FOOD AND DRUGS AUTHORITY

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Technical Advisory Committee on Safety of Vaccines and Biological Products

GUIDELINES FOR REGISTRATION OF HUMAN VACCINES

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8th January 2024	03	General review of the Guideline in line with the current structure.

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Executive Summary

Guidelines for the registration of human vaccines is intended to ensure that vaccines registered in Ghana meet high safety, efficacy, and quality standards. The process requires manufacturers to submit comprehensive quality, nonclinical and clinical data to the FDA. Vaccines must adhere to Good Manufacturing Practices (GMP) and pass rigorous evaluations for purity, potency, and stability. The Food and Drugs Authority (FDA) review the submissions and conduct GMP inspections of manufacturing facilities as part registration process. Post-market surveillance is mandated to monitor vaccine performance and detect any adverse events on the Ghanaian market. These guidelines ensure public health is protected by guaranteeing the availability of safe and effective vaccines.

1.0 Introduction

The Food and Drugs Authority (FDA) has a role to ensure that vaccines coming onto the market meet the quality, safety, and efficacy standards for clinical use. It should be noted that vaccines differ from chemical drugs because of the biological nature of the source materials (such as those derived from microorganisms), the biological methods used to test them, the lack of a classical pharmacokinetic measurable mode of action and because they are highly complex substances. Some vaccines consist of live microorganisms suitably changed or attenuated to ensure that they no longer produce disease but can still produce a suitable immune response. Special expertise and procedures are needed for their manufacture, control, and regulation.

Before a vaccine is considered for approval, sufficient scientific and clinical evidence must be collected to show that it is safe, efficacious and of suitable quality. This scientific evidence includes results from human clinical trials and for acceptance; it should be evident that the benefits of the vaccine outweigh any risks associated.

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.

When all above is in place, additional mechanisms like risk-based lot release program, assessment of post-market changes, post-market surveillance for compliance verifications as well as investigation of potential health hazards and other violations should be implemented.

Furthermore, regular inspections of manufacturers, packagers/labellers, testing laboratories, importers, distributors and wholesalers of vaccines may be conducted to ensure that they comply with Good Manufacturing Practices (GMP) and Good Distribution Practices (GDP).

The FDA evaluates all data 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 vaccineto be used in humans has been established. The guidelines also provide guidance that ensure that products and manufacturers meet the minimum established regulatory requirements to do business in Ghana.

These guidelines should be read in conjunction with other international guidelines on quality, safety and efficacy of vaccines as cited in this guideline, namely the World Health Organization (WHO), European Medicines Agency (EMA) and International Conference of Harmonization (ICH). The objective of this guideline is to streamline the registration process of vaccines in Ghana for human use.

1.1. Legal Basis

This guideline applies to Marketing Authorisation Applications for human vaccines submitted in accordance with Section 118 of the Public Health Act 851, of 2012.

1.2. Scope

These guidelines are intended to provide general considerations and guidance on content and format for required information for regulatory submission of vaccines regardless of where they were manufactured, whether they are registered in the country of origin or not, for the purpose of marketing authorization in Ghana. The vaccine categories include but not limited to:

(a) Microorganisms or toxins inactivated by chemical or physical means that retain appropriate immunogenic properties;

(b) Living microorganisms that have been attenuated whilst retaining immunogenic properties;
(c) Antigens extracted from microorganisms, secreted by them or produced by recombinant DNA technology; or
(d) Antigens produced by chemical synthesis in vitro including chemically conjugated or modified natural antigen.
(e) Inactivated antigens or toxins with enhanced immunogenicity by addition of adjuvants.
The principles expressed in this document may also apply to combined vaccines that are not explicitly mentioned.Definitions and Abbreviations
For the purposes of these guidelines, the following definitions shall apply:

"**Adjuvant**" means a component that potentiates the immune responses to an antigen and/or modulates it towards the desired immune responses.

"Adverse Events Following Immunization" means any untoward medical occurrence which follows immunization, and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom or disease.

"**Batch (or lot)"** means a defined quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. (Refer to ICH Topic Q 7 Good Manufacturing Practice for Active Pharmaceutical Ingredients)

"**Combination Vaccine"** means a combination vaccine consists of two or more live organisms, inactivated organisms or purified antigens combined either by the manufacturer or mixed immediately before administration.

Country of origin: it corresponds to the country where the legalcertifications of the product are generated.

Drug Substance: the antigenic substances (or compounds thereof) that can induce specific responses in humans against an infectious agent, its antigens or toxins.

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: any product 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 vaccinesubmitted 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 QualityControl and includes laboratory testing when it is considered necessary.

Master Cell Bank (MCB): means an aliquot of a single pool of cells which generally has been prepared from the selected cell clone under defined conditions, dispensed into multiple containers and stored under defined conditions. The MCB is used to derive all working cell banks. The testing performed on a new MCB (from a previous initial cell clone, MCB or WCB) should be the same as for the MCB unless justified.

"Manufacturer" means a natural or legal person with responsibility for manufacturing of a medicinal product or Immunogenic substance.

Product development: all studies show that the dose, formulation, manufacturing process and packaging system, as well as the microbiological properties, are appropriate for the proposed purpose.

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 asmicroorganisms, organs and tissues of plant or animal origin, including cellsor 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.

"Vaccines" are a heterogeneous class of medicinal products containing immunogenic substances capable of inducing specific, active and protective host immunity against infectious disease. (Refer to Guidelines on Stability Evaluation of Vaccines).

"Working Cell Bank (WCB)" is prepared from aliquots of a homogeneous suspension of cells obtained from culturing the MCB under defined culture conditions

3.0 Requirements

3.1 Administrative Requirement and Product Information

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

Qualified person responsible for the product release (under the country'slegislation). Submit a document issued by the manufacturer on the individualsresponsible 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 Organization (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 artwork for primary and secondary labels These should be submitted for approval by FDA prior to submission ofapplication, 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 ofthe 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.

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

Four (4) copies of the labels and leaflet inserts, conforming to existinglabelling 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 their shelf-life remaining. This notwithstanding, products with shelf-life less than 24months shall have at least 80% of their 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)

3.3 New Registration

- An application 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 apharmacist in Ghana.

Applications shall be accompanied by:

- A duly signed covering letter
- Two (2) soft copies (preferably on 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 not hand written. These guidelines should be read in conjunction with other guidelines on the Authority's websitewww.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 (ACT851, 2012, Section 112).

The original certificate of analysis for the batch of the vaccine being submitted for registration and issued by a recognized public analystshall be submitted.

The Authority shall approve the application before any importation of thevaccine is made into the country other than those used as samples for the purpose of this application.

3.4 Registration Variation

An application for the variation of marketing authorization of a vaccine shall be made to the Authority. This variation shall be approved by the Authority where applicable 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/VVC/BPU/GL-VAR/2015/07) for the necessary documentation
- Samples as applicable 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 as applicable 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.

Note: In order to ensure the continued effectiveness of certain authorized vaccines including those used in pandemics, it may be necessary to modify the authorized active ingredients (antigens) so as to protect against new or multiple variant strain(s). Such changes, which include the replacement or addition of a serotype, strain, antigen or coding sequence or combination of serotypes, strains, antigens, or coding sequences, are considered as variations to the marketing authorization. For these vaccines, Marketing Authorization Holders are required to monitor the circulating strains of the antigens and make appropriate modifications as variations to the marketing authorization to the FDA in line with FDA's guidelines for reporting variations. The FDA may also inform marketing Authorization Holders to monitor circulating strains of authorized vaccines on a case-by-case basis.

3.5 Registration Renewal

- An application for the registration renewal of a biological product shall bemade three (3) months before expiration of the last registration.

The application shall be accompanied by:

- A covering letter
- Samples of the biological product in the final package as specified in the Authority's samples schedule
- Non-refundable application fee as specified in Authority'sapproved fees schedule.
- Certificate of Analysis (CoA) of the finished product
- Current copies of Summary of Products Characteristics (SmPC) and Patient Information Leaflet (PIL) in the format available on FDA's website.
- 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.
- Long-term/Real-time, real condition stability studies for three production batches (Protocol and Report).
- Risk management plan/Periodic Benefit Risk Evaluation Report (refer to www.fdaghana.gov.gh) as applicable.

- The registration renewal 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.

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 test should be presented as actual data not generally as “Complies, 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 pathogenicity 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 characteristicsof specific antibodies used in the immunochemical or serological assays should also be included.

Imported vaccines

Only registered vaccines should be imported into the country and for such registered products, a permit application should be submitted.

Importation of registered vaccine shall be complied with the requirements per FDA Lot Release Guidelines. The above not withstanding permits may applied for the following situations:

- Application for importation of registration samples. Please note that only required samples per the FDA sample schedule (refer to FDA website for sample schedule) shall be processed.
- Named patient prescription where the vaccines to be imported for use is not available on the Ghanaian market.

Issuance of import permit for registration samples of the vaccine shall not guarantee automatic registration of the product.

Note that import permit applications submitted through the appropriate electronic platform shall be processed only if the necessary release documents have been submitted.

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.

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.

Requirements for registration/marketing authorization reliance

Regarding products that have already been approved by a well-resourced NRA, the FDA may activate its 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 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 institution or the WHO. The FDA may also rely on published assessment reports from well-resourced NRAs as part of the reliance evaluation process.

Vaccine and biological products Lot Release: The FDA shall request an applicant or manufacturer to provide product-specific reagents and working reference materials, as needed for the purposes of lot release of vaccines.

Appealing a rejected registration application

The FDA makes the final decision on an application made under 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
Accra

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.

4.0 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.

RECOMMENDED FORMAT OF THE DOSSIER SUBMISSION

4.1 Module 1 Administrative – Legal Information

1.1 TABLE OF CONTENTS (MODULES 1 TO 5)

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. Theprofessional 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/Local 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 registered 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 Officials 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 registration 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 registration 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 (GMP) of all manufacturers 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.
- Trademark certificate (optional)
- Batch release certificate issued by NRA (imported product). Refers to the lot release certificate issued by the regulatory authority or National Control Laboratory 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, 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

1.3.1.0 The SmPC is the basis of information for healthcare professionals on how to use the vaccine safely and effectively and should be submitted as part of registration.

1.3.2.0 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.

1.3.3.0 Samples

1.3.3.1 Samples of finished product (in accordance with FDA's Sample Schedule). 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.

1.4.0 LIST OF COUNTRIES WHERE THE PRODUCT HAS BEEN REGISTERED 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 registeredin other countries, attach the summary of the conditions under which the market authorization was granted by that regulatory authority.

1.5.0 INFORMATION REGARDING EXPERTS.

A declaration should be sent signed by each of the experts who performed theproduct evaluation from the standpoint of quality, nonclinical studies andclinical 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.

1.6.0 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 beincluded on the product label.

4.2 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 othermodules 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 criticl 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 efficacyand 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

2.5.3 Overview of efficacy

2.5.4 Overview of safety

2.5.5 Conclusions on risk-benefit balance

2.5.6 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 followingorder:

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 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

4.3 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 activeingredients and finished product as indicated below.

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 theWHO 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 includethe 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 (s. Including physicochemicalproperties 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 cellsremain 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 submita 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 step.

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 eachof the components, active ingredient(s), adjuvant, preservatives, stabilizers, andexcipients, stating the function of each of them. For lyophilized products, also includea 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 SPECIFICATIONS.

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 thestudy protocol, specifications, analytical methods, detailed description of thecontainer closure system for the product evaluated, storage conditions (temperatureand relative humidity), summary of results for at least three lots of finished productprepared from different lots of active ingredient, conclusions, and proposed validityperiod. The stability studies should be signed by the professional in charge of thestudy. It is important to provide additional studies on the stability of the vaccine in intermediate stages in the manufacturing method that require different temperaturesfrom the storage temperature, studies of challenge temperatures, photosensitivity orother specifications, depending on the type of vaccine, evaluated for at least three lots. For Lyophilized vaccines demonstrate the compatibility between the lyophilizedproduct 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 eachyear 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 adjacentareas 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 asthe 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 relationto adventitious agents of both viral and non-viral origin should be submitted.

3.2.R REGIONAL INFORMATION

3.3 LITERATURE REFERENCES

Note: For quality requirements for specific vaccines, Applicant are required to refer to WHO Vaccine-specific standardization website for the current WHO Technical Report Series (TRS) that pertains to that vaccine and ensure adherence to these requirements. Applicants are also required to refer and comply to specific quality requirements for vaccines or biotechnological products provided by the International Council for Harmonization as may be applicable

In-cases where there is no WHO TRS for specific-vaccines, Applicants are required to comply with quality requirements for specific vaccines published by FDA reference institutions including the European Medicine Agency, United States Food and Drugs Administration (USFDA).

4.4 Module 4 NON-CLINICAL INFORMATION

Non-clinical studies should comply with the most recent version of the WHO's Guidelines on Non-clinical Evaluation of Vaccines; current scientific knowledge on the non clinical studies of vaccines and any other internationally recognised guidelines for non clinical studies on vaccines.

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. 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 adjuvants, 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

Note: For nonclinical requirements for specific vaccines, Applicant are required to refer to WHO Vaccine-specific standardization website for the current WHO Technical Report Series (TRS) that pertains to that vaccine and ensure adherence to these requirements. Applicants are also required to refer and comply to specific nonclinical requirements for vaccines or biotechnological products provided by the International Council for Harmonization as may be applicable.

In-cases where there is no WHO TRS for specific-vaccines, Applicants are required to comply with nonclinical requirements for specific vaccines published by FDA reference institutions including the European Medicine Agency, United States Food and Drugs Administration (USFDA)

4.5 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 regardto 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.

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 pe 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 Il studies can begin. The main distinction between the two phases is that the phase ll 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 components) and safety in the target population (mainly healthy children). The phase Il studies should define the optimum dose, the vaccination schedule, and most importantly, safety, prior to beginning phase Ill

PHASE III STUDIES.

The Phase Ill 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 components). 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 Ill 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).

THE MODULE 5 OF THE APPLICATION SHOULD INCLUDE AS FOLLOWING CONTENT:

5.5.1 Table of Contents of Module 5

5.5.2 Tabular Listing of All Clinical Studies

5.5.3 Clinical Study Reports

5.5.3.1 Reports of Biopharmaceutic Studies

5.5.3.1.1 Bioavailability (BA) Study Reports

5.5.3.1.2 Comparative BA and Bioequivalence (BE) Study Reports

5.5.3.1.3 In Vitro – In Vivo Correlation Study Reports

5.5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

5.5.3.2 Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials

5.5.3.2.1 Plasma Protein Binding Study Reports

5.5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies

5.5.3.2.3 Reports of Studies Using Other Human Biomaterials

5.5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports

5.5.3.3.2 Patient PK and Initial Tolerability Study Reports

5.5.3.3.3 Intrinsic Factor PK Study Reports

5.5.3.3.4 Extrinsic Factor PK Study Reports

5.5.3.3.5 Population PK Study Reports

5.5.3.4 Reports of Human Pharmacodynamic (PD) Studies

5.5.3.4.1 Healthy Subject PD and PK/PD Study Reports

5.5.3.4.2 Patient PD and PK/PD Study Reports

5.5.3.5 Reports of Efficacy and Safety Studies

5.5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

5.5.3.5.2 Study Reports of Uncontrolled Clinical Studies

5.5.3.5.3 Reports of Analyses of Data from More than One Study

5.5.3.5.4 Other Study Reports

5.5.3.6 Reports of Post-Marketing Experience

5.5.3.7 Case Report Forms and Individual Patient Listings

5.5.3.8 Literature References

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.

Note: For clinical requirements for specific vaccines, Applicant are required to refer to WHO Vaccine-specific standardization website for the current WHO Technical Report Series (TRS) that pertains to that vaccine and ensure adherence to these requirements. Applicants are also required to refer and comply to specific clinical requirements for vaccines or biotechnological products provided by the International Council for Harmonization as may be applicable.

In-cases where there are no WHO TRS for specific-vaccines, Applicants are required to comply with clinical requirements for specific vaccines published by FDA reference institutions including the European Medicine Agency, United States Food and Drugs Administration (USFDA).

ANNEXURES

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 ofthese 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 productis 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 refer to FDA Guidelines for Safety Monitoring of Medicinal Products in Ghana for the format and content of the Risk Management Plans. Applicants should consult the FDA on any questions they may have about their responsibilities relating to this section of the guideline

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 defer or 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 this regulation, unless otherwise revoked, shall be valid for a period up to 5 (five) years and may be renewed. The FDA shall process new registration applications in 6 months (working days), registration renewal applications in 2 months (working days) or as per the current timelines published on the FDA website.

- 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

CRITERIA AND CONDITIONS FOR GRANTING CONDITIONAL MARKETING AUTHORIZATION

The FDA may grant a conditional marketing authorisation for a vaccine if it finds that all of the following criteria are met the benefit-risk balance of the medicine is positive;
it is likely that the applicant will be able to provide comprehensive data post-authorization.
the benefit of the medicine's immediate availability to patients is greater than the risk inherent in the fact that additional data are still required.

Conditional marketing authorisations are valid for one year. Once a conditional marketing authorization has been granted, the Marketing Authorization Holder must fulfil specific obligations within defined timelines as may be given by the FDA.
These obligations could include completing ongoing or new studies or
collecting additional data to confirm the medicine's benefit-risk balance remains positive.
FDA can also take regulatory action if a Marketing Authorization Holder does not
comply with the imposed obligations.

The marketing authorization can be converted into a standard marketing
authorization once the Marketing Authorization Holder fulfils the obligations previously imposed and the complete data confirm that the vaccines benefits continue to outweigh its risks.

ANNEX IV

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 for registration 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 V

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 (Localagent)
- Table of Contents

- Application form(Dated, stamped andsigned)
- 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 toqualify MCB/MSL)
- Certificate of Analysis of Working Cell Bank/Working Seed Lot (Protocol and report toqualify 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 hostorganism
- 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 ofbiological Medicinal product

- Protocol and Report of analytical method validation (AMV) for finished biologicalmedicinal 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 stabilitystudies
- Protocol and report for accelerated stability studies
- Protocol and report for stress stability studies
- Protocol and report on non-clinical and clinicalstudies
- 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 VI

RELEVANT GHFDA GUIDANCE DOCUMENTS

- Guidelines for Registration of Biological products
- Guidelines for Safety Monitoring of Medicinal Products in Ghana
- Guidelines for conducting clinical trials of allopathic drugs, vaccine, and medical devices
- Guidelines for requirements for labeling of drugs
- Template Summary of Product Characteristics
- Template for Labelling