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Technical Advisory Committee on Safety of Vaccines and Biological Products (TAC-VBP)

GUIDELINE ON REGISTRATION OF BIOSIMILAR PRODUCTS

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Acknowledgement

Executive Summary

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

Guideline on Registration of Biosimilar Products

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1.0 INTRODUCTION

Biopharmaceuticals are protein molecules derived from biotechnology methods or other cutting-edge technologies. Biologics are large, highly complex molecular entities manufactured using living cells and are inherently variable. The manufacturing process is highly complex and critical to defining the characteristics of the final product. Maintaining batch-to-batch consistency is a challenge. Subtle variations in the production or even transport or storage conditions may potentially result in an altered safety and efficacy profile of the final product.

Based on the current analytical techniques, two biologics produced by different manufacturing processes cannot be shown to be identical, but similar at best. Therefore, the term biosimilar is appropriate. Immunogenicity of biopharmaceuticals is of concern from clinical and safety perspective. Clinical trials and a robust post-market surveillance/pharmacovigilance plan are essential to guarantee the product is safe and efficacious over time.

These guidelines were developed to describe the regulatory framework for biosimilars in Ghana, which aligns with current global regulation of biosimilars. It is intended to guide applicants on the Chemistry, Manufacturing and Control (CMC) section of a marketing application for a proposed similar biological medicinal product. The marketing application must include information demonstrating biosimilarity, based on data derived from, among other things, analytical studies that demonstrate that the biological is highly similar to the reference product notwithstanding minor differences in clinically inactive components.

Although the regulatory framework applies generally to biological products, this guidance document focuses on biosimilars and provides an overview of the quality, non-clinical and clinical factors to consider in demonstrating biosimilarity between a proposed biological product and the reference product.

Application submitted for the registration of biosimilars under the Ghana Public Health Act 851 of 2012 should contain, among other things, data demonstrating that the biological product is biosimilar to a reference product based upon data derived from;

- Analytical assessment (physicochemical and functional studies) demonstrating the biological product is highly similar to the reference product regardless of minor differences in clinically inactive components
- Animal studies, including the assessment of toxicity

- A clinical study or studies, including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics, that are sufficient to demonstrate safety, purity, and potency in one or more appropriate indications of use for which the reference product is registered and intended to be used and for which registration is sought for the biological product.

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 on 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 this Guideline is made to provide guidance to applicants on the procedure for registering a Similar Biological medicinal Product in Ghana. Applicants are encouraged to acquaint themselves with this document and the above law before completing the registration form.

The concept of a biosimilar applies to biological drug submission in which the manufacture would be based on demonstrated similarity to a reference product, relying in part on publicly available information from a previously approved biological product in order to present reduced non-clinical and clinical data as part of the submission. This guidance document gives an overview of the quality, non-clinical and clinical studies that may be relevant to assessing whether the proposed biosimilar product and a reference product are highly similar, which is part of the biosimilarity assessment. If the reference product and the proposed similar biological medicinal product cannot be adequately characterized with state-of-the-art technology as recommended by this guidance document, the Ghana FDA recommends that the applicant consult the authority for guidance on whether an

application for the proposed biosimilar product is appropriate for submission as a biosimilar.

The demonstration of similarity depends on detailed and comprehensive product characterisation; therefore, information requirements outlined in this document apply to biological medicinal products that contain, as the active pharmaceutical ingredient, a well characterised protein molecule derived via modern biotechnological methods.

Generally, all product applications must include complete and detailed Chemistry, Manufacturing and Controls (CMC) sections that contain the relevant information (e.g. product characterization, adventitious agent safety, process controls, and specifications, etc.) to be reviewed. Certificates for Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP) issued for the facilities used to manufacture and validate the biosimilar product should be contained in the application document. Consideration for additional CMC data may be relevant for the assessment of biosimilarity between a similar biological medicinal product and a reference product with limited clinical exposure.

In addition, an assessment of whether a proposed similar biological medicinal product is biosimilar to a reference product generally will include animal studies (including the assessment of toxicity and a clinical study or studies (including the assessment of immunogenicity and pharmacokinetics and/or pharmacodynamics).

The registration of a product using the biosimilar regulatory framework depends on the analytical procedures, the manufacturing process employed, as well as clinical and regulatory experiences. This guideline should be used in conjunction with other guidance document available from the Ghana FDA, EMEA, ICH and the US FDA that describe the CMC, non-clinical and clinical requirements appropriate for evaluating biological products.

2.0 GLOSSARY

In these Guidelines, unless the context otherwise states:

- **“Antibody”** means a spectrum of proteins of the immunoglobulin family that is produced, in the human (or animal) body, in response to an antigen (e.g., a virus or bacterium, or a foreign protein unknown to the body’s immune system). Antibodies are able to combine with and neutralize the antigen, as well as to stimulate the immune system for defence reactions.
- **“Antigen”** means a substance that causes the immune system to produce antibodies against it.
- **“API” (Active Pharmaceutical Ingredient)** means any substance or mixture of substances intended to be used in the manufacture of a drug product by formulation with excipients and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.
- **“Applicant”** means the product owner or licence holder. Representatives of licence holders may not hold themselves as applicants unless they own the product.
- **“Authority”** means Food and Drugs Authority.
- **“Bioavailability”** means the rate and extent to which the active moiety is absorbed from a pharmaceutical dosage form and becomes available at the site of action.
- **“Bioequivalence”** means that two proprietary preparations of a drug, when administered in the same dose and by the same route, will have the same bioavailability, duration of action and efficacy.
- **“Biologics”** means biological products, which include a wide range of products such as vaccines, blood and blood components, allergenic, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, nucleic acids or complex combinations of these substances, or maybe living entities such as cells and tissues. Biologics isolated from a variety of natural sources - human, animal, or microorganism and may be

produced by biotechnology methods and other cutting-edge technologies. They often are at the forefront of biomedical research and may be used to treat a variety of medical conditions for which no other treatments are available.

- **“Biosimilar or Biosimilarity (similar biological medicinal product)”** means a new biological product claimed to be „similar” to an already approved reference product, which is marketed by an independent applicant, subject to all applicable data protection periods and/or intellectual property rights in the originator product. The requirements for the registration of biosimilars are based on the demonstration of similarity (i.e. no clinically meaningful difference between the biosimilar product and the reference product) in terms of quality, safety and efficacy to an already registered, well- established biological product.
- **“Chemically synthesized polypeptide”** means any alpha amino acid polymer that is (a) made entirely by chemical synthesis, and (b) is less than 100 amino acids in size.
- **“CMC (Chemistry, Manufacturing, and Control)”** means the section of a submission dealing with the substance properties, manufacturing and quality control, intended for evaluating the provided information in the context of the current standards in chemical science and technology, and the current regulations.
- **“Comparability”** means that a given product has highly similar quality attributes before and after manufacturing process changes, and that no adverse impact on the safety or efficacy, including immunogenicity, of the drug product occurred. This conclusion can be based on an analysis of product quality attributes. In some cases, non-clinical or clinical data might contribute to the conclusion.
- **“Comparability exercise”** means the activities including study design, conduct of studies, and evaluation of data, that are designed to investigate whether the products are comparable.
- **“Drug product”** means the dosage form of a pharmaceutical product in the final immediate packaging intended for marketing.
- **“Equivalent”** means equal or virtually identical in the parameter of interest. Small non-relevant differences may exist. Equivalent efficacy of two drug products means they have similar (no better or no worse) efficacy, and any observed differences are of no clinical relevance.

- **“ICH” means International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.** ICH is a project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration. The purpose is to make recommendations on ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines. For more information, see <http://www.ich.org/>.
- **“Immunogenic”** means any substance that is recognized as „foreign” by the immune system in a (particular) higher organism and induces an immune response which may include the formation of antibodies, developing immunity, tolerance or hypersensitivity to the antigen.
- **“Immunogenicity”** means the ability of a substance to trigger an immune response in a particular organism.
- **“Impurity”** means any component present in the final product, intermediate or API that is not the desired entity.
- **“In-process control or Process control”** means checks performed during production to monitor and, if appropriate, to adjust the process and/or to ensure that the intermediate or API conforms to its specifications.
- **“Innovator Product”** means a means a new chemical entity which has received a patent on its chemical formulation or manufacturing process, obtains approval from a regulatory authority after extensive testing and is sold under a brand name.
- **“Interchangeability”** means a product is interchangeable with another if both products are approved for the same indication and can be used for the said indication. For interchangeable products, one or the other can be used (prescribed) but these products cannot be substituted with one another during a treatment period. Hence, interchangeability does not imply substitutability.
- **“International Non-proprietary Name (INN)”** means the approved chemical name of the product.
- **“Lead market brand”** means a branded product which has been determined by criteria including, but not limited to, the following:

- Sales volume
- Safety profile
- Number of prescriptions
- Expert opinion
- **“Medicinal purpose”** means use for treating or preventing a disease, diagnosing or ascertaining the presence and extent of a physiological function, contraception, inducing anaesthesia, altering normal physiologic function permanently or temporarily in any way in humans.
- **“Originator product (Reference product)”** means a product for which a registration is granted to a given applicant for a given active substance based upon a complete dossier.
- **“Pharmacovigilance”** according to the WHO definition means, the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems. The decision to approve a drug is based on a satisfactory balance of benefits and risks within the conditions specified in the product labelling. This decision is based on the information available at the time of approval. The knowledge related to the safety profile of the product can change over time through expanded use in terms of patient populations and the number of patients exposed. In particular, during the early post-marketing period the product might be used in settings different from clinical trials and a much larger population might be exposed in a relatively short timeframe. Detailed evaluation of the information generated through pharmacovigilance activities is important for all products to ensure their safe use.
- **“Pre-clinical (non-clinical)”** means during pre- clinical drug development, a sponsor evaluates the drug’s toxic and pharmacologic effects through in vitro and in vivo laboratory animal testing. Generally, genotoxicity screening is performed, as well as investigations on drug absorption and metabolism, the toxicity of the drug’s metabolites, and the speed with which the drug and its metabolites are excreted from the body.
- **“Protein”** means any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size.

- **“Product”** means intermediates, drug substance, and /or drug product, as appropriate. The use of the term “product” is consistent with the use of the term in **ICH Q5E**.
- **“Reference biological product”** means a single biological drug product registered under the Ghana Public Health Act 851 of 2012 against which a biosimilar product is evaluated. Contains an active biological substance with proven quality, safety and efficacy through non-clinical (toxicity) and clinical studies.
- **“Similarity”** means if a company chooses to develop a new biological product claimed to be “similar” to a reference product, comparative studies are needed to generate evidence substantiating the similar nature, in terms of quality, safety and efficacy, of the new similar biological product and the chosen reference product.
- **“Specification”** means a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance, drug product or materials at other stages of its manufacture should conform to be considered acceptable for its intended use.
- **“Conformance to specification”** means that the drug substance and drug product, when tested according to the listed analytical procedures, will meet the acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.
- **“Substitutability”** means two products are substitutable with each other if they can both be used in lieu of the other during the same treatment period. Substitutable products are interchangeable with each other. Cross-over studies are required to demonstrate substitutability.
- **“Validation”** means the process of demonstrating that the system (or process) under consideration meets in all respects the specification of that system or process. Also, the process of evaluating a system or component during or at the end of the development process to determine whether it satisfies specified requirements. In the manufacturing of medicinal products, production processes, cleaning procedures, analytical methods, in-process control test procedures, and computerized systems all have to be validated.

- **“Variation”** means a change in the indication(s), dosage recommendation(s), drug classification and/or patient group(s) for a previously registered drug being marketed under the same name in Ghana. A variation also includes, but is not limited to, a change in the product name, site of manufacture and/or source of ingredients.
- **“Well-characterized biologic”** means a chemical entity whose identity, purity, impurities, potency and quantity can be determined and controlled. Most of these products are recombinant DNA derived from proteins or monoclonal antibodies. For DNA-derived proteins, determining identity requires establishing the primary and secondary structures, including amino acid sequence, disulphide linkages (if possible), and post-translational modifications such as glycosylation (the attachment of carbohydrate side chains to the protein). Monoclonal antibodies can be identified with „rigorous physicochemical and immunochemical assays. Purity and impurities must be quantified, with impurities being identified if possible; the biological activity and the quantity must be measurable.
- **“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.

2.1 CONCEPT OF BIOSIMILARS

The rationale for creating a new regulatory framework to evaluate biosimilars is that biological products claimed to be highly similar to a reference product do not usually meet all the conditions to be considered as a generic product. The term generic medicine is used for chemically derived products which are identical and therapeutically equivalent to the originator product. For such generics, demonstration of bioequivalence with the originator product is usually appropriate to infer therapeutic equivalence.

However, it is unlikely that a biological product can generally follow this standard approach for generics. The large and complex molecular structure of biologics makes it difficult to adequately characterise in the laboratory.

Based on the current analytical techniques, two biological products produced by different manufacturing processes cannot be shown to be identical, but similar at best. For these reasons, the standard generic approach is scientifically not applicable to development of biosimilar products and additional non-clinical and clinical data are usually required.

Based on the comparability approach and when supported by state-of-the-art analytical systems, the comparability exercise at the quality level may allow a reduction of the non-clinical and clinical data requirements compared to a full dossier. This in turn, depends on the clinical experience with the substance class and will be a case-by-case approach.

The aim of the biosimilar approach is to demonstrate close similarity of the biosimilar product in terms of quality, safety and efficacy to a specific FDA-registered reference product.

2.2 CONCEPTS AND PRINCIPLES

Advances in analytical sciences (both physicochemical and biological) enable some protein products to be characterized extensively in terms of their physicochemical and biological properties. These state-of-the-art analytical techniques have improved the ability to identify and characterize not only the desired active pharmaceutical ingredient but also product-related substances and product-and process-related impurities.

In addition to a complete CMC data submission, the applicant should assess the analytical similarity to the reference. The purpose for the analytical similarity assessment should be clearly described with consideration of the known quality attributes and performance characteristics of the specific reference product.

These fundamental concepts and principles constitute the basis of the regulatory framework for biosimilars:

- The principles within the existing regulatory framework for biological medicinal products and biotechnology-derived medicinal products shall be the basis of the regulatory framework for similar biological medicinal products (also known as biosimilars).
- In implementing this guidance document, all the relevant guidelines on biological medicinal products containing a biotechnology-derived protein as an active substance will be used as the basis for defining the registration requirements and/or process for registration of biosimilars in Ghana.
- Approval of a product through the biosimilar regulatory framework is not an indication that the biosimilar may be automatically substituted/interchanged with its reference product. The decision for substitutability/interchangeability with the reference product shall be based on science and clinical data.
- A biosimilar product cannot be used as a reference product by another manufacturer because a reference product has to be approved on the basis of a complete/full quality, non-clinical and clinical data package.
- Eligibility for a biosimilar pathway hinge on the ability to demonstrate similarity to a reference product. Products employing clearly different approaches to manufacture from the reference product will not be eligible for registration as a biosimilar.
- The manufacturer must conduct a direct and extensive comparability exercise between its product and the reference product, in order to demonstrate that the two products have a similar profile in terms of quality, safety and efficacy. Only **ONE** reference product is allowed throughout this exercise even in situations where multiple registered products are on the market. An applicant must demonstrate that the proposed similar biological medicinal product is highly similar to a single FDA registered reference product. The rationale for the choice of reference products should be provided by the manufacturer to FDA. Also, evidence of purchase of the reference product (reference standard and finished biological product) should be contained in the dossier for evaluation.
- Non-clinical and clinical requirements outlined for similar biological medicinal products submission in this guidance document are applicable to biosimilars that have been demonstrated to be similar to the reference product, based on results of the comparability exercises from chemistry, manufacturing and control

(CMC) perspectives. When similarity of a biosimilar cannot be adequately established, the submission of such a product should be as a stand-alone biological product with a complete quality, non-clinical and clinical data package.

- It should be recognised that there may be subtle differences between biosimilars from different manufacturers or compared with reference products, which may not be fully apparent until greater experience in their use has been established. Therefore, in order to support pharmacovigilance monitoring, the specific biosimilar given to patient should be clearly labelled and identified (preferably by the brand name) by the prescriber.
- Although International Non-proprietary Names (INNs) served as a useful tool in worldwide pharmacovigilance for biological, they cannot be relied upon as the only means of product identification or as an indicator of the interchangeability of biological products, particularly biosimilars.
- A Good Manufacturing Practice (GMP) on-site inspection of the manufacturing facilities is required.

2.3 SCIENTIFIC GUIDELINES APPLICABLE TO ALL BIOSIMILARS

- Where specific guidelines are unavailable, the FDA adopts Committee for Medicinal Product for Human Use (CHMP) Guidelines, which are available at the following websites EMEA: <http://www.emea.europa.eu> and International Conference of Harmonization (ICH) Guidelines: <http://www.ich.org>. Where specific guidelines are unavailable, the FDA adopts Committee for Medicinal Product for Human Use (CHMP) Guidelines, which are available at the following websites EMEA: <http://www.emea.europa.eu> and International Conference of Harmonization (ICH) Guidelines: <http://www.ich.org><http://www.ich.org/>
- Topic **S6**, Step 4 Notes for Preclinical Safety Evaluation of Biotechnology-Derived Products (CPMP/ICH/302/95).
- Guidelines on similar biological products (Biosimilar Guidelines)
- The following guidelines address the quality, non-clinical and clinical aspects for the development of biosimilars. Product-class specific documents on non-clinical and clinical studies to be conducted for the development of defined biosimilar products will be made progressively available.
- Guideline on similar biological medicinal products (EMA/CHMP/437/04)

- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substances: Quality issues (EMA/CHMP/BWP/49348/2005).
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substances: Non-clinical and Clinical issues (EMA/CHMP/42832/2005).
- Annex draft guideline on similar biological medicinal products containing biotechnology-derived proteins as active substances: Non-clinical and Clinical issues - Guidance on similar medicinal products containing recombinant human soluble insulin and insulin analogues (EMA/134217/2012).
- Annex guideline on similar biological medicinal products containing biotechnology-derived proteins as active substances: Non-clinical and Clinical issues - Guidance on similar medicinal products containing Somatropin (EMA/CHMP/94528/2005).
- Annex guideline on similar biological medicinal products containing biotechnology-derived proteins as active substances: Non-clinical and Clinical issues - Guidance on similar medicinal products containing recombinant erythropoietin's (EMA/CHMP/94526/2005).
- Annex guideline on similar biological medicinal products containing biotechnology-derived proteins as active substances: Non-clinical and Clinical issues - Guidance on similar medicinal products containing recombinant granulocyte-colony stimulating factor. (EMA/CHMP/31329/2005).
- Guideline on Immunogenicity Assessment of Biotechnology-derived.
- Therapeutic Proteins (EMA/CHMP/14327/2006).
- Guideline on Risk Management Systems for Medicinal Products for human Use (EMA/CHMP/96268/2005)

3.0 REQUIREMENTS

3.1 ADMINISTRATIVE STATUS OF THE PRODUCT

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

- **Qualified person responsible for product release** (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 release. The information should include the identity and designation of the authorized person in charge of regulatory activities.

- **Certificate of Pharmaceutical Product**

Using the World Health Organisation (WHO) model, this certificate includes information on compliance with good manufacturing practices (GMP). A free sale certificate where applicable should be submitted in addition to the GMP certificate.

- **Certificate of good manufacturing practices of other manufacturers involved in the production of the 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 artwork 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.

- The Ghana Food and Drugs Authority recommends that applicants intending to develop biosimilar products should meet with regulators at the FDA to present their product development plans and establish a schedule of milestones that will serve as standards for future discussions with the authority.

3.2 SPECIFIC REQUIREMENTS

Biopharmaceuticals are protein molecules derived from biotechnology methods or other cutting-edge technologies. Biologics are large, highly complex molecular entities manufactured using living cells and are inherently variable. The manufacturing process is highly complex and critical to defining the characteristics of the final product. Maintaining batch-to-batch consistency is a challenge. Subtle variations in the production or even transport or storage conditions may potentially result in an altered safety and efficacy profile of the final product.

Based on the current analytical techniques, two biologics produced by different manufacturing processes cannot be shown to be identical, but similar at best. Therefore, the term biosimilar is appropriate. Immunogenicity of biopharmaceuticals is of concern from clinical and safety aspects. Clinical trials and robust post

marketing pharmacovigilance are essential to guarantee the product is safe and efficacious over time.

These guidelines were developed to meet the challenges in biotherapy and describe the regulatory framework for biosimilars in Ghana, which aligns with current global regulation of biosimilars.

Specifically, the guidance document is intended to guide applicants on the scientific and technical information on the chemistry, manufacturing and controls (CMC) section of a marketing application for a proposed similar biological medicinal product. The marketing application must include information demonstrating biosimilarity, based on data derived from, among other things, analytical studies that demonstrate that the biology is highly similar to the reference product notwithstanding minor differences in clinically inactive components.

Although the regulatory framework applies generally to biological products, this guidance document focuses on biosimilars and provides an overview of the quality, non-clinical and clinical factors to consider in demonstrating biosimilarity between a proposed biological product and the reference product.

Application submitted for the registration of biosimilars under the Ghana Public Health Act 851 of 2012 should contain, among other things, data demonstrating that the biological product is biosimilar to a reference product based upon data derived from.

- Analytical assessment (physicochemical and functional studies) demonstrates the biological product is highly similar to the reference product regardless of minor differences in clinically inactive components.
- Animal studies, including the assessment of toxicity.
- A clinical study or studies, including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics, that are sufficient to demonstrate safety, purity, and potency in one or more appropriate indications of use for which the reference product is registered and intended to be used and for which registration is sought for the biological product.

3.3 OTHER REQUIREMENTS

3.3.1. New Registration

- An application for the registration of a drug, 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/licence 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
 - A completed application form for Biosimilar products. A downloadable version of the form is available on the FDA's website.
 - Samples of the product in the final package in the appropriate storage condition as specified in the Authority's sample Schedule.
 - Reference/working standard for Active Pharmaceutical Ingredient and related impurities where necessary.
 - All supporting documents in the Common Technical Document (CTD) format 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.
- The original certificate of analysis for the batch of the drug 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 product shall be made into the country other than those used as samples for the purpose of this application.

3.3.2 Registration Variation

- An application for a variation of the registration of a biosimilar prior to its re-registration becoming due may be made to the Authority.
- The application shall be accompanied by:
 - A duly signed covering letter
 - Documentation in support of the variation. Please refer the FDA's Guidelines for Reporting Variations to a Registered Biological Product in Ghana.
 - Samples reflecting the variation as specified in the Authority's sample Schedule, where applicable.
 - A non-refundable variation fee as specified in the Authority's fee schedule.
- This variation shall be approved by the Authority before any importation of the varied biosimilar shall be made into the country, other than those used as samples for the purpose of this application

3.3.2 Registration Renewal

- An application for the re-registration of a biosimilar shall be made 3 (three) months before expiration of the last registration.
- The application shall be accompanied by:
 - A covering letter
 - Supporting documentation for any variations since the biosimilar was last registered
 - Application form
 - Samples of the biosimilar in the final package in the appropriate storage condition as specified in the Authority's sample Schedule
 - Non-refundable application fee as specified in the Authority's fee Schedule.
 - Certificate of analysis of the finished biosimilar.
 - Certificate of Pharmaceutical Product (CoPP) issued by the statutory national drug regulatory authority, in accordance with the World Health Organisation (WHO) Certification Scheme for Pharmaceutical Products Moving in International Commerce.
 - Long-term/Real-time and real condition stability studies for three (3) production batches (protocol and report).
 - Method of analysis (Protocol and Report)

- Analytical Method Validation (Protocol and Report)
- Batch release documents.
- Reference Standard/ 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)

N.B The renewal of registration shall be approved by the Authority before any importation of the biosimilar shall be made into the country, other than those used as samples for the purpose of this application.

3.4 REQUIREMENTS FOR REGISTRATION /MARKETING AUTHORIZATION RELIANCE

Regarding products that have already been approved by a well-resourced NRA or WHO Listed Authorities, 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 the full CTD dossier and the full Assessment reports of the CTD submitted to the well-resourced NRA for approval. The application shall be identical to that submitted, evaluated and approved by the well-resourced NRA or reference NRA. Refer to the current version of the FDA Reliance Policy on the website.

3.5 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.

3.6 EXPERT REPORT

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.

3.7 GUIDANCE FOR IMPLEMENTATION

3.7.0 QUALITY

To be submitted in accordance to CTD Module including:

3.7.1 Comparability Exercise:

- The goal of comparability exercise is to ascertain if the biosimilar and the reference product is similar in terms of quality, safety and efficacy.
- Comparability exercise to demonstrate similarity should involve all aspects of development including full analytical comparability data on quality, and abridged studies for the non-clinical and clinical components. The dossier must contain detailed sections on substitution and interchangeability where applicable.
- Comparative physicochemical and functional characterization studies should be sufficient to establish relevant quality attributes including those that define a product's identity, quantity, purity, potency and consistency.

- The same reference product should be used throughout the comparability program and evidence of purchase of the reference product (i.e. active pharmaceutical ingredient and the final formulation) should be provided.
- Comparability with the reference product should address both the active substance and drug product characteristics.
- It is not expected that the quality attributes in the biosimilar and the reference product will be identical. For example, minor structural differences in the active substance such as variability in posttranslational modifications may be acceptable, however they should be justified.
- Quality differences may impact on the amount of non-clinical and clinical data needed.
- If the reference drug substance used for characterisation is isolated from a formulated reference drug product, additional studies should be carried out to demonstrate that the isolation process does not affect the important attributes of the drug substance.
- When considering the similarity of products, the manufacturer should evaluate, for example:
 - Relevant physicochemical and biological characterization data regarding quality attributes.
 - Results from analysis of relevant samples from the appropriate stages of the manufacturing process (i.e. drug substance and drug product).
 - Stability data, including those generated from accelerated or stress conditions, provide insight into potential product differences in the degradation pathways of the drug product and, hence, potential differences in product-related substances and product-related impurities.
 - Data obtained from multiple batches of the biosimilar and the reference biologic drug to help generate an understanding of ranges in variability. This evaluation may not entail performing all tests on all batches; a matrix approach may be possible but should be rationalized.
- In addition to evaluating the data, the manufacturer should consider if the results provide insights regarding the following:

- Critical control points in the manufacturing process that affect product characteristics.
- Adequacy of the in-process controls including critical control points and in-process testing in-process controls for the biosimilar should be confirmed, modified, or created, as appropriate, to maintain the quality of the product.
- Comparative structural and functional studies will determine the type and extent of data to be derived from non-clinical and clinical studies on the drug product.

3.7.2 Manufacture:

- Manufacturers should critically consider the following factors when demonstrating similarity between a biosimilar and a reference product:
- Expression system: differences between the chosen expression system of the proposed biosimilar product and that of the reference product should be carefully considered and appropriately documented by the applicant. Characterization of the expression construct, including its genetic stability, should be demonstrated in accordance with principles recommended in **ICH Q5B**.
- Evaluation of Physicochemical Properties: physicochemical analysis of the proposed biosimilar product and the reference product should consider all relevant characteristics of the protein product (e.g. the primary, secondary, tertiary, and quaternary structures, post-translational modifications, and functional activity(ies)). Applicants should provide detailed reports that address the concept of the desired product (and its variant) in accordance with **ICH Q6**, when designing and conducting the characterization studies. It is recommended that the analytical test method is selected to address the full range of physicochemical properties or biological activities adequately. Information concerning the ability of a method to discern relevant differences between a proposed biosimilar product and a reference product should be submitted as part of the comparison.
- Functional Activities: manufactures should clearly provide the potential limitation of some functional assays such as high variability that might preclude detection of small but significant differences between the

proposed biosimilar product and the reference product. Since a highly variable assay may not provide a meaningful assessment as to whether the proposed biosimilar product is highly similar to the reference product. Applicants are encouraged to develop and apply essays that are sensitive to changes to functional activities of their products.

- Receptor binding and Immunochemical properties: appropriate analytical assessments should be carried out to characterize the specific binding or immunochemical attributes of the biological product (e.g. if binding to a receptor is inherent in the protein function, the property should be measured and used in comparative studies, see **ICH Q6B** for further details). Applicants should provide detailed protocols and reports on the kinetics and thermodynamics of the binding attributes of the product.
- Impurities: applicants should characterize, identify and quantify impurities (product- and process-related as stated in **ICH Q6B**) in the proposed biosimilar and reference product. Note: if a comparative physicochemical study reveals comparable product-related impurities at similar levels between the two products, pharmacological/toxicological studies to characterize potential biological effect of specific impurities may not be necessary. In contrast, if the manufacturing process used to generate the proposed biosimilar product introduces different impurities or higher levels of impurities than those present in the reference product, additional pharmacological/toxicological or other studies may be necessary. As stipulated in **ICH S6**, it is desirable to rely on purification processes to remove impurities rather than rely on non-clinical programmes for their qualification. In addition to product-related impurities, status of process related impurities (e.g. host cell DNA, host cell proteins, antibiotics, media components, reagent, residual solvent, leachable, endotoxin, bioburden, etc.) should be clearly defined in the quality section of the dossier. The potential impact of differences in the impurity profile on safety should be clarified and supported by appropriate data. The applicant should ensure that the chosen analytical procedures are adequate to detect, identify and accurately quantify biologically significant levels of impurities (consult **ICH Q2B**). Regarding safety of the proposed biosimilar product, as with all

biological products, with regards to adventitious agents or endogenous viral contaminations, applicants are requested to provide evidence of screening of critical raw materials and confirmation of robust viral removal and inactivation achieved by the manufacturing process (see **ICH Q5A** for guidance).

- Finished drug product: product characterization assessment should be carried out on the most downstream intermediate best suited for the analytical procedures used and should be performed on the bulk drug substance. Impact on reformulated bulk drug substance should be documented. Comparative analysis to show the type, nature and extent of variation between the finished biosimilar product and the finished reference product should be evaluated and supported by appropriate data and rationale. New excipients in the biosimilar product should be supported by toxicological data for the excipient or by additional toxicity studies with the formulation of the biosimilar product.
- Stability: a suitable physicochemical and functional comparison of the suitability of the proposed biosimilar product with that of the reference product should be initiated. Accelerated and stress stability studies, or forced degradation studies, should be carried out and applied to establish degradation profiles and provide direct comparison of the proposed biosimilar product with the reference product. Note: the comparative studies should be carried out under multiple stress conditions (e.g., high temperature, freeze thaw, light exposure, and agitation) that can lead to incremental product degradation over a defined time period (see **ICH Q5C** and **Q1A (R)**). Adequate real time, real condition stability data should be provided to support the proposed dating period.
- A separate comparability exercise, as described in **ICH Q5E**, should be conducted whenever change is introduced into the manufacturing process.

3.7.3 Reference Product/Reference Standard:

- A biosimilar application should contain a thorough analytical comparison between the biosimilar and the reference product.
- A thorough physicochemical and biological evaluation of the reference product should provide a quantum of information from which to develop the

proposed biosimilar and justify reliance on certain existing scientific knowledge about the reference product.

- Sufficient data demonstrating that the proposed biosimilar is highly similar to the reference product must be demonstrated in an appropriate time frame to support a selective and targeted approach in early product development (e.g. reduced non-clinical studies, and /or dose-finding clinical studies).
- A comparative test performed with the isolated active substance obtained from the formulated reference product is usually required except, quality attributes of the active substance can be tested using the finished product. However, if the active biological substance has been extracted from the reference product to perform analytical similarity, the applicant must describe the extraction procedure and provide literature/results to demonstrate that the extraction procedure itself does not alter the quality of the extracted active biological substance.
- The manufacturer should demonstrate that the active substance used in the comparability studies is “representative of the active substance” contained in the reference product.
- Comparing the active substances contained in both the biosimilar and the reference product on the basis of pharmacopoeia/scientific publications is not sufficient to demonstrate similarity.
- An applicant may seek to use data derived from animal or clinical studies by comparing a proposed biosimilar to a non-registered FDA product to address, in part the requirement for registering a biosimilar product. In such a case, the applicants should provide sufficient data to scientifically justify the relevance of this comparative information to an assessment of biosimilarity and to establish an acceptable link to the FDA-registered reference product. The scientific link between the non-FDA registered product and the FDA registered reference product may include comparative physicochemical characterization, bioassays/functional assays, and comparative clinical and /or nonclinical PK and/or PD data, as appropriate, and data to address any difference in formulation and packaging.
- As stipulated in **ICH Q6B**, an in-house reference standard(s) should always be qualified and used for control of the manufacturing process and products

- The same reference product should be used for all the three segments of the dossier (i.e. Quality, Safety and Efficacy).
- To justify a selective and targeted approach to a clinical programme, a comprehensive physicochemical and functional comparison to the reference product should be performed during early product development. An analytical similarity assessment should support the use of the lots that demonstrate the biosimilarity of the biosimilar product used in the principal clinical trial to the reference and the proposed commercial product.
- The chosen reference product should have a suitable duration and volume of marketed use such that the demonstration of similarity will bring into relevance a substantial body of acceptable data dealing with safety and efficacy.
- The brand name, pharmaceutical form, formulation and strength of the reference product used in the comparability exercise should be clearly stated.
- The shelf life of the reference product and its effect on the quality profile of the product should be adequately addressed.

3.7.4. Analytical procedure/technique:

- Extensive state-of-the-art analytical methods should be applied to increase the likelihood of detecting subtle variations in the quality attributes of the product.
- Methods used in both the characterisation studies and comparability studies should be appropriately qualified and validated [as in **ICH Q2(R1)**]
- If appropriate, reference standards and international reference material should be used for method qualification and validation.

3.7.5. Product Characterisation:

- Characterisations of a biological product by appropriate techniques, as described in **ICH Q6B**, include the determination of physicochemical properties, biological activity, immunochemical properties, dissolution data, purity, impurities, contaminants, and quantity. Product-related impurities, product-related substances, and process-related impurities should be identified,

characterized as appropriate, quantified and compared to those of the reference product to the extent feasible and relevant, as part of an assessment of the potential impact on the safety, and potency of the product.

- Key points to consider in the characterisation exercise:
 - Physicochemical properties: In determining the composition and physical properties, the general concept of the desired product (and its variants) as defined in **ICH Q6B** should be considered. The complexity of the molecular entity with respect to the degree of molecular heterogeneity should also be considered and properly identified.
 - Biological activity: Bioactivity includes an assessment of the biological properties of the product. These are directed towards confirmation of the quality attributes that are useful for characterisation and batch analysis of the product.
 - Immunochemical properties: When immunochemical properties are included as part of product characterisation, the manufacturer should confirm that the biosimilar product is comparable to the reference product making use of some specific product class epitopes through western blot analysis.
 - Purity, impurities and contaminants: Purity of the product should be assessed both qualitatively and quantitatively using state-of-the-art technologies. Product and process-derived impurities/ contaminants should also be properly documented. A firm conclusion on the purity and impurity profiles should be provided.
- A complete side-by-side characterisation is generally warranted to directly compare the biosimilar and the reference product. However, additional characterisations may be indicated in some cases.
- Manufacturers should perform in-depth chemical, physical, and bioactivity in comparison with side-by-side analyses of an appropriate number of lots of the proposed biosimilar product and the reference product and, where available and appropriate a comparison with the reference product for specific attributes (e.g. potency).

- Accelerated stability studies of the reference and the biosimilar can be used to further define and compare the degradation pathways/stability profiles.
- Process-related impurities are expected; the impact of process related impurities should be determined by appropriate studies (including non-clinical and/or clinical studies).
- Measurement of quality attributes in the characterisation studies does not necessarily involve the use of validated assays, but the assay should be scientifically sound and provide results that are reliable. Methods used to measure quality attributes for batch release should be validated in accordance with ICH guidelines (ICH Q2A, Q2B, Q5C, Q6B), as appropriate.

3.7.6 Setting Specifications:

- The analytical procedures chosen to define drug substance or drug product specifications alone are not considered adequate to assess product differences since they are chosen to confirm the routine quality of the product rather than to fully characterise it. The manufacturer should confirm that the specifications chosen are appropriate to ensure product quality.
- Specification limits should not be wider than the range of variability of the reference product.

3.7.7 Product stability:

- Accelerated and stress stability studies are useful tools to establish degradation profiles and can therefore contribute to a direct comparison of the biosimilar and reference product. Appropriate studies should be conducted to confirm the storage conditions and controls that are selected.
- Manufacturers have two options for stability testing with respect to design and data analysis. The first method is based on compliance with the acceptance criterion and determination of shelf-life as the time associated with the last measurement within the specification whilst the second method involves the use of statistical evaluation to define an expiry date through extrapolation of the data. The manufacturer is encouraged to discuss method suitability with the FDA in the early stages of development.

- For a biosimilar approach, it would be worth comparing a biosimilar with reference product by accelerated stability studies as these studies at elevated temperatures may provide complementary supporting evidence for the comparable degradation profile.

3.8 NON-CLINICAL AND CLINICAL GUIDELINES

3.8.1 Introduction

The information in this section provides only general guidance on non-clinical and clinical data requirements for biosimilars. The non-clinical studies should be conducted before the initiation of any clinical assessment. These studies should be comparative and directed towards the detection of the differences between the biosimilar and the reference product.

The requirements for the drug classes (for example: insulin, growth hormone) may vary. The requirements may also vary depending on various clinical parameters such as therapeutic index and the type and number of indications applied. Efficacy and safety for each indication will either have to be demonstrated or an extrapolation from one indication to another should be justified.

The final biosimilar product (using the final manufacturing process) should be used for nonclinical and clinical studies. Clinical comparability is done in phases, much like a traditional program.

Proposed indications for the biosimilar must be identical or within the scope of indications granted for the reference product. In case the reference product has more than one therapeutic indication, the efficacy and safety of the biosimilar has to be justified or, if necessary, demonstrated separately for each of the claimed indications. In certain cases, it may be possible to extrapolate therapeutic similarity shown in one indication to other indications of the reference product, but this is not automatic.

The non-clinical section addresses the pharmaco-toxicological assessment. The clinical section addresses the requirements for immunogenicity, pharmacokinetics, pharmacodynamics and efficacy. The section on clinical safety and pharmacovigilance addresses clinical safety studies as well as the

risk management plan (RMP) with special emphasis on studying immunogenicity of the biosimilar.

3.8.2 Non-Clinical Requirements

- Biosimilars should undergo appropriate non-clinical testing sufficient to justify the conduct of clinical studies in healthy volunteers or patients. These studies should be comparative and aim to detect differences between the biosimilar and the reference product.
- On-going consideration should be given to the use of emerging technologies (e.g. in vitro techniques such as real-time binding assays). Pharmacodynamics studies: comparative in vitro bioassays for affinity/binding, as well as test for intrinsic activity should be performed

In vitro analysis:

- Receptor-binding studies or cell-based assays (e.g. cell-proliferation essay) should be conducted.

In vivo studies:

- Animal pharmacodynamics study where relevant to clinical use.
- At least one repeat-dose toxicity study, including toxico-kinetic measurements, should be conducted in relevant species that demonstrate a pharmacological response.
 - Relevant safety observations (e.g. local tolerance) can be made during the same toxicity study.
- The rationale for request of antibody measurements in the context of the repeat dose toxicity study:
 - Generally, the predictive value of animal models for immunogenicity in humans is considered low or relatively non-existent. Nevertheless, antibody measurements (e.g. antibody titres, neutralising capacity, cross reactivity) as part of repeated dose toxicity studies is required to aid in the interpretation of the toxico-kinetic data and to help assess, as part of the comparability exercise, if structural differences exist between the biosimilar and the reference product.

- Other toxicological studies, including safety pharmacology, reproductive and developmental toxicity, mutagenicity and carcinogenicity studies are not warranted when the proposed biosimilar product and reference product have been demonstrated to be highly similar through extensive structural and functional characterization and animal toxicity studies. However, if specific safety concern arises based on the clinical use of the reference product, some of or all such additional animal studies with the proposed product may be warranted (See Annex IV)

3.8.3 Clinical requirements

- The applicant of the biosimilar product must include in its submission to the FDA, information demonstrating that there are no clinically meaningful differences between the biological product and the reference product in terms of Safety, Quality and Efficacy of the biosimilar product.
- Clinical programmes for a biosimilar application should be conducted in a facility with Good Clinical Practice (GCP) and a certificate should be present in the application to confirm this. The application should contain a clinical study or studies, including an assessment of immunogenicity and PK or PD, sufficient to demonstrate safety, purity and potency in varied conditions of use for which the reference product is registered and intended to be used and for which registration is sought for the biosimilar in accordance with the Ghana Public Health Act, Act 851 of 2012.
- The scope of the study will be based on the magnitude of uncertainty about the biosimilarity of similar biological medicinal products and the reference product following structural and functional characterization and possible animal studies.
- Narrowing the scope of any type of clinical studies (i.e. human PK, PD, clinical immunogenicity, or clinical safety and effectiveness) should be scientifically justified by the applicant.

3.8.4 Pharmacokinetic (PK) Studies

- Comparative pharmacokinetic studies should be conducted to demonstrate the similarities in pharmacokinetic (PK) parameters between biosimilar and the reference product.

- If appropriate from an ethical point of view, healthy volunteers will in most cases represent a sufficiently sensitive and homologous model for such comparative PK studies.
- Choice of designs must be justified and should consider factors such as clearance and terminal half-life, linearity of PK parameters, where applicable, the endogenous level and diurnal variations of the protein under study, production of neutralizing antibodies, conditions and diseases to be treated.
- The acceptance criteria to conclude clinical comparability should be defined prior to the initiation of the study, taking into consideration known PK parameters and their variations, assay methodologies, safety and efficacy of the reference product.
- Other PK studies such as interaction studies or PK studies in special populations (e.g. children, elderly, and patients with renal or hepatic insufficiency) may be applicable.

3.8.5 **Pharmacodynamics (PD) Studies**

Chosen parameters should be clinically relevant. A surrogate marker which is clinically validated may be employed. The PD study may be combined with a PK study, and the PK/PD relationship should be characterised. PD studies should be comparative in nature.

3.8.6 **Confirmatory**

Comparative PK/PD studies may be sufficient to demonstrate similar clinical efficacy, provided all the following are met:

PK and PD properties of the reference product are well documented and characterised.

- Sufficient data on the PD parameters is available.
- At least one PD marker is accepted as surrogate marker for efficacy, and the relationship between exposure to the product and this surrogate marker is well known.
- Dose response is sufficiently characterised (refer to **ICH E10**).

- Equivalence margin is pre-defined and appropriately justified.

3.8.7 Clinical Efficacy Trials

- Comparative clinical trials (head-to-head adequately powered, randomised, parallel group clinical trials, so-called “equivalence trials”) are required to demonstrate the similarity in the efficacy and the safety profiles between the biosimilar and the reference product. Assay sensitivity must be ensured (refer to **ICH E10**).
- Equivalence margins should be pre-specified and adequately justified on clinical grounds.
- Equivalent rather than non-inferior efficacy should be shown in order for the biosimilar to adopt the posology of the product and to open the possibility of extrapolation to other indications, which may include different dosages.

3.8.8 Clinical Safety and Effectiveness

The existence of residual uncertainty about the biosimilarity between the biological product and the reference product based on structural and functional characterization, animal testing, human PK and PD data, and clinical immunogenicity assessments makes it imperative that comparative safety and effectiveness data is made available to the FDA upon submission. The applicant may provide scientific justification if it is believed that some or all of these clinical safety and effectiveness data are irrelevant.

The under-listed are factors that may affect the type and degree of comparative clinical safety and effectiveness data required.

- The nature and complexity of the reference product, the extensiveness of structural and functional characterization, and the findings and limitations of comparative structural, functional, and nonclinical testing, including the extent of observed differences.
- The extent to which differences in structure, function and nonclinical pharmacology and toxicology predict differences in clinical outcomes, as well as the degree of understanding of the mechanism of action (MOA) of the reference product and disease pathology.

- The extent to which human PK or PD predicts clinical outcomes (e.g., PD measures known to be clinically relevant to effectiveness).
- The extent of clinical experience with the reference product and its therapeutic class, including the safety and risk/benefit profile (e.g., whether there is a low potential for off-target adverse events), and appropriate endpoints and biomarkers for safety and effectiveness (e.g., availability of established, sensitive clinical endpoints).
- The extent of any clinical experience with the proposed product.
- Applicants should provide scientific justification for how it intends to integrate these factors to determine whether and what types of clinical trials are needed and the design of any necessary trials. Generally, the safety and effectiveness study encompass the following:
 - The safety of a biosimilar should be demonstrated to be similar to the reference product in terms of nature, seriousness and frequency of adverse events. Thus, data from a sufficient number of patients and adequate study duration with sufficient statistical power to detect major safety and effectiveness differences are needed.
 - For products intended for use for more than 6 months, the size of the safety database should typically conform to the recommendations of **ICH E1**.
 - Data from pre-approval studies are insufficient to identify all differences in safety. Therefore, safety monitoring on an on-going basis after approval including continued benefit-risk assessment is mandatory. A detailed plan and the strategy to execute the plan should be contained in the submission for the FDA.

3.8.9 Clinical Immunogenicity

The essence of the clinical immunogenicity studies is to evaluate potential differences between the proposed biosimilar product and the reference product in the incidence and severity of human immune responses. Establishing that there are no clinically meaningful differences in immune response between a proposed product and the reference product is a key factor in the demonstration of

biosimilarity. Structural and functional studies as well as animal data are generally not adequate to predict immunogenicity in humans. Therefore, at least one clinical study that includes a comparison of the immunogenicity of the proposed biosimilar product to that of the reference product will generally be expected.

In situations where the immune response to the reference product is rare, two separate studies may be sufficient to evaluate immunogenicity:

- A pre-market study powered to detect major differences in immune responses between the biosimilar product and the reference product.
- A post-market study designed to detect more subtle differences in immunogenicity.

The FDA recommend the use of a comparative parallel design (i.e., a head-to-head study) to assess potential differences in the risk of immunogenicity and support appropriate labelling. It is only necessary to demonstrate that the immunogenicity of the proposed biosimilar product is not increased, thus a one-sided design will ordinarily be enough to compare the immunogenicity of the proposed biosimilar product and the reference product.

Variations in immune responses between a proposed biosimilar product and the reference product in the absence of observed clinical sequelae may be of concern and may warrant further evaluation to assess whether there are clinically meaningful variances between the biosimilar and the reference product.

In situations where an applicant is seeking to extrapolate immunogenicity data for one indication to another indication, the applicant should consider using the population and regimen for the reference product for which development of immune responses with adverse outcomes is most likely to occur.

The selection of clinical immunogenicity endpoints or PD parameters linked to immune responses to protein-based medicines (e.g., antibody formation and cytokine levels) should take into consideration the immunogenicity issues that have emerged during the use of the reference biological product. Applicants should define clinical immune response criteria, using established criteria where available, for each type of potential immune response.

The follow-up period should be chosen based on:

- The time course for the generation of immune responses (including the development of neutralizing antibodies, cell-mediated immune responses, etc.), and expected clinical sequelae (informed by experience with the reference biological product)
- The time course of disappearance of the immune responses and clinical sequelae following cessation of therapy. The length of administration of the product.

The minimal follow-up period for chronically administered agents should be **one year**, unless a shorter duration can be justified by the applicant.

As a scientific matter, it is expected that the following will be assessed in clinical immunogenicity studies:

Binding antibody: titer, specificity, relevant isotype distribution, time course of development, persistence, disappearance, and association with clinical sequelae

Neutralizing antibody: all of the above, plus neutralizing capacity to all relevant functions (e.g., uptake and catalytic activity, neutralization for replacement enzyme therapeutics)

A written rationale on the strategy for testing immunogenicity should be provided. Validated state-of-the-art assays/methods should be used. Special attention should be given to the possibility that the immune response seriously affects the endogenous protein and its unique biological function.

The FDA recommends that immunogenicity assays be developed and validated with respect to both the proposed biosimilar product and reference biological product early in development. The proposed biosimilar product and reference biological product should be evaluated in the same clinical trial of sufficient duration with the same patient sera whenever possible. The duration of the study should be at least **12 months** using subcutaneous administration. The comparative phase of the study should be at least **6 months**, to be completed pre-approval.

Note: Data at the end of the 12 months should be presented as part of the post-marketing commitment

3.8.4.3.7 Pharmacovigilance Plan/Risk Management Plan (RMP)

- Any post-market risk management plan should include detailed information of a systematic testing plan for monitoring post-market immunogenicity of the biosimilar product.
- The RMP should include additional monitoring activities to address the specific safety concerns associated with these products in addition to routine pharmacovigilance activities.
- For Safety Monitoring requirements, refer to FDA Guideline for Reporting Adverse Reactions (www.fdaghana.gov.gh).
- Educational materials.
 - The product licence holder should provide additional educational materials to the physicians to inform them of the specific risks linked to the biosimilar product and measures on how to reduce them.
 - Patient information leaflets should be submitted by the applicant. The leaflet should contain the necessary information on the potential risk associated with the use of the product. These should include signs and symptoms which should be reported to healthcare providers.

3.9 POST-MARKET REQUIREMENTS

Robust and comprehensive post market safety monitoring is a crucial component in ensuring the safety and effectiveness of biological products, including biosimilars. Due to the product-specific nature of some aspects of post-marketing safety monitoring, it is recommended that applicants consult with FDA to discuss the applicant's proposal for post-marketing safety monitoring. There should be sufficient mechanism in place to differentiate between the adverse events associated with the proposed biosimilar product and those associated with the reference biological product, in addition to adverse events linked to the proposed biosimilar product that have not been previously associated with the reference biological product. Rare and in some instances, serious safety risks, including immunogenicity, may not be uncovered during pre-registrations clinical testing due to the limited size of the trial population. Like any other biological products, the FDA may take any appropriate

action to ensure that the safety and effectiveness of a proposed biosimilar product is assured.

In addition to the above, the following must also be considered during the preparation for submission:

- Pharmacovigilance plan must be approved prior to approval of the product, and the system must be in place to conduct monitoring.
- Pharmacovigilance plan should be designed to monitor and detect both known inherent safety concerns and potentially unknown safety problems that may have resulted from the impurity profiles of the product.
- Pharmacovigilance, as part of a comprehensive RMP, should include regular laboratory testing of the product for batch-to-batch consistency.
- Pharmacovigilance plan should be able to distinguish between the tracking of different products and manufacturers of the products in the same class (e.g. Epoetins, Insulins, and Interferons). This ensures that adverse events are properly attributed to the specific product (i.e. traceability).
- Traceability of the product should involve product identification defined in terms of product name, brand name, pharmaceutical form, formulation, strength, manufacturer's name and batch number(s).
- Periodic Safety Update Reports (PSURs) of biosimilars should be submitted and evaluation of benefit/risk ratio of the biosimilar post-market should be discussed. Such systems should include provisions for passive pharmacovigilance and active evaluations such as registries and post marketing clinical studies.

(Please refer to “Guidelines for registration of Biological Products), www.fdaghana.gov.gh, for more information about the preparation of a RMP specific for Ghana)

3.10 ORGANISATION OF DATA / DOSSIER

With regards to the data requirements for a biosimilar application, the “one size fits all” approach cannot be applied. This is due to the wide spectrum of molecular

complexity among the various products concerned. Thus, the requirements to demonstrate safety and efficacy of a biosimilar are essentially product class specific.

The application documents for submission should contain complete quality data, a comparability exercise and abridged studies of the non-clinical and clinical components.

The biosimilar approach requires a thorough comparability exercise to generate evidence substantiating the similar nature, in terms of quality, safety and efficacy, of the biosimilar product and the chosen reference product. In other words, the quality data needs to be supplemented by the comparability exercise.

The demonstration of similarity at the quality level may allow a reduction of the non-clinical and clinical data requirement compared to a full dossier. Demonstration of similarity may also allow extrapolation of efficacy and safety data to other indications of the reference product.

3.11 NAME OF PRODUCTS

In order to facilitate effective pharmacovigilance monitoring and tracing of adverse safety events and to prevent inappropriate substitution, the specific medicinal product (innovator or biosimilar) prescribed by the treating physician and dispensed to the patient should be clearly identified. Therefore, all biosimilars should be distinguishable by name i.e. assign a brand name explicitly, using names that are not suggestive towards the originator nor towards other biosimilars.

RECOMMENDED FORMAT FOR DOSSIER SUBMISSION

MODULE 1

4.0 ADMINISTRATIVE - LEGAL INFORMATION

The requirements include:

4.1 COVER LETTER

4.2 TABLE OF CONTENTS (MODULES 1 TO 5):

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

4.3 APPLICATION FORM

GHFDA minimum requirement:

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

4.3.2 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.

4.3.3 Concentration. State the concentration of the active ingredient(s) contained in the product.

4.3.4 Dosage Form. Indicate the dosage form of the product, for example, injectable solution, and injectable suspension.

4.3.5 Senior Executive Officer / Senior Medical or Scientific Officer. 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.

4.3.6 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.

4.3.7 Applicant. Give the full name of the market authorization holder of the product, also address, telephone, fax, and e-mail.

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

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

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

4.3.11 Official responsible for batch release of finished product. Give the full name and position of the person responsible for the release of the product.

4.3.12 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.

4.3.13 Route of administration. Indicate the route of administration of the product.

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

4.3.15 Strength indicates the strength of the product.

4.3.16 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.

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.

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

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.

Certificate of Good Manufacturing Practices (GMP) of all manufacturers 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.

Trademark certificate (optional)

Patent certificate (under national legislation)

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

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

4.4 SUMMARY OF PRODUCT CHARACTERISTICS AND PRODUCT LABELING

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

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

4.4.2.1 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 Route of administration
- 1.4.2.1.7 Storage temperature
- 1.4.2.1.8 Warnings
- 1.4.2.1.9 Lot number
- 1.4.2.1.10 Expiry date
- 1.4.2.1.11 Manufacturer
- 1.4.2.1.12 Registration number from country of origin

1.4.2.2 Secondary packaged label. Include the text proposed for the biosimilar'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
- 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

4.4.2.3 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

1.4.2.3.5 Content/Volume

1.4.2.3.6 Volume/dose

1.4.2.3.7 Composition

1.4.2.3.8 Excipients

1.4.2.3.9 Cell substrate

1.4.2.3.10 Route of administration

1.4.2.3.11 Indications

1.4.2.3.12 Proper use

1.4.2.3.13 Precautions

1.4.2.3.14 Warnings

1.4.2.3.15 Contraindications

1.4.2.3.16 Use during pregnancy and breast feeding

1.4.2.3.17 Adverse events

1.4.2.3.18 Use during pregnancy and breast feeding

1.4.2.3.19 Storage of the product/storage conditions

1.4.2.3.20 Name and address of the manufacturer of the finished product

1.4.2.3.21 Name and address of the company responsible for packaging

4.4.2.4 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.

4.4.2.5 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.

4.4.3 Samples

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

4.4.3.2 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.

4.5 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.

4.6 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.

4.7 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.

4.8 DECLARATIONS. 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.

5.0 IMPORTED BIOSIMILARS

Applicants should obtain clearance from the FDA prior to the importation of a biosimilar product for either retail or registration. Issuance of import permit for registration samples (biological product) does not automatically lead to FDA registration of the product.

Subsequent importation of biosimilar products shall be accompanied by the Batch release document, and the corresponding Batch Release certificate. Note that import permit application submitted through the ICUMS shall be processed only if the necessary release documents have been submitted to the Authority in advance.

6.0 ANNEXURES

ANNEX I:

OUTLINE OF THE EVALUATION OF APPLICATION

The Authority, in considering an application:

- shall satisfy itself that there is a need to have the drug registered in Ghana.
- shall request the applicant to submit a manufacturer's authorization to register the drug.
- may consult with other bodies and experts with knowledge of the drug.
- reserves the right to conduct a Good Manufacturing Practice (GMP) audit inspection on the manufacturing facility for the product at a fee prescribed by the Authority.
- may ask the applicant to supply such other information as may be required to enable it to reach a decision on the application.
- Where the Authority is satisfied that there is the need to register a drug, 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 drug under these regulations, 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 drug 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 Ghana Public Health Act 851 of 2012

ANNEX II

SANCTIONS

- The Authority shall cancel, suspend, or withdraw the registration of a drug if:
- The information on which the drug was registered is later found to be false
- The circumstances under which the drug was registered no longer exist.
- Any of the provisions under which the drug 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 drug 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, packaging or storage of the drug.
- Where the registration of a drug is suspended, withdrawn or cancelled, the Authority shall cause the withdrawal from circulation of that drug and shall accordingly cause the suspension, cancellation or withdrawal to be published in the Gazette.

ANNEX III:

Relevant Information to be Included in Dossier (Pre-Submission Planning Page)

In addition to the product registration requirements contained in the application form and this guided 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