# FOOD AND DRUGS AUTHORITY

## GUIDELINES FOR REGISTRATION OF BIOLOGICAL PRODUCTS

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## 1.0 INTRODUCTION

The responsibility for the quality, safety and efficacy of biological products lies first and foremost with the manufacturer. These revised 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 labeling 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).

To ensure easy access to medical products, the FDA has developed and implemented alternative /non-routine product registration authorization pathway (refer to FDA Reliance Policy) to the standard approval pathway especially for applications where the drug product has already been approved in a well-resourced setting and by a well-resourced regulatory authority. The Authority relies and uses relevant regulatory decisions, reports or information from well-resourced regulatory authority or from regional and international bodies.

That notwithstanding, it is equally important to note that Authority reserves the right to request information or material, or define conditions not specifically described in this guideline or the FDA's Reliance Policy, in order to allow the Department to adequately assess the safety, efficacy or quality of a product. The Authority is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

### 1.1 SCOPE

In pursuance of Section 118 of the Public Health Act 2012, Act 851, these revised 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. The guidance document applies to all registration application intended for use in humans, regardless of where they were manufactured.

The guidance document consisted of five modules (i.e. Module 1- Module 5) and it is in Common Technical Document format.

## 2.0 GLOSSARY

In these guidelines, unless the context otherwise states:

- **"Authority"** means Food and Drugs Authority
- **"Applicant"** means the product owner or license holder. Representatives of license holders may not hold themselves as applicants unless they own the product.
- **"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.
- **Biological product** 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)

- **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.
- **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.
- **Country of origin** means the country where the legal certifications of the product are generated, where is the legal or titular representative and can or not agree with the country where the vaccine makes.
- **Dosage form** means the physical form in which a product is prepared for administration to the recipient.
- **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.
- **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.

- **Final bulk product** means any product that has gone through all stages of processing, including formulation but not final packaging.
- **Good Manufacturing Practices (GMP)** means 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.
- **License** (**Registration**) **means p**rocedure whereby the National Regulatory Authority grants permission for the product in question to be sold and distributed in the country.
- **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.

- **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.
- **Products** means biological product
- **Product development means** all studies to show that the dose, formulation, manufacturing process and packaging system, as well as the microbiological properties, are appropriate for the proposed purpose.
- **Raw materials means** any substance used to make or extract the active ingredient but from which the active ingredient is not directly derived.
- **Residual pathogenicity** means the potential of viruses or bacteria which have been attenuated for specific route of administration to retain different levels of pathogenicity.

- **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.
- **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”).
- **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.
- **Starting material** means any substance of biological origin, such as microorganisms, organs and tissues of plant or animal origin, including cells or fluids of human or animal origin and recombinant cell substrates.
- **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.

- **Validation** means 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.
- **"Well-resourced or reference National Regulatory Authority"** means a member of ICH prior to 23 October 2015, namely: the US Food and Drug Administration, the European Commission and the Ministry of Health, Labour and Welfare of Japan also represented by the Pharmaceuticals and Medical Devices Agency; or an ICH observer prior to 23 October 2015, namely: the European Free Trade Association, as represented by Swissmedic and Health Canada; or a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement prior to 23 October 2015, namely: Australia, Iceland, Liechtenstein and Norway.
- **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.

## 3.0 REQUIREMENTS FOR SUBMISSION

### 3.1 General Requirements

3.1.1. 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.

3.1.2 All samples submitted should conform to existing labelling regulations as specified in these guidelines and on the FDA website "guidelines for labeling of finished pharmaceuticals"

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

3.1.4 Four (4) copies of the labels and leaflet inserts, conforming to existing labelling regulations in Ghana.

3.1.5 If the product is produced on contract manufacture, evidence of the contract agreement shall be produced in the documentation submitted.

3.1.6 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.

3.1.7 The use of an International Non-proprietary Name (INN) as a brand name shall not be permitted.

3.1.8 The packages of all products submitted for registration shall include package inserts/patient information leaflet (where applicable).

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

3.1.10 The application should be submitted through the authorized local agent by the regulatory contact person to the following address:

**The Chief Executive Officer**
**Food and Drugs Authority**
**P. O. Box CT 2783**
**Cantonments**
**Accra**

## 3.2 New Registration

3.2.1 An applicant for the registration of a biological product, either locally manufactured or imported, shall be made in writing.

3.2.2 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. Refer from FDA website for application form.

3.2.3 If the applicant is a foreign company; it shall appoint a local agent through whom the application shall be submitted.

3.2.4 The local agent shall be a registered pharmaceutical wholesale company or an accredited manufacturer's representative registered as a pharmacist in Ghana.

3.2.5 Applications shall be accompanied by:

3.2.5.1 A duly signed covering letter

3.2.5.2 Two (2) soft copies of all documentation been submitted which includes a completed application form and all supporting documents (dossier module 1-5)

3.2.5.3 Samples of the product in the final package as specified in the Authority's sample schedule. Refer to www.fdaghana.gov.gh

3.2.5.4 Reference /working standards for Active Pharmaceutical Ingredients (API) and related impurities where necessary.

3.2.5.5 Clinical trial and/or bioequivalence trial certificate where applicable

3.2.5.6 Non-refundable application fee as specified in the Authority's fee schedule.

3.2.6 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).

3.2.7 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.

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

3.2.9 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.

3.2.10 A new application will be processed within 240 working days of receipt of the application.

### 3.3 Renewal of Registration

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

3.3.2 The application shall be accompanied by:

3.3.2.1 A covering letter

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

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

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

3.3.2.5 Certificate of Analysis (CoA) of the finished product

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

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

3.3.2.8 Method of analysis (Protocol and Report)

3.3.2.9 Analytical Method Validation (Protocol and Report)

3.3.2.10 Batch release documents.

3.3.2.11 Reference Standard/ Reference Product.

3.3.2.12 Certificate of Analysis of the reference standard/Reference Product

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

3.3.4 A renewal application will be processed within 3 months of receipt of the application.

### 3.4 Registration Variation

3.4.1 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.

3.4.2 The application shall be accompanied by:

3.4.2.1 A duly signed covering letter

3.4.2.2 Application form for variation. Refer to FDA website

3.4.2.3 Documentation in support of the variation.

3.4.2.4 Samples reflecting the variation as specified in the Authority's samples schedule where applicable

3.4.2.5 Non-refundable variation fee as specified in Authority's approved fees schedule where applicable

3.4.3 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.

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.

3.4.4 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.

3.4.5 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.

3.4.6 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.

3.4.6 Trademark certificate **(**optional)

3.4.7 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.

3.4.8 Invention patent certificate (based on the country of origin's legislation)

3.4.9 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.

## 3.5 REQUIREMENTS FOR REGISTRATION/MARKETING AUTHORIZATION RELIANCE

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

NRA or the WHO. The application shall be identical to that submitted, evaluated and approved by the well-resourced or reference NRA or the WHO.

### 3.6 APPEALING A REJECTED REGISTRATION APPLICATION

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

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

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

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

**The Chief Executive Officer**

**Food and Drugs Authority**

**P. O. Box CT 2783**

**Cantonments**

**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.

**RECOMMENDED FORMAT FOR DOSSIER SUBMISSION**

**MODULE 1**

## 1.0 ADMINISTRATIVE - LEGAL INFORMATION

The requirements include:

### 1.1 COVER LETTER

### 1.2 TABLE OF CONTENTS (MODULES 1 TO 5):

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

### 1.3 APPLICATION FORM

GHFDA minimum requirement:

**1.3.1 Proprietary, commercial or trade name of product**. It corresponds to the name

under which the product will be registered.

**1.3.2 Non-proprietary name or common name of product.** The name adopted by the

World Health Organization, the common international name, or the name contained

in official pharmacopeias recognized in the country.

**1.3.3 Concentration**. State the concentration of the active ingredient(s) contained in the

product.

**1.3.4 Dosage Form**. Indicate the dosage form of the product, for example, injectable

solution, and injectable suspension.

**1.3.5 Senior Executive Officer / Senior Medical or Scientific Officer**. The professional

responsible for the product in the country where licensing is applied for. Give the

full name, address, telephone, fax, e- mail, professional license number, and the

registration number of his/her degree, as per the country's legislation.

**1.3.6 Legal Representative (Local Agent).** 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.

**1.3.7 Applicant**. Give the full name of the market authorization holder of the product if in the country of origin, also address, telephone, fax, and e-mail.

1.3.8 **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)

1.3.9 **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.

**1.3.10 Other manufacturer(s)**. In the event that some parts of the manufacturing process are performed by a different company, give name, address, telephone, fax, and e-mail involved in the production process of the product.

**1.3.11 Official responsible for batch release of finished product**. Give the name and position of the person responsible for the release of the product.

**1.3.12 Commercial presentation of product**. Indicate whether the product 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.

**1.3.13 Route of administration**. Indicate the route of administration of the product.

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

**1.3.15 Strength** of each unit of dose.

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

**1.3.16.1** 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 product 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 licensing.

**1.3.16.2** Authorization of representative. Document issued by the applicant of the product authorizing the company to represent it and market the product in the country.

**1.3.16.3** Certificate of Pharmaceutical Product (CPP). Using WHO model. Required for imported products since it is the certificate issued by the regulatory authority that grants the license in the country of origin. This certificate includes information on compliance with GMP. Some countries issue a Free Sales Certificate (FSC); this should be submitted in addition to the GMP certificate.

**1.3.16.4** Certificate of Good Manufacturing Practices (GMP) of all manufacturer(s) involved in the production process. This should include manufacturers that are involved in any stage of the production process. It is important that the certificate indicates the procedures that the establishment is authorized to perform.

**1.3.16.5** Trademark certificate (optional)

**1.3.16.6** Patent certificate (under national legislation)

**1.3.16.7** Batch release certificate issued by NRA (imported product). Refers to the lot release certificate issued by the regulatory authority of the country of origin of the product or the regional regulatory authority responsible for its release. The certificate should correspond to those samples submitted with the application for licensing, as applicable.

**1.3.16.8** 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 product that are incomplete or have been abandoned and/or completed tests related to indications not covered by the application.

## 1.4 SUMMARY OF PRODUCT CHARACTERISTICS AND PRODUCT LABELING

**1.4.1 Summary of product characteristics**. A summary should be submitted of the characteristics of the product under evaluation.

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

**1.4.2.1 Primary package label**. Submit the label proposed for the primary package or container, which should provide the following information as a minimum:

1.4.2.1.1 Proprietary, commercial or trade name

1.4.2.1.2 Non-proprietary name or common name

1.4.2.1.3 Dosage form

1.4.2.1.4 Concentration, potency, or viral titer

1.4.2.1.5 Content/volume

1.4.2.1.6 Volume/dose

1.4.2.1.7 Number of doses per vial (for multidose presentations)

1.4.2.1.8 Route of administration

1.4.2.1.9 Storage temperature (if the size of the package so permits)

1.4.2.1.10 Warnings

1.4.2.1.11 Lot number

1.4.2.1.12 Expiry date

1.4.2.1.13 Manufacturer

1.4.2.1.14 Registration number from country of origin

**1.4.2.2 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:

1.4.2.2.1 Proprietary, commercial or trade name

1.4.2.2.2 Non-proprietary name or common name

1.4.2.2.3 Dosage form

1.4.2.2.4 Concentration, potency, or viral titer

1.4.2.2.5 Content/Volume

1.4.2.2.6 Volume/dose

1.4.2.2.7 Number of doses per vial (for multidose presentations)

1.4.2.2.8 Composition

1.4.2.2.9 Excipients

1.4.2.2.10 Product storage

1.4.2.2.11 Route of administration

1.4.2.2.12 Instructions for preparation

1.4.2.2.13 Mode of use

1.4.2.2.14 Warnings

1.4.2.2.15 Identification marks (some countries require that an identification mark indicating the type of product be included, for example a yellow band for pediatric products)

1.4.2.2.16 Lot number

1.4.2.2.17 Date of expiry

1.4.2.2.18 Name and address of the manufacturer of the finished product

1.4.2.2.19 Name and address of the company responsible for packaging

1.4.2.2.20 Name and address of the owner, representative, or distributor

1.4.2.2.21 Name of the professional in charge

1.4.2.2.22 Registration number from country of origin

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

1.4.2.3.1 Proprietary, commercial or trade name

1.4.2.3.2 Non-proprietary or common name

1.4.2.3.3 Pharmaceutical form

1.4.2.3.4 Concentration, potency, or viral titer

1.4.2.3.5 Content/Volume

1.4.2.3.6 Volume/dose

1.4.2.3.7 Number of doses per vial (for multidose presentations)

1.4.2.3.8 Composition

1.4.2.3.9 Excipients

1.4.2.3.10 Cell substrate

1.4.2.3.11 Route of administration

1.4.2.3.12 Indications

1.4.2.3.13 Immunization plan

1.4.2.3.14 Proper use

1.4.2.3.15 Precautions

1.4.2.3.16 Warnings

1.4.2.3.17 Adverse events allegedly associated with vaccination and immunization

1.4.2.3.18 Contraindications

1.4.2.3.19 Use during pregnancy and breast feeding

1.4.2.3.20 Storage of the product/storage conditions

1.4.2.3.21 Name and address of the manufacturer of the finished product

1.4.2.3.22 Name and address of the company responsible for packaging

**1.4.2.4 Final packaging.** Samples, or alternatively labels and cartons, of the primary and secondary packaging of the product, including the package insert and accessories should be submitted. 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.

**1.4.2.5** Monograph for health professionals or information for prescription in extended or reduced form. Submit the proposed monograph on the product to be distributed to health professionals.

### 1.4.3 Samples

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

**1.4.3.2** 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 product submitted for market authorization. These protocols are published in the WHO's Technical Report Series. For novel products 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.

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

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

**1.6 INFORMATION REGARDING EXPERTS.**

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

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

**1. 8 DECLARATION**. The applicant / license holder should indicate that the information submitted is true and correct. Information on the name, position and signature of the applicant should be provided. The application should be dated and stamped by the applicant.

**MODULE 2.**

## 2. 0 QUALITY OVERALL SUMMARY (QOS)

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 product, 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:

The italicised text indicates where tables, figures, or other items can be imported directly from Module 3.

### 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 product, composition, immunological mechanism, and indications proposed for the product.

### 2.3 OVERALL QUALITY SUMMARY.

A general summary of the quality of the product should be presented, related to the chemical, pharmaceutical, and biological aspects. This summary should refer exclusively to the information, data, and justifications included in module 3 or in other modules of the registration document. The format to be followed is:

### 2.3.S Summary of biological drug substance

#### 2.3.S.1 General Information

Information from 3.2.S.1 should be included.

### 2.3.S.2 Manufacture

Information from 3.2.S.2 should be included:

- Information on the manufacturer;
- A brief description of the manufacturing process (including, for example, reference to starting materials, critical steps, and reprocessing) and the controls that are intended to result in the routine and consistent production of material(s) of appropriate quality;
- A flow diagram, as provided in 3.2.S.2.2;
- A description of the Source and Starting Material and raw materials of biological origin used in the manufacture of the drug substance, as described in 3.2.S.2.3;
- A discussion of the selection and justification of critical manufacturing steps, process controls, and acceptance criteria. Highlight critical process intermediates, as described in

3.2.S.2.4;

- A description of process validation and/or evaluation, as described in 3.2.S.2.5.
- A brief summary of major manufacturing changes made throughout development and conclusions from the assessment used to evaluate product consistency, as described in 3.2.S.2.6. The QOS should also cross-refer to the non-clinical and clinical studies that 1 The Common Technical Document - Quality used batches affected by these manufacturing changes, as provided in the CTD-S and CTD-E modules of the dossier.

### 2.3.S.3 Characterisation

A description of the desired product and product-related substances and a summary of general properties, characteristic features and characterisation data (for example, primary and higher order structure and biological activity), as described in 3.2.S.3.1, should be included.

The QOS should summarise the data on potential and actual impurities arising from the synthesis, manufacture and/or degradation, and should summarise the basis for setting the acceptance criteria for individual and total impurities. The QOS should also summarise the impurity levels in batches of the drug substance used in the non-clinical studies, in the clinical trials, and in typical batches manufactured by the proposed commercial process. The QOS should state how the proposed impurity limits are qualified.

A tabulated summary of the data provided in 3.2.S.3.2, with graphical representation, where appropriate should be included.

### 2.3.S.4 Control of Drug Substance

A brief summary of the justification of the specification(s), the analytical procedures, and validation should be included.

Specification from 3.2.S.4.1 should be provided.

A tabulated summary of the batch analyses from 3.2.S.4.4, with graphical representation where appropriate, should be provided.

### 2.3.S.5 Reference Standards or Materials

Information from 3.2.S.5 (tabulated presentation, where appropriate) should be included.

### 2.3.S.6 Container Closure System

A brief description and discussion of the information, from 3.2.S.6 should be included.

### 2.3.S.7 Stability

This section should include a summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions, the proposed storage conditions, retest date or shelf-life, where relevant, as described in 3.2.S.7.1.

The post-approval stability protocol, as described in 3.2.S.7.2, should be included.

A tabulated summary of the stability results from 3.2.S.7.3, with graphical representation where appropriate, should be provided.

**2.3.P Summary of drug product**

**2.3.P.1 Description and Composition of the Drug Product** Information from 3.2.P.1 should be provided.

Composition from 3.2.P.1 should be provided.

**2.3.P.2 Pharmaceutical Development**

A discussion of the information and data from 3.2.P.2 should be presented.

A tabulated summary of the composition of the formulations used in clinical trials and a presentation of dissolution profiles should be provided, where relevant.

**2.3.P.3 Manufacture**

Information from 3.2.P.3 should include:

Information on the manufacturer.

A brief description of the manufacturing process and the controls that are intended to result in the routine and consistent production of product of appropriate quality.

A flow diagram, as provided under 3.2.P.3.3.

A brief description of the process validation and/or evaluation, as described in 3.2.P.3.5.

**2.3.P.4 Control of Excipients**

A brief summary on the quality of excipients, as described in 3.2.P.4, should be included.

**2.3.P.5 Control of Drug Product**

A brief summary of the justification of the specification(s), a summary of the analytical procedures and validation, and characterisation of impurities should be provided.

Specification(s) from 3.2.P.5.1 should be provided.

A tabulated summary of the batch analyses provided under 3.2.P.5.4, with graphical representation where appropriate should be included.

### 2.3.P. 6 Reference Standards or Materials

Information from 3.2.P.6 (tabulated presentation, where appropriate) should be included.

### 2.3.P.7 Container Closure System

A brief description and discussion of the information in 3.2.P.7 should be included.

### 2.3.P.8 Stability

A summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions of the stability studies and analysis of data should be included. Conclusions with respect to storage conditions and shelf-life and, if applicable, in-use storage conditions and shelf-life should be given.

A tabulated summary of the stability results from 3.2.P.8.3, with graphical representation where appropriate, should be included.

The post-approval stability protocol, as described in 3.2.P.8.2, should be provided.

## 2.3.A APPENDICES

### 2.3.A.1 Facilities and Equipment

A summary of facility information described under 3.2.A.1 should be included.

### 2.3.A.2 Adventitious Agents Safety Evaluation

A discussion on measures implemented to control endogenous and adventitious agents in production should be included.

A tabulated summary of the reduction factors for viral clearance from 3.2.A.2, should be provided.

### 2.3.A.3 Excipients

### 2.3.R REGIONAL INFORMATION

A brief description of the information specific for the region, as provided under "3.2.R" should be included, where appropriate.

### 2.4 OVERVIEW OF NON-CLINICAL STUDIES

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

2.4.1 Introduction
2.4.2 Written pharmacological summary
2.4.3 Tabulated pharmacological summary
2.4.4 Written pharmacokinetic summary (when appropriate)
2.4.5 Tabulated pharmacokinetic summary (when appropriate)
2.4.6 Written toxicological summary
2.4.7 Tabulated toxicological summary

### 2.5 OVERVIEW OF CLINICAL STUDIES.

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

**2.5.1** Detailed discussion of product development

**2.5.2** Overview of immunogenicity

**2.5.4** Overview of efficacy

**2.5.5** Overview of safety

**2.5.6** Conclusions on risk-benefit balance

**2.5.7** Literature References

## 2.6 NON-CLINICAL SUMMARY.

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

**2.6.1** Introduction

**2.6.2** Written pharmacological summary

**2.6.3** Tabulated pharmacological summary

**2.6.4** Written pharmacokinetic summary (when appropriate)

**2.6.5** Tabulated pharmacokinetic summary (when appropriate)

**2.6.6** Written toxicological summary

**2.6.7** Tabulated toxicological summary

## 2.7 CLINICAL SUMMARY.

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

Introduction

Table of contents

**2.7.2** Summary of the clinical immunogenicity studies

**2.7.3** Summary of the clinical efficacy studies

**2.7.4** Summary of the clinical safety studies

**2.7.5** Literature References

**MODULE 3**

## 3.0 QUALITY INFORMATION (CHEMISTRY, MANUFACTURE AND CONTROL)

This module is intended to provide guidance on the format of a registration application for drug substances and their corresponding drug products as defined ICH Guideline Q 6 B ("Biotech)

## 3.1 TABLE OF CONTENTS OF MODULE 3.

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

## 3.2 CONTENTS.

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

### 3.2. S Active biological substance.

The information requested under this point should be supplied individually for each active substance where applicable.

### 3.2.S.1 General information, starting materials and raw materials

### 3.2. S.1.1 Nomenclature

Information on the nomenclature of the drug substance should be provided based on the WHO or Pharmacopoeia requirements as appropriate. The Trade and or non-proprietary name, compendia name where appropriate, Chemical name, company or laboratory code.

### 3.2.S.1.2 Structure

Structural formula, molecular formula and relative molecular weight (if applicable) should be provided. The schematic amino acid sequence, indicating the

glycosylation sites or other posttranslational modifications and relative molecular mass should be provided.

#### 3.2.S.1.3 General Properties

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

### 3.2.S.2 Manufacture

#### 3.2.S.2.1 Manufacturer(s)

Applicants must provide evidence that the product is manufactured to a standard comparable to the World Health Organization current Good Manufacturing Practices. The name, address and responsibility of each manufacturer, including contractors should be provided. The facilities involved in the manufacturing, packaging, labelling, testing and storage of the drug substance should be listed. If certain companies are responsible only for specific steps this should be clearly indicated.

#### 3.2.S.2.2 Description of Manufacture Process and Process Controls

The description of the drug substance manufacturing process represents the applicant’s commitment for the manufacture of the drug substance. Information should be provided to adequately describe the manufacturing process and process controls.

Information should be provided on the manufacturing process, which typically starts with a vial(s) of the cell bank, and includes cell culture, harvest(s), purification and modification reactions, filling, storage and shipping conditions. 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, lyophilization, as relevant. Reference ICH Guidelines Q5A, Q5B and Q6B

### 3. 2. S. 2.3 Control of 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.

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.**

Applicant should also provide data on;

- Control of source and starting materials of biological origin
- Sources, history and generation of the cell substrate
- Cell banking system, characterization and testing

**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

### 3.2. S.2.4 Controls of Critical Steps and Intermediates

Critical Steps: Tests and acceptance criteria (with justification including experimental data) performed at critical steps identified in 3.2.S.2.2 of the manufacturing process to ensure that the process is controlled should be provided.

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

Stability data supporting storage conditions should be provided.

### 3.2.S. 2. 5 Process Validation and /or Evaluation

Information should be Sufficient to demonstrate that the manufacturing process (including reprocessing steps) is suitable for its intended purpose and to substantiate selection of critical process controls (operational parameters and in-process tests) and their limits for critical manufacturing steps (e.g., cell culture, harvesting, purification, and modification).

The plan for conducting the study should be described and the results, analysis and conclusions from the executed study(ies) should be provided. The analytical procedures and corresponding validation should be cross-referenced (e.g., 3.2.S.2.4, 3.2.S.4.3) or provided as part of justifying the selection of critical process controls and acceptance criteria.

For manufacturing steps intended to remove or inactivate viral contaminants, the information from evaluation studies should be provided in 3.2.A.2.

3.2.S.2.6 **Manufacturing Process Development**

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

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

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

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

Reference should be made to the drug substance data provided in section 3.2.S.4.4.

Reference ICH Guideline: Q6B

### 3.2.S.3 Characterisation

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

#### 3.2.S.3.1 Elucidation of structure and other characteristics

For the intended product and product-related substances, details should be provided, if applicable, on primary, secondary and higher-order structure, post-translational forms (e.g. glycoforms), biological activity, purity, and immunochemical/immunogenicity properties.

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

Reference ICH Guideline: Q6B

#### 3.2.S.3.2 Impurities

Information on impurities should be provided. All potential impurities, including process related impurities and degradation products for purification arising from

manufacturing, storage or found in stability study batches, should be described regardless of whether they have been detected in any batches.

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

The information should also include a discussion of results which are close to or outside limits. A rationale should be provided for the choice of tests used, the proposed limits and their qualification.

A rationale for excluding any impurity test(s) from routine release testing due to trace levels should also be provided, where applicable.

### 3.2.S.4 Control of Drug Substance

#### 3.2.S.4.1 Specification

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

Reference ICH Guideline: Q6B

#### 3.2.S.4.2 Analytical Procedures

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

#### 3.2.S.4.3 Validation of Analytical Procedures

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

### 3.2.S.4.4 Batch Analysis

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

### 3.2.S.4.5 Justification of Specification

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

### 3.2.S.5 Reference Standards or Materials

A detailed protocol of the preparation, characterization, and stability of primary and working reference standards or mateials 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. Certificates of analysis should be provided, if applicable.

### 3.2.S.6 Container Closure System

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

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

### 3.2.S.7 Stability

### 3.2.S.7.1 Stability Summary and Conclusions

The types of studies conducted, protocols used, and the results of the studies should be summarized. Should include the study conditions, including all of the storage conditions (temperature, humidity, light) in which the drug substance is evaluated, analytical methods, specifications, summary of results, and conclusions.

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

The post-approval stability protocol and stability commitment should be provided.

### 3.2.S.7.3 Stability Data

Results of the stability studies (e.g., forced degradation studies and stress conditions) should be presented in an appropriate format such as tabular, graphical, or narrative. Information on the analytical procedures used to generate the data and validation of these procedures should be included.

**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

## 3.2.P DRUG PRODUCT

### 3.2.P.1 Description and Composition of the Drug Product

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

### 3.2.P.2 Pharmaceutical Development

The Pharmaceutical Development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are appropriate for the purpose specified in the application. The studies described here are distinguished from routine control tests conducted

according to specifications. Additionally, this section should identify and describe the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance and drug product quality. Supportive data and results from specific studies or published literature can be included within or attached to the Pharmaceutical Development section. Additional supportive data can be referenced to the relevant nonclinical or clinical sections of the application. The following aspects should be included:

### 3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

The compatibility of the drug substance with excipients listed in 3.2.P.1 should be discussed. Additionally, key physicochemical characteristics (e.g., water content, solubility, particle size distribution, polymorphic or solid state form) of the drug substance that can influence the performance of the drug product should be discussed.

For combination products, the compatibility of drug substances with each other should be discussed.

3.2.P.2.1.2 Excipients

The choice of excipients listed in 3.2.P.1, their concentration, and their characteristics that can influence the drug product performance should be discussed relative to their respective functions.

### 3.2.P.2.2 Drug Product

#### 3.2.P.2.2.1 Formulation Development

A brief summary describing the development of the drug product should be provided, taking into consideration the proposed route of administration and usage. The differences between clinical formulations and the formulation (i.e. composition) described in 3.2.P.1 should be discussed. Results from comparative

in vitro studies or comparative in vivo studies should be discussed when appropriate.

#### 3.2.P.2.2.2 Overages

Any overages in the formulation(s) described in 3.2.P.1 should be justified.

#### 3.2.P.2.2.3 Physicochemical and Biological Properties

Parameters relevant to the performance of the drug product, such as pH, ionic strength, dissolution, redispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency, and/or immunological activity, should be addressed.

### 3.2.P.2.3 Manufacturing Process Development

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

### 3.2.P.2.4 Container Closure System

Full description of the packaging and container closure system should be provided. The information should include identification of all the materials that constitute the container closure system and their specifications. The suitability of the container closure system should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the drug product, including adsorption to container and leaching, and/or safety.

### 3.2.P.2.5 Microbiological Attributes

Where appropriate, the microbiological attributes of the dosage form should be discussed, including, for example, the rationale for not performing microbial limits testing for non-sterile products and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. For sterile products,

the integrity of the container closure system to prevent microbial contamination should be addressed.

### 3.2.P.2.6 Compatibility

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

## 3.2.P.3 Manufacture

### 3.2.P.3.1 Manufacturer(s)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

### 3.2.P.3.2 Batch Formula

A batch formula should be provided that includes a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis, including overages, and a reference to their quality standards.

### 3.2.P.3.3 Description of Manufacturing Process and Process Controls

- Flow chart of manufacturing process. Showing all of the steps in the process and indicating the points at which the material enters the process, identifying the critical steps and control points in the process, intermediate products, and final product.
- Batch and Scale Definition. An explanation of the batch numbering system and scale at each stage of manufacture (e.g. filing, lyophilisation, and packaging).
- Formulation process. Description of the formulation process, the in-process controls, acceptance criteria and the critical steps identified. Information regarding any pooling of bulks or intermediates should be provided.

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

**3.2.P.3. Control of Critical Steps and Intermediates**

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

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

**3.2.P.3.5 Process Validation and/or Evaluation**

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

The suitability of any proposed reprocessing procedures and the criteria for the reprocessing of any intermediate or the drug product should be discussed. It is also necessary to provide information on the viral safety of the product, when applicable (e.g. products derived from cell lines of human or animal origin).

**3.2.P.4 Control of Excipients**

### 3.2.P.4.1 Specifications

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

### 3.2.P.4.2 Analytical Procedures

The analytical procedures used for testing the excipients should be provided.

### 3.2.P.4.3 Validation of Analytical Procedures

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

### 3.2.P.4.4 Justification of Specifications

Justification for the proposed excipient specifications should be provided, where appropriate.

### 3.2.P.4.5 Excipients of Human or Animal Origin

For excipients of human or animal origin, information should be provided regarding adventitious agents (e.g., sources, specifications, description of the testing performed, viral safety data).

Excipients from animal origin, a letter of attestation should be provided confirming that the excipients used to manufacture the drug product are without risk of transmitting agents of animal spongiform encephalopathies.

### 3.2.P.4.6 Novel Excipients

For excipient(s) used for the first time in a drug product or by a new route of administration, full details of manufacture, characterisation, and controls, with cross references to supporting safety data (nonclinical and/or clinical) should be provided according to the drug substance format. (Details in 3.2.A.3).

### 3.2.P.5 Control of Drug Product

#### 3.2.P.5.1 Specification(s)

Indicate the specifications for the drug product.

#### 3.2.P.5.2 Analytical Procedures

Information on the analytical procedures used for quality control of the drug product. Nonpharmacopeia methods, summaries or references may be accepted (e.g. when pharmacopeia methods are unavailable or inappropriate and appropriately validated in-house methods are used). Additional information could be requested.

#### 3.2.P.5.3 Validation of Analytical Procedures

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

#### 3.2.P.5.4 Batch Analyses

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

#### 3.2.P.5.5 Characterisation of Impurities

Information on the characterisation of impurities should be provided, if not previously provided in “3.2.S.3.2 Impurities”.

A discussion should be provided of all impurities that are potential degradation products (including those among the impurities identified in 3.2.S.3.2 as well as potential degradation products resulting from interaction of the drug substance with other drug substance, excipients or the container closure system) and drug product process-related impurities (e.g. residual solvents in the manufacturing process for the drug product).

#### 3.2.P.5.6 Justification of Specification(s)

Provide justification of the specifications proposed for the drug product.

### 3.2.P.6 Reference Standards or Materials

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

### 3.2.P.7 Container Closure System

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

### 3.2.P.8 Stability

#### 3.2.P.8.1 Stability Summary and Conclusion

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include, for example, conclusions with respect to storage conditions and shelf-life, and, if applicable, in-use storage conditions and shelf-life.

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.

**3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment** The post-approval stability protocol and stability commitment should be provided.

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

### 3.2.P.8.3 Stability Data

Results of the stability studies should be presented in an appropriate format (e.g. tabular, graphical, narrative). Information on the analytical procedures used to generate the data and validation of these procedures should be included.

Information on characterisation of impurities is located in 3.2.P.5.5.

## 3.2.A APPENDICES

### 3.2.A.1 Facilities and Equipment

A diagram should be provided illustrating the manufacturing flow including movement of raw materials, personnel, waste, and intermediate(s) in and out of the manufacturing areas. Information should be presented with respect to adjacent areas or rooms that may be of concern for maintaining integrity of the product.

Information on all developmental or approved products manufactured or manipulated in the same areas as the applicant's product should be included.

A summary description of product-contact equipment and its use (dedicated or multi-use) should be provided. Information on preparation, cleaning, sterilisation, and storage of specified equipment and materials should be included, as appropriate.

Information should be included on procedures (e.g., cleaning and production scheduling) and design features of the facility (e.g., area classifications) to prevent contamination or cross contamination of areas and equipment, where operations for the preparation of cell banks and product manufacturing are performed.

### 3.2.A.2 Adventitious Agents Safety Evaluation

Information assessing the risk with respect to potential contamination with adventitious agents should be provided in this section.

**For non-viral adventitious agents:**

Detailed information should be provided on the avoidance and control of non-viral adventitious agents (e.g., transmissible spongiform encephalopathy agents, bacteria, mycoplasma, fungi). This information can include, for example, certification and/or testing of raw materials and excipients, and control of the production process, as appropriate for the material, process and agent.

**For viral adventitious agents:**

Detailed information from viral safety evaluation studies should be provided in this section. Viral evaluation studies should demonstrate that the materials used in production are considered safe, and that the approaches used to test, evaluate, and eliminate the potential risks during manufacturing are suitable. The applicant should refer to Q5A, Q5D, and Q6B for further guidance.

Materials of Biological Origin

Information essential to evaluate the virological safety of materials of animal or human origin (e.g. biological fluids, tissue, organ, cell lines) should be provided. (See related information in 3.2.S.2.3, and 3.2.P.4.5). For cell lines, information on the selection, testing, and safety assessment for potential viral contamination of the cells and viral qualification of cell banks should also be provided. (See related information in 3.2.S.2.3).

Testing at appropriate stages of production

The selection of virological tests that are conducted during manufacturing (e.g., cell substrate, unprocessed bulk or post viral clearance testing) should be justified. The type of test, sensitivity and specificity of the test, if applicable, and frequency of testing should be included. Test results to confirm, at an appropriate stage of manufacture, that the product is free from viral contamination should be provided. (See related information in 3.2.S.2.4 and 3.2.P.3.4 ).

Viral Testing of Unprocessed Bulk

In accordance with Q5A and Q6B, results for viral testing of unprocessed bulk should be included.

Viral Clearance Studies

In accordance with Q5A, the rationale and action plan for assessing viral clearance and the results and evaluation of the viral clearance studies should be provided. Data can include those that demonstrate the validity of the scaled-down model compared to the commercial scale process; the adequacy of viral inactivation or removal procedures for manufacturing equipment and materials; and manufacturing steps that are capable of removing or inactivating viruses. (See related information in 3.2.S.2.5 and 3.2.P.3.5).

### 3.2.A.3 Excipients

This appendix is required where applicable.

Novel Excipients - For any novel excipient, including adjuvants, preservatives and stabilizers, used for the first time in a drug product for human use or for a new route of administration, information to support the quality, safety, and suitability for use should be provided in this appendix.

This section should be submitted according to the drug substance and/or drug product CTD format described in this document along with cross references to nonclinical studies (Module 4) and clinical studies (Module 5) supporting the safety of a novel excipient.

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

### 3.2.R REGIONAL INFORMATION

### 3.2.R.1 Production documentation

### 3.2.R.1.1 Executed production documents

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

### 3.2.R.1.2 Master production documents

Copies of the FPP master production documents should be provided for each proposed strength, commercial batch size and manufacturing site.

### 3.2.R.2 Medical Devices

For a drug product supplied with a medical device, a description of the device(s), including its application, manufacturer, and confirmation that it has been notified or approved for use by GHFDA should be provided.

## 3.3 LITERATURE REFERENCES

Key literature referenced should be provided, if applicable.

**MODULE 4:**

## 4.0 NONCLINICAL STUDY REPORTS

This guideline presents the organisation of the nonclinical reports in the applications that will be submitted. This guideline is not intended to indicate what studies are required. It merely indicates an appropriate format for the nonclinical data that have been acquired.

The appropriate location for individual-animal data is in the study report or as an appendix to the study report.

### 4.1 Table of Contents of Module 4

A Table of Contents should be provided that lists all of the nonclinical study reports and gives the location of each study report in the Common Technical Document.

### 4.2 Study Reports

The study reports should be presented in the following order:

#### 4.2.1 Pharmacology

4.2.1.1 Primary Pharmacodynamics

4.2.1.2 Secondary Pharmacodynamics

4.2.1.3 Safety Pharmacology

4.2.1.4 Pharmacodynamic Drug Interactions

#### 4.2.2 Pharmacokinetics

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

4.2.2.2 Absorption

4.2.2.3 Distribution

4.2.2.4 Metabolism

4.2.2.5 Excretion

4.2.2.6 Pharmacokinetic Drug Interactions (nonclinical)

4.2.2.7 Other Pharmacokinetic Studies

**4.2.3 Toxicology**

4.2.3.1 Single-Dose Toxicity (in order by species, by route)

4.2.3.2 Repeat-Dose Toxicity (in order by species, by route, by duration; including

supportive toxicokinetics evaluations)

4.2.3.3 Genotoxicity

4.2.3.3.1 In vitro

4.2.3.3.2 In vivo (including supportive toxicokinetics evaluations)

4.2.3.4 Carcinogenicity (including supportive toxicokinetics evaluations)

4.2.3.4.1 Long-term studies (in order by species; including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)

4.2.3.4.2 Short- or medium-term studies (including range-finding studies that cannot) appropriately be included under repeat-dose toxicity or pharmacokinetics

4.2.3.4.3 Other studies

4.2.3.5 Reproductive and Developmental Toxicity (including range-finding studies and supportive toxicokinetics evaluations) (If modified study designs are used, the.) following subheadings should be modified accordingly

4.2.3.5.1 Fertility and early embryonic development

4.2.3.5.2 Embryo-fetal development

4.2.3.5.3 Prenatal and postnatal development, including maternal function

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

4.2.3.6 Local Tolerance

4.2.3.7 Other Toxicity Studies (if available)

4.2.3.7.1 Antigenicity

4.2.3.7.2 Immunotoxicity

4.2.3.7.3 Mechanistic studies (if not included elsewhere)

4.2.3.7.4 Dependence

4.2.3.7.5 Metabolites

4.2.3.7.6 Impurities

4.2.3.7.7 Other

**4.3 Literature References**

**MODULE 5:**

**CLINICAL STUDY REPORTS**

This module provides guidance on the organization of the study reports, other clinical data, and references within an application for registration of a pharmaceutical product. These elements should facilitate the preparation and review of a marketing application.

This module is not intended to indicate what studies are required for successful registration.

It indicates an appropriate organization for the clinical study reports that are in the application. This module recommends a specific organization for the placement of clinical study reports and related information to simplify preparation and review of dossiers and to ensure completeness. The placement of a report should be determined by the primary objective of the study. Each study report should appear in only one section. Where there are multiple objectives, the study should be cross-referenced in the various sections. An explanation such as —not applicable or —no study conducted should be provided when no report or information is available for a section or subsection.

**5.1 Table of Contents of Module 5**

A Table of Contents for study reports should be provided.

**5.2 Tabular Listing of All Clinical Studies 5.3 Clinical Study Reports**

**5.3.1 Reports of Biopharmaceutic Studies**

5.3.1.1 Bioavailability (BA) Study Reports

5.3.1.2 Comparative BA and Bioequivalence (BE) Study Reports

5.3.1.3 In vitro-In vivo Correlation Study Reports

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

**5.3.2 Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials**

5.3.2.1 Plasma Protein Binding Study Reports

5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies

5.3.2.3 Reports of Studies Using Other Human Biomaterials

**5.3.3 Reports of Human Pharmacokinetic (PK) Studies**

5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports

5.3.3.2 Patient PK and Initial Tolerability Study Reports

5.3.3.3 Intrinsic Factor PK Study Reports

5.3.3.4 Extrinsic Factor PK Study Reports

5.3.3.5 Population PK Study Reports

**5.3.4 Reports of Human Pharmacodynamic (PD) Studies**

5.3.4.1 Healthy Subject PD and PK/PD Study Reports

5.3.4.2 Patient PD and PK/PD Study Reports

**5.3.5 Reports of Efficacy and Safety Studies**

5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the claimed Indication

5.3.5.2 Study Reports of Uncontrolled Clinical Studies

5.3.5.3 Reports of Analyses of Data from More Than One Study

5.3.5.4 Other Clinical Study Reports

**5.3.6 Reports of Post-Marketing Experience**

**5.3.7 Case Report Forms and Individual Patient Listings**

**5.4 Literature References**

## APPENDIX I

## RISK MANAGEMENT PLAN (RMP)

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

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

  activities and interventions
- Communicating this information to the GHFDA in a timely manner

The GHFDA will request that a RMP is submitted before the biological product is registered. Also, the GHFDA 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; o 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 GHFDA that submission of a RMP is not required
- on the request of the GHFDA (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 GHFDA on any questions they may have about their responsibilities relating to this section of the guidelines.

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

## APPENDIX III

## SANCTIONS AND PENALTIES

- The Authority shall cancel, suspend or withdraw the registration of a product if:
    - The information on which the product was registered is later found to be false
    - The circumstances under which the product was registered no longer exist Any of the provisions under which the product was registered has been contravened
    - The standard of quality, safety and efficacy as prescribed in the documentation 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.

**APPENDIX IV:**

**RELEVANT INFORMATION TO BE INCLUDED IN DOSSIER**

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

- Evidence of payment for evaluation and registration (a copy of payment receipt) o 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 o 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 o Report on the choice of host organism
- Report on process validation o 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, GHFDA)
- Quantity and number of samples (biological medicinal product) received (client service, GHFDA)
- Programme for post-market surveillance/Pharmacovigilance and risk management plan
- Report on substitution and interchangeability (if applicable)
- Package Insert

**APPENDIX V:**

**RELEVANT GHFDA 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 VIII:**

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