FOOD AND DRUGS AUTHORITY

GUIDELINES FOR REGISTRATION OF BIOLOGICAL PRODUCTS IN GHANA

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FOREWORD

The Ghana Public Health Act 851 of 2012 requires that biological products, including vaccines intended to be marketed in Ghana meet the acceptable standards of quality, safety and efficacy and at the same time be assessed to have been produced in facilities that comply with current Good Manufacturing Practices (cGMP).

This document is intended to provide guidance to applicants for the preparation of submissions according to the requirements for registering biological products in Ghana.

The Ghana Food and Drugs Authority (FDA) register biological products before they are retailed in Ghana and monitor the products once they are on the market. FDA will also assess the suitability of the biological products for export from Ghana.

Submission of satisfactory information on quality, safety and efficacy of biological products will assist the FDA to assess the suitability of the product for its intended use in Ghana.

CONTENTS

1.0. INTRODUCTION

These guidelines describe the data requirements of an application to register a biological product, and the format in which dossiers should be presented in support of the application.

These guidelines should be read in conjunction with other guidelines on the Ghana Food and Drugs Authority (FDA) website <www.fdaghana.gov.gh>. Those documents provide specific guidance on the batch release requirements.

The FDA 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).

1.1. Scope

In pursuance of Section 118 of the Public Health Act 2012, Act 851, these Guidelines are hereby made to provide guidance to applicants on the procedure for registering a Biological Product in Ghana. Applicants are encouraged to familiarize themselves with this document and the above law before completing the registration form.

1.2. Definition of Terms

In these guidelines, unless the context otherwise states:

- **Biological products** means items derived from living organisms (ranging from normal or genetically modified microorganisms to fluids, tissues and cells derived from various animal and human sources) or containing living organisms that are used to;
  - Treat or prevent diseases or manage injury
  - Diagnose medical condition
  - Alter the physiological processes
  - Test the susceptibility to diseases

Such items include;

  - Products of genetically modified organisms (e.g. insulin etc.)
  - Traditional vaccines (bacterial, viral, combination etc.)
  - Immunotherapy products (e.g. cell based tumour vaccines, human cellular vaccines etc.)
  - Peptides and Polypeptides (e.g. insulin, cytokine etc.)
  - Monoclonal antibodies
  - Other human cell based products (e.g.. fibroblast, epithelial cells, chondrocytes)

- **Authority** means Food and Drugs Authority

- **Products** means biological product

- **Applicant** means the product owner or license holder. Representatives of license holders may not hold themselves as applicants unless they own the product.

- **Variation** means a change in the indication(s), dosage recommendation (s), drugs classification and / or patients group(s) for a previously registered biological product been marketed under the same name in Ghana.

- A variation also includes, but not limited to, a change in the product name, site of manufacture and / or source of ingredients.

- **Vaccines** means a heterogeneous class of medicinal products containing immunogenic substances capable of inducing specific, active and protective host immunity against infectious disease.

- **Traditional vaccines** in the context of the expedited review procedure means Diphtheria and Tetanus toxoids and (whole cell) Pertussis vaccine (DTP), Bacille Calmette-Guerin (BCG), Oral Poliovirus Vaccines (OPV), products containing Diphtheria and Tetanus toxoids (DT/Td/TT), Measles, Yellow fever, Hepatitis B, and/or *Haemophilus Influenzae* type b conjugated (Hib) vaccines.

- **Combined vaccine** means vaccine that consists of two or more antigens, combined by the manufacturer at the final formulation stage or mixed immediately before administration. Such vaccines are intended to protect against more than one disease, or against one disease caused by different strains or serotypes of the same organism.

- **Conjugated vaccine** means a vaccine produced by covalently binding an antigen to a carrier protein with the intention of improving the immunogenicity of the attached antigen. This technique is most often applied to bacterial polysaccharides for the prevention of invasive bacterial disease.

- **Adjuvant** means substance which when given in combination with an antigen augments the immune response to that antigen.

- **Vaccination schedule** means the basic vaccination schedule and revaccination schedule combined.

- **Re-vaccination schedule** means one or more administrations of a vaccine used to maintain the initial protective effects induced by the basic vaccination schedule

- **Manufacturer** means any person involved in any stage of the manufacturing process, including any person involved in packaging and labelling, sterilising and testing, up to and including release for supply.

- **Master seed lot (MSL)** means a homogenous suspension of the original cells or organisms on which production is based and aliquot into individual containers for storage.

- For genetically modified products, the cells in the MSL are normally already transformed by the expression vector containing the desired gene. In some cases, the MSL for the expression vector and MSL for host cells may be distinct.

- **Working seed lot (WSL)** means a homogenous suspension of cells or organisms derived from the MSL under defined conditions and aliquot into individual containers for storage.

The WSL is used at a defined passage level for routine production. Containers of MSL and WSL, once removed from storage, must not be returned to the seed lot stock.

- **Batch (final lot)** means collection of closed, final containers or other final dosage units that are expected to be homogenous and equivalent with respect to risk of contamination during filling or preparation of the final product. Preparation is from the same final bulk lot of the biological product, freeze-dried together (if applicable) and closed in one continuous working session.

- **Stability of vaccines** means the ability of a vaccine to retain its chemical, physical, microbiological and biological properties within specified limits throughout its shelf-life.

- **Stability tests** means a series of tests designed to obtain information on the stability of a vaccine in order to define its shelf-life and utilization period under specified packaging and storage conditions.

- **Accelerated stability studies** means studies designed to determine the rate of change of vaccine properties over time as a consequence of the exposure to temperatures higher than those recommended for storage. These studies may provide useful support data for establishing the shelf-life or release specifications but should not be used to forecast real time real condition stability of a vaccine. They could also provide preliminary information on the vaccine stability at early developmental stages and assist in assessing stability profile of a vaccine after manufacturing changes.

- **Stress Testing** means studies performed to determine the impact of extreme environmental factors such as light and extreme temperature. These studies are not usually performed as part of a stability program, but are used instead to establish protective packaging and container conditions, and to support exclusionary labelling.

- **Supporting stability data** means supplementary data, such as stability data on small-scale batches, related formulations, and products presented in containers other than those proposed for marketing, and scientific rationales that support the analytical procedures, the proposed re-test period or the shelf-life and storage conditions.

- **Storage period** means time period during which an intermediate may be held under appropriate storage conditions.

- **Shelf-life** means the period of time during which a product, if stored correctly, is expected to comply with the specification as determined by stability studies on a number of batches of the product. The shelf-life is used to establish the expiry date of each batch. Shelf-life is used for the final product; storage period is used for the intermediates. “Shelf-life specifications” are those specifications that should be met throughout the shelf-life of the product (should not be confused with “release specification”).

- **Expiry date** means the date given on the individual container (usually on the label) of a final biological product up to and including which, the product is expected to remain within specifications, if stored as recommended. It is established for each batch by adding

the shelf-life period to the date of manufacturing or the starting date of the last potency test.

- **Clinical trial or study** means a scientific investigation to assess efficacy and/or safety of a product under field conditions in a subjects and using the product in accordance with the label.

- **Residual pathogenicity** means the potential of viruses or bacteria which have been attenuated for specific route of administration to retain different levels of pathogenicity.

- **Overdose** means 2× the maximum concentration but may be as high as 10x in the case of live biological. Refer to relevant pharmacopoeia monographs where applicable.

- **Finished product** means the formulated product, in its final dosage form and held in the final sealed container and packaging in a form that is intended to be released for supply.

2.0. REQUIREMENTS

2.1. 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.

- **Document confirming the Senior Executive Officer / Senior Medical or Scientific Officer responsible for the product** (under the country's legislation). Submit a document issued by the manufacturer of the biological product giving information on the individuals responsible for the product. 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 biological product**
  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.

2.2. SPECIFIC REQUIREMENTS

- The presentation of the product shall not have any resemblance in spelling and pronunciation of name, or packaging to another product, that has been previously registered by the Authority.

- All samples submitted should conform to existing labelling regulations as specified in page 15 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)

- Verifiable evidence shall be provided and an undertaking made by the applicant to the effect that the patent of the innovator product has expired.

2.3. Other requirements

2.3.1. New Registration

- An applicant for the registration of a biological product, 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
    - One(1) hard copy and one (1) soft copy of completed application forms
    - 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 and/or bioequivalence 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 biological product 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 biological product is made into the country other than those used as samples for the purpose of this application.

2.3.2. Registration Variation

- An application for the variation of registration of a product 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.
    - 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.

2.3.3. Re-Registration

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

- The application shall be accompanied by:
    - A covering letter
    - Supporting documentation for any variations since the biological product was last registered.
    - 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's approved fees schedule.
    - Certificate of Analysis (CoA) of the finished product
    - 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)
    - Method of analysis (Protocol and Report)
    - Analytical Method Validation (Protocol and Report)
    - Batch release documents.
    - Reference Standard/ Reference Product
    - Certificate of Analysis of the reference standard/Reference Product

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

- 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.

2.4. Imported biological products

Applicant should obtain clearance from the FDA prior to the importation of biological products for either retail or registration.

Issuance of import permit for registration samples (biological product) shall no guarantee automatic registration of the product.

Subsequent importation of biological products 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).

2.5. 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.

3.0. 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.

SECTION I APPLICATION FORM AND OVERVIEW

Application form

Refer to FDA website and Appendix 1of this document

Overview

The purpose of the Overview section of the combined Application Form and Overview is to provide a brief outline of the application. The Overview is intended to lead reviewers through the application. The Overview may contain other general information on the product, and a summary of all data in the application.

If an applicant considers that certain data are not required, a statement to that effect must be provided under the appropriate heading, together with scientific argument for not including the data.

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 product is intended to control.

A summary of the detailed information on the product characteristics must also be provided. The information must include the immunological properties and the clinical particulars of the product.

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.

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.

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 section 1 of the application.

In all cases the details of any current or previous application or approvals for this formulation overseas must be provided.

SECTION 2 CHEMISTRY AND MANUFACTURE

GMP status of the manufacturing facility

Applicants must provide evidence that the product is manufactured to a standard comparable to the World Health Organization current Good Manufacturing Practices. For local manufacturers, compliance is by provision of an appropriate FDA Manufacturer's Licence. For products manufactured abroad, applicants must supply evidence of compliance with good manufacturing practice (GMP):

- if manufacture takes place in another country whose GMP program is recognised by the FDA, the evidence required is a current and acceptable certificate of GMP compliance, a licence and/or an audit report from the national regulatory authority.
- if manufacture takes place in a country whose regulatory program is not recognised by the FDA , the acceptable evidence of GMP compliance might include:
    - a current and acceptable certificate of GMP from a regulatory authority recognised by the FDA.
    - a satisfactory audit report by an auditor from a regulatory authority recognised by the FDA, confirming that the premises comply with a GMP Code recognised by the FDA as comparable to the relevant WHO GMP Code.

- a satisfactory audit report by the FDA -authorised GMP inspectors, confirming that the premises comply with the WHO cGMP. All fees incurred for such an audit must be met by the applicant.

Formulation/composition of product

This information is best presented in a table:

- Active constituent(s): maximum and minimum release titres and end of shelf-life titre must be provided
- Adjuvant(s)
- Excipients: including diluents, preservatives, stabilisers, emulsifiers, colouring matter, markers
- Reference to standards where applicable
- Function of each constituent
- Quantity of each constituent in the formulation: this must be expressed in appropriate units.

Containers

The specifications for the immediate container and stoppers/closures (including acceptable tolerances) must be supplied.

The material used for the immediate container must be shown to be compatible with the type of product. The choice of material should take into consideration the potential for toxicity.

The method of closure and opening must be specified.

Summary of product characteristics and product labelling

Summary of the characteristics of the product.

A summary of the characteristics of the biological product 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 biological 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

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

Primary package label
Submit the label proposed for the biological product'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
- Content/volume
- Volume/dose
- Number of doses per vial (for multi-dose presentations)
- Route of administration
- Storage temperature (if the size of the package so permits)
- Warnings
- Lot number
- Expiry date
- Manufacturer
- Registration number in country of origin

Secondary Package Label
Include the text proposed for the biological product's secondary packaging which should provide the following information as a minimum:

- Proprietary, commercial or trade name
- Non-proprietary name or common name
- Dosage form
- Concentration ,potency
- Content/Volume
- Volume/dose
- Number of doses per vial (for multi-dose presentations)
- Composition
- Excipients
- Product storage
- Route of administration
- Instructions for preparation
- Mode of use
- Warnings (for hospital use only, keep out of reach and sight of children, and any warning specific to the product)
- Distribution level
- Identification marks (where applicable)
- lot number
- Date of manufacture
- 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 from country of origin

Package inserts
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
- Content/Volume
- Volume/dose
- Number of doses per vial (for multi-dose presentations)
- Composition
- Excipients
- Cell substrate
- Route of administration
- Indications
- Immunization schedule (where applicable)
- Proper use
- Precautions
- Warnings
- Adverse events (allegedly associated with vaccination and immunization)
- Contraindications
- Use during pregnancy and breast feeding
- Storage conditions
- Name and address of the manufacturer of the finished product
- Name and address of the company responsible for packaging
- Name and address of the local agent
- Date of publication review

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

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

Manufacturing process of the final product

A flow chart of the manufacturing process must be provided, showing each step from production of the active constituent to formulation of the final product in final containers, including any critical in-process control testing steps. The manufacturing process must be validated and the validation study protocol and report provided.

Applicants should also present a detailed description of each process step in the flow chart,

e.g. amplification/culture, harvesting, purification, inactivation procedures, blending, adjuvanting, bulk antigen storage, filling, lyophilization, as relevant.

Production, control and testing of starting materials

Starting materials means all components used in the production of the biological product. Official monograph requirements must apply to all substances in the product. References to other compendia standards will be considered on their merits.

Documentation from suppliers, such as certificates of analysis and/or raw material specifications, must be provided in an appendix to this part of the application dossier.

Raw materials

Specifications and functions of all raw materials must be provided. If biological raw materials of animal origin are used, the manufacturer's specification should be provided. Where appropriate, the applicant should indicate the methods used to determine that starting materials of biological origin are free from contaminants.
Materials from defined and reliable sources should be used. The specification should note the manufacturer(s) and origin of the raw material.

Note: All raw materials should be accompanied by a comprehensive DMF.

Starting materials of biological or non-biological source listed in a pharmacopoeia

Note: Biological sources may include but not limited to the following; Animal sources, virus sources, Microbial cellular sources, Animal cells (primary cells - cell lines)

Applicants must provide:

- the name and code identifying the starting material
- title of monograph, year of publication, preferably together with a copy of the monograph
- certificate(s) of analysis

Starting materials of biological and non-biological origin not listed in a pharmacopoeia

Applicants must provide:

- the name(s) of the starting material (trade name, scientific synonyms)
- description and function of the starting material
- material specifications (identification and purity)
- controls and tests performed on the starting material and/or certificate(s) of analysis

Evidence that biological materials of animal origin used in the manufacture of the master seed are free from agents which cause transmissible diseases must be provided.

Genetically modified starting materials

The following information is required on all genetically engineered starting materials;

Source materials

- gene of interest, name, origin, isolation, sequence analysis

Construction of expression vector

- name, origin, replicon function, regulator elements
- genes for and method of selection
- mode of introduction into producer strain
- constitutive or controlled expression
- cloning and fusion (if relevant)

Description of producer strain or cell line

- name, origin, identification
- potential microbial and/or viral contaminants

Genetic stability

- construct stability
- stability up to and beyond the maximum passage level used for full-scale production
- occurrence of the vector inside the cell (extra chromosomal or integrated)
- copy number
- amplification of gene construct

Master seed organism

Whenever possible, biological production should be based on a seed lot system and on established cell banks. Each master seed lot must be assigned a specific code description for identification purposes.

For production of antisera and biological where production is carried out in animals, the origin, general health and immune status of the producing animals must be verified. Defined pools of source materials must be used.

A record of the origin, date of isolation, storage conditions and passage history of all seed materials including purification and characterisation procedures and substrates used, must be provided.

Characterisation of the micro-organism must include as a minimum:

- the genus and species
- Strain/serotype

Information on the biological characteristics of the master seed must include information on growth characteristics and environmental distribution.

Studies and tests carried out to demonstrate purity, identity, safety/pathogenicity, and immunogenicity of the master seed lot must be provided. A brief description should be provided of the methods of identifying each strain by biochemical, serological and morphological characteristics and distinguishing it as far as possible from related strains.
The method of determining the purity of the strain must be described.
Applicants must also demonstrate that the master seed is free from extraneous agents. Tests to demonstrate that the master seed lot is pure and free from extraneous agents must be performed as per official monographs, where monograph exist. For live attenuated biological products, proof of the genetic and phenotypic stability of the attenuation characteristics of the seed must be provided.
The minimum and maximum number of passage levels from master seed to production level

must be specified and should not exceed five unless justified by data. The methods, substrates used, testing and storage of seed lots and seed passages must be specified and appropriately documented.
The applicant must demonstrate that the characteristics of the seed material (e.g. dissociation or antigenicity) are not changed by these subcultures. The conditions under which each seed lot is stored must be documented.

A release specification of the master seed organism must be provided.

Working seed organism
The method of preparation and description of the working seed lot must be provided.
Description must include the range of passage levels to be used for production, controls applied, tests carried out on working seed lot and storage conditions.
A release specification for the working seed organism must be provided.
Cell substrate/production medium
There are essentially three classes of cell substrate/production medium:

- live animal culture, e.g. specific pathogen-free (SPF) eggs, chickens, cattle
- tissue culture (continuous cell lines or primary cells)
- microbiological media

If cell substrate/production medium consists of SPF eggs, primary SPF chicken cells or SPF chickens, compliance with official reference monographs must be demonstrated.
The following information must also be provided:

- the source of SPF eggs or chickens or other animals
- SPF status of source flock/herd
- history
- test monitoring procedures and specification
- Disease prevention protocols, e.g. isolation, vaccination.
- Disease/agent monitoring procedures and testing specification

If cell substrate/production medium consists of tissue culture substrates (continuous cell lines), the following information must be provided:

- source of the master cell seed
- treatment of the master cell seed since origin
- seed lot system
- designation/identification of master cell seed
- Master cell seed testing method and results to demonstrate sterility, freedom from extraneous agents and freedom from specific adventitious virus contamination.
- FDA import permit where appropriate
- proof of freedom from Mycoplasma (where applicable)
- evidence that master cell seed tests comply with official monographs (Where applicable)

If the cell substrate/production medium consists of microbiological media the following information must be provided:

- name of the medium and composition
- raw material specifications including any tests required for freedom from specific agents such as prion agents of transmissible spongiform encephalopathy.
- FDA import permits where appropriate

- method of preparation and sterilisation should be described under the heading "Media Preparation"

Full details of the cell substrate/production medium must be provided for products where guidelines are yet to be provided.

End of Production Cells (EPC)

For r-DNA derive biological substances, a detailed description of the characterization of the EPC that demonstrates that the biological production system is consistent during growth shall be provided. The results of the analysis of the EPC for phenotypic or genotypic markers to confirm identity and purity shall be included. This section should also contain the results of test supporting the freedom of the EPC from contamination by adventitious agents.

The results of restriction enzyme analysis of the gene constructs in the EPC shall be submitted. Detailed information on the characterization and testing of banked cell substrates shall be submitted. This shall include the results of testing to confirm the identity, purity and suitability of the cell substrate for manufacturing use.

Media preparation

The methods of preparation and sterilisation of all media used in such a way that they become ingredients of the product must be provided in detail, including the controls applied, the testing carried out and the certificates of analysis of ready-to-use media.

In-process control tests during production

All critical analytical test procedures must be described in sufficient detail to enable the procedures to be assessed. Procedures must be validated where appropriate and the results of validation studies on all key procedures as identified by the manufacturer must be provided.

Current pharmacopoeial monographs must be used, where applicable. Copies of the pharmacopoeial monographs, specifications and certificates should be given in an appendix to this part of the application dossier.

With a view to verifying the consistency of the production process and the final product, a flowchart of the production process showing the stages at which critical in-process control tests are carried out should be provided. This may be cross-referenced to the section headed 'Manufacturing process of the final product' if that contains the flowchart.

Applicants must provide information on critical tests performed for each control stage, as follows:

- title and company test code
- timing and frequency
- function of test
- a brief description of the test (a more detailed description should be given as appendix to Section 2 with details and results of the validation studies which should include data on propagation, harvest, inactivation, purification, and microbiology as appropriate). The detailed description should contain sufficient information to enable the FDA to assess the adequacy of the test method and (if

applicable) whether it is consistent with the cited monograph. A copy of the test procedure should be provided as detailed description.

Only details of tests which are considered critical to allow the manufacturing process to continue to the next stage should be provided. The FDA reserves the right to request additional information.

The assay methodology for detoxified or inactivated biological products must be provided in detail and the limit of detection specified. This may be cross-referenced to the section headed 'Manufacturing process of the final product' if that contains the assay methodology.

Each pilot production batch must be shown to have been appropriately detoxified or inactivated using relevant test standards wherever available. Kinetics of inactivation or detoxification must be provided.

A detailed description of the impurity profile of the biological product should be provided. The identity and quantity of the impurity should be stated along with the analytical protocol used to generate the data (i.e. gel migration profiles, elution profiles, etc.). Impurities that should be characterized and quantified include the following; biological product related impurities (e.g. variants or alteration of protein products generated during production or storage, process related impurities (e.g. process reagents, media component, cell substrate proteins and nucleic acid etc.).

Reference Standards

A detailed protocol of the preparation, characterization, and stability of primary and working reference standards should be submitted. A detailed description of the procedures to qualify new lots of reference standards and acceptance criteria for a new reference standard should be provided.

Release Testing

Release (acceptance criteria) testing results and other (for information only) characterization data (e.g. certificates of analysis) for each batch should be provided.

Control tests on the final product

Detailed information on final product tests performed on each batch, including the batch release specification, must be provided. This should include as appropriate;

- physical state (lyophilized solid, powder, liquid),
- Colour and clarity
- identification assay for active ingredients
- identification assay for adjuvants
- clinical particulars/indication (s)
- sterility
- moisture (as required)
- safety.
- extraneous agents including Mycoplasmas.

For each test, applicants must provide information on:

- title and company test code (specify monographs where appropriate)
- timing and frequency

- function of the test
- brief description of the test. (A detailed description should be given as an appendix to Section 2 with details and results of the validation studies where appropriate. The detailed description should contain sufficient information to enable the FDA to assess the adequacy of the test method and (if applicable) whether it is consistent with the cited monograph. A copy of the test procedure document may be provided as the detailed description)
- The fate of material that has failed the test (e.g. any re-test provisions).

The batch release specification must indicate the following:

- provision for identification of the batch undergoing test and the test date
- the name of each test
- the company test code
- limits of acceptance of results
- actual test results.

(***Refer to FDA website for guidance on batch release document***)

Summary of test results from three (3) consecutive pre-registration batches

A summary of results of tests on three consecutive batches of finished product must be provided to support the application for registration of the product. These batches may be pilot or production batches. If they are pilot batches, they must be representative of production batches.

The summary of results should also contain the protocols used to generate data to establish the physical state of the biological product, the identity of the biological product, the purity and impurities profile of the final product (i.e. identification and quantification of impurities and degradation products in the final dosage form) and potency.

The method of analysis of the finished product and the analytical method of validation protocol and report must be contained in the dossier submitted for registration.

Stability of the finished product

The storage shelf-lives of conventional biological products may vary from days to several years, therefore it is difficult to provide uniform guidelines regarding the stability study duration and testing frequency that would apply to all types of conventional biological products. However, with only a few exceptions, the shelf-lives for existing products and potential future products will be within the range of six months to five years. Therefore, this guidance is based upon expected shelf-lives in that range.

Manufacturers have two options for stability testing with respect to the design and data analysis: first method based on the compliance with the acceptance criterion and determination of shelf-life as the time associated with the last measurement within the specification and the second where statistical evaluation is used to define expiry date through extrapolation of the data.

When shelf-lives of less than one year are expected, real-time/real-temperature stability must be provided.

Studies should be conducted approximately monthly during the first three months and at

three-month intervals thereafter, so as to generate multiple measurements (a minimum of five tests three months apart) for the purpose of assessment.

For products with expected shelf-lives of greater than one year, the studies should be conducted every three months during the first year of storage, every six months during the second year, and annually thereafter.

While the testing intervals described above are appropriate in the pre-registration stage, reduced testing may be appropriate after approval or licensing/registration where data are available that suggest adequate stability.
While not mandatory, stability testing (at least potency/titre) should be conducted to three months past the claimed shelf-life.

A summary of the proposed shelf-life, storage conditions and justification for the proposed shelf-life must be provided. Real-time studies must be carried out on the final finished product in the marketed container. If there are insufficient real-time stability data to support the proposed shelf-life of the product, a stability testing protocol and timetable for testing the product must be provided with the application dossier.

Information must be supplied for three batches as follows:

- a description of the product packaging during testing
- a description of storage conditions (e.g. temperature ranges)
- A brief description of each test (a detailed description to be given as an appendix to Section 2, if this information has not been provided earlier). The tests should include (as appropriate) physical, chemical, biological and microbiological aspects of the product, and should indicate those tests claimed to be critical stability indicating measures.
- For multi-dose, not-for-immediate-use formulations, preservative efficacy testing must be conducted to validate inclusion of the preservative chosen. The tests should be consistent with those indicated on the batch release specification. A test for sterility and safety (where included on the batch release specification) must be conducted at the final time-point of the stability test protocol.
- A table of results with batch number, date of manufacture, dates of testing and storage conditions.

The results of the stability testing must be consistent with and confirm the minimum release titre and end-of-shelf-life specifications for the product.
For inactivated multi-dose, not-for-immediate-use products which may or may not require reconstitution or dilution before use, stability data will be required to support the recommended storage time and conditions after broaching, if not used within 12 hours.

For live multi-dose, not-for-immediate-use products which may or may not require reconstitution or dilution before use, stability data will be required to support the recommended storage time and conditions after broaching.

The FDA may request additional data for products containing one or more ingredients which are recognised to be inherently unstable. Where reference is made to official monographs for a shelf-life exceeding 12 hours, provision of adequate data or justification may be acceptable.

Information must be provided on the effect of external influences, such as sunlight and temperature, on the stability of the product when in use.

Each antigen or active ingredient in combination biological products must be tested. Stability data for a multivalent formulation may be extrapolated to formulations of lower valency provided that the quantity of each antigen, adjuvant and excipients of each combination biological product under consideration are approximately identical and providing that the market packaging and recommended storage conditions are also identical. Variation in any of these parameters will require the generation of separate stability data for each formulation.

Single-dose/single-application products requiring reconstitution or dilution will require data to support the proposed shelf-life for the reconstituted product, if not used within 30 minutes of reconstitution.

SECTION 3 TOXICOLOGY

Toxicity data should contain the following information;

- Table of contents
- Overall summary
- Acute toxicity studies
  - Studies on the active constituent
  - Studies on the product
- Short term toxicity studies (repeat dose)
- Sub-chronic toxicity studies
- Long term toxicity studies (repeat dose)
  - Carcinogenicity studies
  - Chronic toxicity and/or carcinogenicity studies
- Reproduction studies
- Developmental studies
- Genotoxicity studies
- Additional studies
  - Toxicity of metabolites and impurities
  - Other adverse effects
  - Toxicity of mixtures
- Human toxicological data
- No-observed-effect level (NOEL)
- Acceptable daily intake (ADI)
- Acute reference dose (ARFD)
- First aid instructions and safety directions
- Toxicological database.

SECTION 4 METABOLISM AND KINETICS

Metabolism and kinetic data should contain the following information;

- Table of contents
- Metabolism and Toxicokinetic Studies.

The following information would normally be expected:

- The degree of absorption after oral administration. An investigation of the extent of absorption after dermal application is required if applicable

- Distribution and storage in tissues, including bioaccumulation, if applicable
- Biotransformation and a description of any metabolites produced
- The mode and extent of excretion or elimination of the parent compound, and/or its degradation products.

- Metabolism and Pharmacokinetic Studies.

The aims of the studies are;

- to identify the rates of absorption, distribution, biotransformation and excretion of the parent compound and its metabolites (if active)
- to quantify the metabolites
- to provide an estimate of the total terminal residues
- to identify the major components of the total terminal residues
- to indicate the distribution and nature of residues
- to identify the mode and extent of excretion or elimination of the parent compound, and/or its degradation products to detect any potential for bioaccumulation (where applicable).

SECTION 5 OCCUPATIONAL HEALTHS AND SAFETY

Potential occupational health and safety risks associated with the manufacture and use of the product must be addressed in the application. This may include any or all of:

- safety instructions
- use of personal protective equipment
- first aid instructions
- information for medical practitioners.

SECTION 6 ENVIRONMENT

Information must be provided on the extent of exposure of the product, its active constituents or relevant metabolites to the environment, and proposed disposal methods for unused or waste product.

SECTION 7 SAFETY AND EFFICACY

Introduction

Efficacy of a vaccine means induction of immunity to provide protection against a specified disease. The nature, degree, onset and duration of immunity are the main parameters of the protection. The FDA requires all claims for the efficacy of vaccines, including the duration of protection and the administration schedules to be fully supported by data from specific pre-clinical and clinical trials.

Efficacy data generated in Ghana are required for the registration of all biological products intended for use in Ghana, unless the applicant can provide strong scientific argument that overseas data are applicable to Ghana's climatic conditions, genetic profile and disease prevalence.

The acceptance of such argument will be at the discretion of the FDA.

Requirements for safety and efficacy data

The following trials are normally required to generate data in support of efficacy and safety claims:

- **Pre-clinical trials**

Efficacy trials

- establishment of minimum protective dose and vaccination schedule
- confirmation of protection against challenge.
- influence of passively acquired and/or maternally derived antibodies on efficacy if appropriate.
- onset of immunity
- duration of protection
- timing of, and response to, booster vaccination
- compatibility with other treatments (vaccines) administered within seven days of administering the product under evaluation.

Safety studies

- single dose studies
- repeat single dose studies (where applicable)
- overdose studies (10× for live vaccines, 2× for inactivated vaccines)
- immunological effects
- reproductive effects (where appropriate)
- compatibility with other known products administered within seven days of administering the product under evaluation.

For live vaccines also include:

- spread to non-vaccinates
- reversion to virulence
- recombination

- **Clinical trials**

Safety and efficacy trials

The trials must:

- use the recommended dose and vaccination schedule as per proposed label instructions, using product which is at, or close to, the proposed end of shelf-life titre
- use representative batches manufactured using procedures outlined in the dossier
- replicate the proposed major uses of the product (route, method, administration, schedule, including the most sensitive subject)
- The dossier must document any adverse reactions.

Specific clinical studies protocol shall include the following:

- Objectives

- Identity and qualifications of key personnel involved
- Location(s) of study
- Dates of study
- Design
    - Selection of subjects (inclusion, exclusion criteria)
    - Selection of controls
    - Selection of control treatment (if applicable)
    - Number of subjects
    - Response variables - end points
    - Minimisation of bias - randomisation, blinding, compliance
- Treatments given - identity and quality of the investigational and control products used, dosage used, duration of treatment, duration of observation periods, any concurrent treatments and their justification.
- Analytical methods for determining immunogenic concentrations in body fluids and tissues
- Analysis of results including statistical analysis
- Discussions and conclusions on efficacy and safety.

Guidelines for trials to generate safety and efficacy data

Parameters of efficacy trials

The parameters to be measured in efficacy trials must be clearly defined in the study protocol and justified in relation to the indications and specific claims for the product. Conversely, justification should be given for not measuring parameters that are usually related to the disease concerned.

Three types of parameters exist:

- clinical parameters
- Indicators of immune response (e.g. serological response). For an indicator to be acceptable as a correlate of efficacy, it should be shown that a sufficient qualitative and quantitative correlation exists between the indicator measured and the claimed protection.
- indicators of infection or transmission (e.g. serological response).

Controls and trial design

Unless otherwise justified, the efficacy trial should compare a group of treated subject with an equivalent group of untreated or placebo-treated controls.

The selection and utilisation of the controls must be justified. It is necessary to define in the study protocol what purpose the control group serves. This may include:

- evidence that exposure to infection took place (untreated controls)
- evidence of the test product's efficacy in comparison with a registered reference product with the same indications for use (reference product as control).

When investigating a combined biological, the control group may comprise subjects treated with a product formulated to contain all the components of the product except the component under study. Data must be submitted to support efficacy of each component in the multivalent/combined biological for which registration is sought. The data must be generated using the formulation or particular combination for which registration is sought.

Ideally, the trials should be double blinded, randomized and placebo-controlled.

Establishment of the minimum protective dose and treatment plan/vaccination schedule
This can be undertaken as a dose-response study or as a study to confirm that the chosen dose and treatment/vaccination schedule is efficacious. From this study the end of shelf-life titre may be established. Allowance may need to be given for assay variation in setting the end of shelf-life from the minimum protective dose.

The method for determining the minimum protective dose must be justified, particularly if a suitable laboratory challenge model or serological (or other) marker of protection is not available. It may be appropriate to use official monograph where that 'standard' has a long history of satisfactory use.

Efficacy of each component of a combination product must be demonstrated following inoculation/administration of the combination product rather than from an evaluation of each component as a monovalent product. The potential for interference between the components must be evaluated, unless valid scientific argument is presented.

Clinical efficacy trials
The product dose used must be at a potency level equivalent to, or lower than that expected at the end of the product's shelf-life. The product used in the trial must be taken from a batch or batches manufactured according to procedures described in the application for registration. The formulation of the product submitted for registration approval must be identical to that used in the efficacy trials.

Applicants should note that the data generated from efficacy trial should support the proposed expiry or end-of-shelf-life titre and will form the basis for establishing the expiry titre or potency for the product.

The active component of the product may be diluted to achieve an 'expiry titre or potency' for the study. A complete description of the dilution process should be provided. The titre or potency of the batches used for the trials must be clearly specified. All adjuvants and excipients should be present in the same concentrations as in the proposed formulation.

Reference product
The reference product and the product under study must have the same efficacy claims. The level of efficacy of the reference product should be established by using a product currently registered by a Stringent Regulatory Authority (SRA). An evidence of purchase of the reference product must be provided.

Intercurrent infections
The potential for infection with intercurrent agents other than those under study should be considered in the trial design.

Pre-existing antibodies
Unless justification can be provided, clinical trials must not be carried out in subjects that have been previously treated/ vaccinated with products containing the same active substances as the product under study.

Interactions with other products

If a product is recommended for administration in combination with or at the same time as another product including a vaccine, compatibility, efficacy and safety must be demonstrated. Any known interactions with other products must be declared.

Analysis and interpretation of clinical trial data

The analysis of the clinical efficacy trial data must be related to the indication and specific claims made for the product and the parameters measured. The analysis of clinical safety trial data must be related to the recommendations for the administration of the product, i.e. the product must be shown to be safe under the recommended pattern of use. Careful consideration should especially be given to:

- the study plan
- the plan for analysis
- evaluation of the data
- the method of statistical evaluation
- randomisation
- the use of blinding in the study method
- justification of the number of subject used
- inclusion and exclusion criteria.

Duration of protection

The level of protection against challenge should be consistent with the label claim for the entire nominated duration of protection or revaccination interval.

In order to reduce the frequency of vaccination, it is recommended that wherever possible, studies demonstrate the actual duration of protection provided (i.e. end point studies). The duration of immunity to each antigen in a multivalent vaccine should be determined.

Where the primary vaccination course involves more than one administration and/or a follow-up or booster vaccination is required, the level of protection afforded between administrations should be assessed.

Where there is no recommendation for more than one administration of a vaccine or for only a primary vaccination course, this implies life-long protection. The claimed duration of protection should be specified and supported by adequate data.

In case of seasonal diseases, it may be sufficient to demonstrate the duration of protection in the year after vaccination until the end of the natural occurrence of the disease, provided that the vaccination is undertaken at the appropriate time in respect of anticipated disease occurrence. Persistence of protection in subsequent years, with or without revaccination, should be addressed.

It is not possible to generalise concerning the minimum period for which a vaccine should be expected to provide protection. However, in all cases the duration of protection must be relevant to the length of time during which the subject is likely to be at risk.

The duration of protection provided from the primary vaccination schedule should be demonstrated (Active immunity and acquired passive immunity).

Duration of protection from the re-vaccination schedule

Applicants must demonstrate via serological studies or other markers of protection that the

level of response before revaccination or at the end of the protection period is consistent with the efficacy claims made for the product.
The data generated for a multivalent vaccine may be used to support the protection claimed for a vaccine containing fewer active constituents, provided the latter vaccine is manufactured according to the same process, has the same composition (with the exception of the deleted antigens) and there is no evidence of a negative or positive interference from the other active ingredients present in the multivalent vaccine.

Biological product safety trials
Safety trials must be conducted in the most sensitive members of the trial cohort with the dosage that is recommended for use and preferably with the maximal titre or potency for which the application is made.

For live vaccines, the vaccine agents should be at the lowest attenuated passage level that will be present in the vaccine to be registered. Applicants should note that the titre or potency of the batches used for safety testing, particularly the overdose studies, will form the basis for establishing the maximum release titre or potency for batch release.

The vaccine used for testing should be taken from a batch or batches produced according to the manufacturing process as described in the dossier. Once the maximum release titre has been established, the FDA will not accept release of product batches with a higher titre or potency, unless results of additional safety testing at the higher titre or potency are provided.

Potential risks versus potential benefits from the use of the product must be stated. If the product contains live organisms, especially organisms which could be shed, the potential risk should be evaluated.

Laboratory tests
For each test, applicants must specify the following;

- title of the test with reference number names of collaborators in the study
- introduction and objective of the test or study
- reference to the relevant monographs
- dates of start and end of the study
- summary of study materials and methods
- results
- assessment criteria
- discussion
- conclusions.

Tests should be repeated using each recommended route of administration. The titre or potency of the batches used for testing must be clearly specified. The choice of the controls must be justified.

Any adverse systemic and/or local reactions must be described in detail.

Single dose effect
Adverse systemic and/or local reactions must be documented. Where appropriate macroscopic and microscopic examination of the injection site should be carried out to determine if a recorded abscess is aseptic or secondary to a skin or product contaminant.

The safety studies should in the first instance verify the safety of the vaccine after one administration of one dose of vaccine as well as after repeated administrations, depending on usage recommendations. The single dose should also be used to investigate the possible systemic side-effects of vaccination with the product.

In the case of live vaccines, the behaviour of the vaccine agents should be documented. In terms of local reactions, the size, duration and nature of any lesions appearing at the sites of injection must be monitored and recorded.

Repeat administration of a single dose
This may be required to reveal any adverse events induced by repeated administration.

Overdose effects
Both overdose and repeat administration studies should be carried out using the most sensitive subjects.

Abnormalities detected should (where possible) be thoroughly investigated to assess the likely incidence, aetiology or sequelae.

Reproductive studies
Safety studies are required unless an exclusion statement is included on the label. For example, use during pregnancy is not recommended or safety during pregnancy has not been determined.

If reproductive studies are not considered necessary, the reasons must be clearly stated.

Examination of immunological functions
Where the vaccine is known to affect, or could be expected to adversely affect the immune response (e.g. by immunosuppression, autoimmunity, or hypersensitivity) of the subjects or their progeny, suitable tests on their immunological function must be carried out. Alternatively, a rationale for no detrimental effect on immune response should be provided.

Other information required:

- the possibility of reversion to virulence in the case of attenuated strains
- the possibility of recombination or genomic reassortment
- the possibility of spread of the vaccine strain (live vaccine) to non-vaccinated population unless acceptable argument can be provided to show that this cannot happen

Interactions with other products
Claims that the vaccine can be administered simultaneously or in combination with other products must be substantiated. Any known interactions with other products must be declared.

SECTION 8 GENETICALLY MODIFIED ORGANISMS (GMO)

Submission should clearly state whether the biological product is derived from and/or contain a genetically modified organisms (GMOs). A summary of the protocol used to generate the GMO should be provided.

SECTION 9 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 FDA 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;
    - any biological medicinal product containing a new biological drug substance
    - a highly similar biological medicinal product
    - a hydrid medicinal product where the reference product has a RMP and a safety concern requiring additional risk minimisation activities has been identified with the reference biological medicinal product
- 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, new

manufacturing process of a biotechnologically derived product, 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 with a biological medicinal product at any stage of the life cycle of the product

In some cases, biological medicinal products not listed in the above category may require a RMP, e.g,

- known biological drug substance
- hybrid biological medicinal products where the changes relative to the reference medicinal biological product suggest different risks
- combination therapy application

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

4.0 OUTLINE OF THE EVALUATION OF APPLICATION

4.1 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.

4.2 An appeal for the review of an application may be made in writing to the Authority within 60 (Sixty) days of receipt of the rejection notice.

4.3 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.

4.4 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.

4.5 The Authority shall from time to time, publish a notice in the Gazette notifying the registration of a product under these regulations.

4.6 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)

5.0. SANCTIONS AND PENALTIES

5.1 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.

5.2 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.

APPENDIX I:

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
- 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
- Evidence of purchase of reference product
- Protocol and report for isolation of reference product drug substance, (if applicable)
- Certificate of Analysis of biological drug substance
- Protocol and report of analytical method of validation (AMV) for drug substance reference product (if applicable)
- Protocol and Report of analytical method validation (AMV) for reference product (if applicable)
- 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 of process validation
- Certificate of Pharmaceutical Product/Certificate of Analysis of biological drug 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 reference product received (client service, FDA)
- Quantity and number of samples (biological medicinal product) received (client service, FDA)
- Programme for post-market surveillance/Pharmacovigilance and risk management plan
- Report on substitution and interchangeability (if applicable)
- Package Insert

APPENDIX II:

RELEVANT FDA GUIDANCE DOCUMENTS

I. Guidelines for Registration of Biological products
II. Guidelines for Safety Monitoring
III. Guidelines for conducting clinical trials of allopathic drugs, VACCINES, and medical devices
IV. Guidelines for requirements for labelling of products.

APPENDIX III:

ABBREVIATIONS AND ACRONYMS

AMV	Analytical Method of Validation
API	Active Pharmaceutical Ingredient
BMR	Batch Manufacturing Record
cGMP	current Good Manufacturing Practice
EPC	End of Production Cells
FDA	Ghana Food and Drugs Authority
MCB	Master Cell Bank
MSL	Master Seed Lot
RMP	Risk Management Plan
SRA	Stringent Regulatory Authority
WCB	Working Cell Bank
WHO	World Health Organization
WSL	Working Seed Lot

APPENDIX IV:

Batch release document for vaccines, refer to www.fdaghana.gov.gh

APPENDIX V:

Application form for the registration of biological products, refer to www.fdaghana.gov.gh