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

3.2. P.4.3 VALIDATION OF ANALYTICAL PROCEDURES.

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

3.2. P.4.4 JUSTIFICATION OF SPECIFICATIONS.

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

3.2. P.4.5 SUBSTANCES OF HUMAN OR ANIMAL ORIGIN.

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

3.2.P.4.6 USE OF NEW ADJUVANT, PRESERVATIVES, STABILIZERS AND EXCIPIENTS.

When used for the first time in a vaccine for human use or for a new route of administration, provide all information on the manufacture, characterization, and control, and data supporting safety established in nonclinical and clinical studies in relation to the active ingredient used.

3.2. P.5 CONTROL OF FINISHED PRODUCT

3.2. P.5.1 SPECIFICATIONS.

Indicate the specifications for the finished product

3.2. P.5.2 ANALYTICAL PROCEDURES.

Information on the analytical procedures used for quality control of the finished product. For non Pharmacopeia methods summaries or references are not accepted. Additional information could be requested.

3.2. P.5.3 VALIDATION OF ANALYTICAL PROCEDURES.

Include information on the validation of the analytical procedures for the finished product including experimental data.

3.2. P.5.4 BATCH ANALYSIS AND CONSISTENCY RESULTS.

The production and control protocols for at least three lots of finished product should be submitted and an analysis of the results for those lots in terms of production consistency.

3.2. P.5.5 DETERMINATION AND CHARACTERIZATION OF IMPURITIES.

As applicable, depending on the method used to manufacture the vaccine submitted for licensing.

3.2. P.5.6 JUSTIFICATION OF SPECIFICATIONS.

Provide justification of the specifications proposed for the finished product.

3.2.P.5.7 Analytical certificates signed by manufacturer and applicant for licensing

3.2.P.6 REFERENCE STANDARDS OR MATERIALS.

Provide information on the reference standards and/or materials used in the tests to control the finished product.

3.2.P.7 PACKAGING/CONTAINER CLOSURE SYSTEM

Describe in detail the type and form of container closure system of the finished product, including the materials of which they are made and quality specifications.

3.2. P.8 STABILITY

3.2. P.8.1 PROTOCOL OF STABILITY STUDY, SUMMARY AND CONCLUSIONS.

Submit the stability study that complies with each Ghana's legislation, including the study protocol, specifications, analytical methods, detailed description of the container closure system for the product evaluated, storage conditions (temperature and relative humidity), summary of results for at least three lots of finished product prepared from different lots of active ingredient, conclusions, and proposed validity period. The stability studies should be signed by the professional in charge of the study. It is important to provide additional studies on the stability of the vaccine in intermediate stages in the manufacturing method 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. For Lyophilized vaccines demonstrate the compatibility between the lyophilized product and the diluents.

3.2. P.8.2 POST-APPROVAL STABILITY PROGRAM.

Include the stability program or stability commitment to be carried out once the vaccine is in 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.8.3 STABILITY DATA.

Should include the complete results of each lot evaluated during stability studies.

3.2. P.8.4 DESCRIPTION OF PROCEDURES TO GUARANTEE COLD CHAIN.

Describe in detail the measures used to guarantee adequate temperature and humidity conditions for shipping the finished product from the place of production to the place of final sale, including all the storage and distribution stages and indicating the controls performed in each of the stages. This description should be signed by the professional responsible for it.

3.2. A APPENDIX.

Provide the following information in the appendixes to Module 3:

3.2.A.1 EQUIPMENT AND FACILITIES.

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. Also submit information on all 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 SAFETY EVALUATION OF ADVENTITIOUS AGENTS.

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.

3.3 LITERATURE REFERENCES

MODULE 4

NON CLINICAL INFORMATION

Non-clinical studies should comply with the WHO's Guidelines on Non-clinical Evaluation of Vaccines, WHO Technical Report Series **No. 927, 2005**, or most recent version.

4.1 TABLE OF CONTENTS OF MODULE 4

4.2 REPORT ON STUDIES

4.2.1 PHARMACOLOGY

4.2.1.1 Pharmacodinamic studies (immunogenicity of the vaccine)

4.2.1.2 Pharmacodinamic studies of adjuvant (if applicable)

4.2.2 PHARMACOKINETICS

4.2.2.1 Pharmacokinetics studies. When applicable, depending on the type of vaccine or when new substances are used in the formulation of the product, new routes of administration, or pharmaceutical forms that require the respective pharmacokinetic evaluation.

4.2.3 TOXICOLOGY

4.2.3.1 General toxicology. Information should be presented on:

- Design of study and justification of animal model
- Animal species used, age and size of groups
- Dose, route of administration and size group
- Parameters monitored
- Local tolerance

4.2.3.2 Special toxicology (for vaccines to which it applies). Information should be presented on:

- Special immunological investigations
- Toxicity studies in special populations
- Genotoxicity and carcinogenicity studies, when applicable
- Reproductive toxicity studies for vaccines to be administered to pregnant women or individuals of fertile age

4.2.3.3 Toxicity of new substances used in formulation (new adjuvant, stabilizers, and additives). In the case of new substances incorporated into the formulation (new

adjutants, stabilizers, additives) other routes of administration, and new combined vaccines, submit the corresponding toxicology studies.

4.2.4 SPECIAL CONSIDERATIONS

4.2.4.1 For attenuated vaccines evaluation of possibility of microorganism shedding through natural avenues of excretion should be submitted.

4.3 LITERATURE REFERENCES

MODULE 5

CLINICAL INFORMATION

The clinical studies should follow the WHO's Guidelines on Clinical Evaluation of Vaccines: Regulatory Expectations. WHO Technical Report Series No. 924, 2005, or most recent version, and the FDA's guidelines for Clinical Trials.

GENERAL COMMENTS

Before beginning the clinical studies, it is necessary to have in-depth knowledge of the epidemiology of the pathogens or disease of interest in the study population. This knowledge makes it possible to statistically define the size of the sample required for the studies and to weigh the magnitude of the results for efficacy and safety.

All clinical studies should comply with the international and local standards for good clinical practices.

The clinical studies necessary to evaluate the clinical efficacy of a vaccine that contains one or more new antigens can involve substantial requirements with regard to the size of the population, compared to known and previously evaluated antigens.

It is reasonable to require immunogenicity and safety studies only for vaccines that contain known, widely-used antigens and where safety/reactogenicity/immunogenicity of protection have been well established.

5.1 TABLE OF CONTENTS OF MODULE 5

5.2 CONTENTS: REPORTS OF CLINICAL STUDIES

PHASE I STUDIES.

These are intended to define the safety and reactogenicity of the vaccine and to seek preliminary information on immunogenicity. Dose and route of administration should be evaluated with respect to these parameters. Generally, these studies are conducted on small groups of immune competent healthy adults (50 to 200) who present low risk of being infected by the vaccine or related complications.

PHASE II STUDIES.

After the studies in phase I have been completed or sufficient information is obtained to demonstrate satisfactory results, the phase II studies can begin. The main distinction between the two phases is that the phase II studies involve a large number (200 to 600) of subjects and are usually controlled and randomized. The

main objectives of these studies are to demonstrate the immunogenicity of the active component(s) and safety in the target population (mainly healthy children). The phase II studies should define the optimum dose, the vaccination schedule, and most importantly, safety, prior to beginning phase III

.

PHASE III STUDIES.

The Phase III studies are large scale studies designed to obtain data on the efficacy and safety of the vaccine. These studies are usually carried out in large populations to evaluate the efficacy and safety to the formulation(s) of the immunologically active component(s). Several thousand subjects can be enrolled in these studies (the number will be defined by the end point of the study). Serological data are collected (for at least one immunized population subgroup) with the

idea of establishing a correlation between clinical efficacy and immunogenicity, although this cannot always be established.

- The type of vaccine and other relevant factors (incidence of disease, immunological markers, and safety) will determine the duration of the follow-up on these studies and the number of participants.
- The phase III clinical studies should be performed using at least three lots manufactured on the industrial or production scale to be used routinely (in the majority of countries).

SPECIAL CONSIDERATIONS

Depending on the type of vaccine, apart from the clinical studies on immunogenicity, efficacy, and reactogenicity, it may be necessary to evaluate microorganism shedding in the case of live vaccines, interaction with other vaccines, and interference with maternal antibodies.

ADJUVANT

Evidence and scientific support that justifies the use of adjuvant, when applicable.

COMBINED VACCINES OR VACCINES MADE BY NEW MANUFACTURERS

Submit information on bridging studies performed to ensure the non-inferiority of the vaccine under evaluation compared with the reference vaccine, supporting immunogenicity, reactogenicity, safety, and efficacy, when applicable.

CO-ADMINISTRATION STUDIES WITH OTHER VACCINES

5.3 CLINICAL STUDY REPORTS

5.3.6 PHASE IV STUDIES AND/OR PHARMACOVIGILANCE PLAN (IF APPLICABLE).

Depending on the type of application for registration approval in other countries, or depending on the type of vaccine, a phase IV study protocol or the results of studies that have already been performed will be required. For new vaccines, a pharmacovigilance and a risk management plan depending on the type of vaccine should be presented.

5.4 LITERATURE REFERENCES

All literature references used in the study.

ANNEXURE

ANNEX I

RISK MANAGEMENT PLAN (RMP)

A Risk Management Plan (RMP) is a set of pharmacovigilance activities and interventions designed to identify, characterize, and manage risk relating to a medicine. The plan encompasses the entire life cycle of the product, and has to be periodically updated to reflect new knowledge and understanding of the safety profile of the product. Thus, the applicant is responsible for:

- developing a RMP
- updating the RMP as new safety information emerges
- implementing the activities and interventions outlined in the RMP
- Collecting information and performing an analysis regarding the efficacy of these activities and interventions
- Communicating this information to the GHFDA in a timely manner

The FDA will request that a RMP is submitted before the biological product is registered. Also, the FDA can request a RMP be submitted for a biological product which has already been registered, when a safety issue arises.

A RMP should include, but not limited to the following:

- an overview of the safety profile of the biological product
- a pharmacovigilance plan
- a risk management plan

A RMP should be submitted:

- with an application for a new vaccine
- with an application for paediatric use registration application
- with an application involving a significant change in registration approval (e.g. new dosage form, new route of administration, significant change in indication, including new paediatric indication) unless it has been agreed with the FDA that submission of a RMP is not required
- on the request of the FDA (pre- and post-registration)

- in the initiative of applicant/ marketing Authorization holder when they identify a safety concern at any stage of the life cycle of the vaccine

Applicants should consult the FDA on any questions they may have about their responsibilities relating to this section of the guidelines.

ANNEX II

OUTLINE OF THE EVALUATION OF APPLICATION

The authority in considering an application,

- Shall satisfy itself that there is a need to have the product registered in Ghana
- Shall request the applicant to submit a manufacturer's authorization to register the product.
- May consult with other bodies and experts with knowledge of the product.
- Reserves the right to conduct a Good Manufacture Practice (GMP) audit inspection on the manufacturing facility for the product at a fee prescribed by the Authority.

Where the FDA is satisfied with the representations submitted, the FDA may approve the registration of the medicinal product or if the FDA is still not satisfied, it shall reject the application.

- Where the Authority is satisfied that there is the need to register a product, and all requirements for its registration have been satisfied, it shall do so and issue to the applicant a certificate of registration, subject to such conditions as may be prescribed by the Authority from time to time.
- The registration of a product under these regulation, unless otherwise revoked, shall be valid for a period of 3 (three) years and may be renewed.
- The Authority shall from time to time, publish a notice in the Gazette notifying the registration of a product under these regulations.
- No information given in this application shall be disclosed by the Food and Drugs Authority to a third party, except;
    - With the written consent of the licence holder
    - In accordance with the directive of the Board of Directors of the FDA
    - For the purpose of a legal process under the Public Health Act, 2012 (Act 851)

ANNEX III

SANCTIONS AND PENALTIES

- The Authority shall cancel, suspend or withdraw the registration of a product if:
  - The information on which the product was registered is later found to be false
  - The circumstances under which the product was registered no longer exist
  - Any of the provisions under which the product was registered has been contravened
  - The standard of quality, safety and efficacy as prescribed in the documentation forregistration is not being complied with
  - The premises in which the product or part thereof is manufactured, packaged or stored by or on behalf of the holder of the certificate of registration is unsuitable for the manufacture, package or storage of the product

  Where the registration of the product is suspended, withdrawn or cancelled, the Authority shall cause the withdrawal from circulation of that product and shall accordingly cause the suspension, cancellation or withdrawal to be published in the Gazette.

ANNEX IV:

RELEVANT INFORMATION TO BE INCLUDED IN DOSSIER

In addition to the product registration requirements contained in the application form and this guidance document, please ensure that the information below is included in the dossier submitted for the registration of the biological products.

- Evidence of payment for evaluation and registration (a copy of payment receipt)
- Covering letter (Applicant)
- Covering letter (Local agent)
- Table of Contents

- Application form (Dated, stamped and signed)
- Signed Declaration
- Manufacturing License
- Contract Agreement Documents
- Application Overview (content: section 1)
- Full characterization of the host organism including the relevant genotypic and phenotypic properties
- Certificate of Analysis of Master Cell Bank/Master seed Lot (Protocol and report to qualify MCB/MSL)
- Certificate of Analysis of Working Cell Bank/Working Seed Lot (Protocol and report to qualify WCB/WSL)
- Certificate of Analysis of Starting Raw Materials (cDNA, vector, expression system), (from supplier)
- Certificate of Analysis of Starting Raw Materials (cDNA, vector, expression system), (from manufacturer)
- Certificate of Analysis of Inactive Raw materials (enzymes including; restriction enzymes, phosphatase, polymerase, transcriptase, S1, etc., buffer ingredients, growth media and additives, compressed gases, etc.)
- Complete Drug Master File (DMF) containing development genetics, protein expression Protocols, protein purification protocols, protein identification and characterization formulation, etc.
- Map of empty expression vector/ map of expression construct
- Genetic make-up of empty expression vector and expression system
- Report on genetic make-up of empty expression vector and expression system
- Report on genetic material coding desired biological drug substance (API)
- Relevant genotype and phenotype of host organism

- Report on the choice of host organism
- Report on process validation
- Certificate of Analysis of biological drug substance
- Certificate of Analysis of reference standards
- Protocol and Report of analytical method validation (AMV) for drug substance of biological Medicinal product
- Protocol and Report of analytical method validation (AMV) for finished biological medicinal product
- Analytical Control Procedures
- BMR for finished biological medicinal product (Should be recent and in English language)
- Protocol and report for process validation
- Certificate of Pharmaceutical Product
- Certificate of Analysis of the finished biological product
- Batch release abstract and Batch release document (completed, dated and signed)
- Protocol and report for real time/long term stability studies
- Protocol and report for accelerated stability studies
- Protocol and report for stress stability studies
- Protocol and report on non-clinical and clinical studies
- Protocol and report on animal studies (if applicable)
- Quantity and number of samples received (client service, FDA)
- Program for post-market surveillance/Pharmacovigilance and Risk Management Plan (RMP
- Package Insert

ANNEX V:

RELEVANT GHFDA GUIDANCE DOCUMENTS

- Guidelines for Registration of Biological products
- Guidelines for Safety Monitoring
- Guidelines for conducting clinical trials of allopathic drugs, VACCINES, and medical devices
- Guidelines for requirements for labeling of product