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| | **Title: GUIDELINES FOR REGISTRATION OF BIOSIMILAR PRODUCTS** | |
| **Rev No: 02** | **Doc No: PBSL/GL/033** | Version no. 03 |
| **Issue date: 15 May 2024** | **Effective date: 17 May 2024** | Approved by: Registrar |

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| **Adopted By PBSL** | |
| **Start of public Consultation** | |
| **End of public Consultation** | |
| **Agreed by QMS committee** | |
| **Approved by Board** | |

**Pharmacy Board of Sierra Leone,**

**PMB 322**

**Central Medical Stores Compound**

**New England Ville**

**Freetown**

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## Table of Contents

**ACKNOWLEDGEMENTS**

**EXECUTIVE SUMMARY**

## 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 Sierra Leone, 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 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.

## 2.0 OBJECTIVES

The objectives of this guideline are:

(1) To introduce and outline the principles for biosimilars approval.

(2) To provide applicants with a "user guide," showing regulations and relevant scientific information in the various current international guidelines, in order to substantiate the claim of similarity

## 3.0 SCOPE

In pursuance of section 44 of the Pharmacy and Drugs Act 2001, this guideline is made to provide guidance to applicants on the procedure for registering a similar biological medicinal product in Sierra Leone. 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 Pharmacy Board 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 characterization; therefore, information requirements outlined in this document apply to biological medicinal products that contain, as the active pharmaceutical ingredient (api), a well characterized protein molecule derived via modern biotechnological methods.

Generally, all product applications must include a 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 Guidelines should be used in conjunction with other guidance document available from the PBSL, EMEA,ICH and the USFDA that describe the CMC, non-clinical and clinical requirements appropriate for evaluating biological products.

It is PBSL's intention to harmonise as much as possible with other competent and stringent NRA's and International organizations such as

World Health Organization (WHO) and the International Conference of harmonization (ICH). The PBSL will work toward worldwide harmonization of scientific protocols used to evaluate and register biosimilars.

### 3.1 Concept of biosimilars

The rationale for creating the 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 them difficult to adequately characterize 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 PBSL-registered reference product.

### 3.2 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 for 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:

3.2.1. The principles within the existing regulatory framework for biological medicinal products and Biotechnology-derived medicinal product shall be the basis of the regulatory framework for similar Biological medicinal products (also known as biosimilars).

3.2.2. 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 Sierra Leone.

3.2.3. 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, clinical data, and at the level of the treating physician/clinician

3.2.4. 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.

3.2.4. Eligibility for a biosimilar pathway hinges on the ability to demonstrate similarity to a reference product. Product employing clearly different approaches to manufacture from the reference product will not be eligible for registration as a biosimilar.

3.2.6. 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 PBSL-registered reference product. The rationale for the choice of reference product should be provided by the manufacturer to PBSL. Also, evidence of purchase of the reference product (reference standard and finished biological product) should be contained in the dossier for evaluation.

3.2.7. 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.

3.2.8. 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 have 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.

3.2.9. 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.

3.2.10 A Good Manufacturing Practice (GMP) on-site inspection of the manufacturing facilities is required.

## 4.0 REQUIREMENTS

### 4.1 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.

- document confirming the senior executive officer / senior medical or scientific officer responsible for the product (under the country's legislation). Submit a document issued by the manufacturer of the biological product giving information on the individuals responsible for the product. The information should include the identity and designation of the authorized person in charge of regulatory activities.
- certificate of pharmaceutical product using the world health organisation (who) model, this certificate includes information on compliance with good manufacturing practices (GMP). A free sale certificate where applicable should be submitted in addition to the GMP certificate.
- certificate of good manufacturing practices of other manufacturers involved in the production of the biological product this should include manufacturers that are involved in any stage of the production process, for example manufacturer(s) of the active ingredient(s), the diluents, and those responsible for labelling and packaging of the finished product. It is important that the certificate indicates the procedures that the establishment is authorized to perform.
- trademark certificate (optional)

- proposed brand name and art work for primary and secondary labels these should be submitted for approval by PBSL 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 PBSL 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 Pharmacy Board of Sierra Leone recommends that applicants intending to develop biosimilar products should meet with regulators at the PBSL to present their product development plans and establish a schedule of milestones that will serve as standards for future discussions with the authority.

### 4.2 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 biologicals 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 a 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 Sierra Leone, 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 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 biosimilar 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.

### 4.3 Other requirements

#### 4.3.1. 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/license holder.
- If the applicant is a foreign company, it shall appoint a local agent through whom the application shall be submitted.
- The local agent shall be a registered pharmaceutical wholesale company or an accredited Manufacturer's representative registered as a pharmacist in Sierra Leone.

❖ Applications shall be accompanied by:
- a duly signed covering letter
- two (2) completed application forms
- samples of the product in the final package as specified in the authority sample schedule.

- reference/working standard for active pharmaceutical ingredient and related impurities where necessary.
- all supporting documents as specified on the application form
- clinical trial and/or bioequivalence trial certificate where applicable
- non-refundable application fee as specified in the authority's fee schedule.
- all documentation submitted shall be in english, and must be legibly printed and not hand-written.
- 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

### 4.3.2. 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
- samples reflecting the variation as specified in the authority's sample schedule.
- 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

### 4.3.3 Re-registration

❖ 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
- samples of the biosimilar in the final package 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.pharmacyboard.gov.sl)

- the re-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.

### 4.4 Imported biosimilars

Applicant should obtain clearance from the PBSL 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 PBSL 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 to the Board shall be processed only if the necessary release documents have been submitted to the authority in advance (five working days prior to issuance of gc-net import permit).

### 4.5 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 rã©sumã© for each expert must be provided and their professional relationship to the applicant must be stated.

### 4.6 Guidance for Implementation

#### 4.6.1 Introduction

Biosimilars can be approved based in part on an exercise to demonstrate similarity to an already approved reference product. The same reference product should be used throughout the comparability program in order to generate coherent data and conclusions. Comparative quality, non-clinical and clinical studies are needed to substantiate the similarity of structure/composition, quality, safety and efficacy between the biosimilar and the reference product. The pharmaceutical form, strength/concentration and route of administration should be the same as that of the reference product. Any differences between the biosimilar and the reference product should be justified by appropriate studies.

### 4.6.2 Application form and overview

Application form

Refer to PBSL website: www.pharmacyboard.gov.sl

**Overview**

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

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

An executive summary within the overview must include the reasons for the application. For a Biosimilar, this should include whether the product contains a new active constituent and scientific Argument for registration of the product. The argument should outline the importance, prevalence and (if applicable) the regional distribution of the disease the product is intended to control.

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

### 4.6.3 Quality guidelines

The quality part of a biosimilar, like all other biological products should comply with established scientific and regulatory standards.
A biosimilar product is derived from a separate and independent master cell bank, using independent manufacturing and control methods, and

should meet the same quality standards as required for innovator products. A full quality dossier is always required.

In addition, the biosimilar manufacturer is required to submit extensive data focused on the
Similarity, including comprehensive comparative side-by-side physicochemical and biological characterization (these may include bioassays, biological assays, binding assays, and enzyme Kinetics) of the biosimilar and the reference product. A meaningful assessment as to whether the Biosimilar product is highly similar to the reference product will depend on, among other things, the capability of available state-of-the-art analytical assays to assess, for example, the molecular weight of the protein, complexity of the protein (higher order structure and post-translational modification), degree of heterogeneity, functional properties, impurity profiles and degradation profile denoting stability. Note; the capabilities of the methods used in the analytical assessment as well as their limitations should be described by the applicant.

The basis of all data contained in a dossier must demonstrate that the biosimilar is highly similar to the reference product. Due to the heterogeneous nature of therapeutic proteins, the

Limitations of analytical techniques and the unpredictable nature of clinical outcome to structure/biophysical differences, it is not possible to define the exact degree of biophysical similarity that would be considered sufficiently similar to be regarded as biosimilar, and this will be judged for each product independently.

Applicants should note that the comparability exercise for a biosimilar versus the reference product is an additional element to the requirements of the quality dossier and should be dealt with separately when presenting the data.

Information on the development studies conducted to establish the dosage form, the formulation, manufacturing process, stability study and container closure system including integrity to prevent microbial contamination and usage instructions should be documented.

A summary of the analytical results (these may be in a form of a report) on three consecutive batches of finished product must be provided to support the application for registration. These batches may be pilot or production batches. If they are pilot batches, they must be representative of production batches.

### 4.6.4. 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 a 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.
- comparative physicochemical and functional characterization studies should be sufficient to establish relevant quality attributes including those that define a products 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

post-translational 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.

**4.6.4. Manufacture:**

- the biosimilar product is defined by its own specific manufacturing process for both active substance and finished product. The process should be developed and optimised taking into account some state-of-the-art technology in relation to the manufacturing processes and consequences on product characteristics. A well-defined manufacturing process with its associated process controls assures that an acceptable product is produced consistently.
- 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.

- manufacturing process: characterization tests, process controls, and specifications that willemerge from information gained during process development must be specific for the proposed biosimilar product and the manufacturing process. The use of quality-by-design approaches is recommended to assure consistent manufacturing of high-quality product. The manufacturing process validation protocol and report is required.

A full drug master file (DMF) is required, type ii DMF will not be sufficient since the applicant is expected to have knowledge of and control over the manufacturing process for the biosimilar Product.

- 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)). Applicant 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. Test use for characterization should be reproducible and reliable. 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 assays 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). Applicant 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 the 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 that 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, bio-burden, 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 support 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).

- reference product and reference standard: analytical studies performed to support the approval of a proposed biosimilar product should not focus solely on the characterization of the proposed biosimilar product in isolation. The analysis should form part of a wider comparison that include, but not limited to, the proposed similar biological medicinal product, the reference product, applicable reference standards and consideration of relevant publicly available information.
- 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 toxicology 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 tine, 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.

### 4.6.6. Reference product/reference standard:

- ❖ a biosimilar application should contain a thorough analytical comparison between the similar biological medicinal product 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 similar biological medicinal product and justify reliance on certain existing scientific knowledge about the reference product.
- ❖ sufficient data demonstrating that the proposed biosimilar product 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 API has been extracted from the reference product in order 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 API.

- ❖ 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 comparing a proposed similar biological medicinal product to a non-registered PBSL product to address, in part the requirement for registering a biosimilar product. In such as 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 PBSL-registered reference product. The scientific link between the Non-PBSL registered product and the PBSL registered reference product may include comparative physicochemical characterization, bioassays/functional assays, and comparative clinical and /or non-clinical 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.

### 4.6.7. 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.

### 4.6.8. Product characterization:

- characterizations of a biological product by appropriate techniques, as described in ICH Q6B,includes 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.

- most biological products (i.e. Protein molecules) undergo post-translational modification that may alter the clinical functions of the protein. Post-translational modifications can be as a result of intracellular activities during cell culture or by deliberate modification of the protein, for example pegylation or as a result of manufacturing process operations such as glycosylation. Storage conditions may also precipitate certain degradation pathways such as oxidation, deamidation, or aggregation. As all of these product related variants may alter the biological properties of the expressed recombinant protein, identification and determination of the relative levels of these protein variants should be included in the comparative analytical characterization studies.
- methods such as x-ray crystallography and multi-dimensional nuclear magnetic resonance (NMR) spectroscopy can help define tertiary protein structure and, to a varying extent, quaternary structure, and can add to the body of information supporting the biosimilarity. Although a protein structure can often be difficult to define accurately using current physicochemical analytical technology,difference in higher order structure between a proposed biosimilar and a reference product should be evaluated in terms of a potential effect on protein function. Thus, functional assays are also

critical tools for evaluating the integrity of the higher order structures.

- key points to consider in the characterization 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: bio-activity includes an assessment of the biological properties of the product. These are directed towards confirmation of the quality attributes that are useful for characterization and batch analysis of the product.
  - immunochemical properties: when immunochemical properties are included as part of product characterization, 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 characterization is generally warranted to directly compare the biosimilar and the reference product. However, additional characterizations may be indicated in some cases.
- manufacturers should perform in-depth chemical, physical, and bioactivity 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 andcompare the degradation pathways/stability profiles.
- process-related impurities are expected, the impact of process related impurities should bedetermined by appropriate studies (including non-clinical and/or clinical studies).
- measurement of quality attributes in the characterisation studies do 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.

### 4.6.9 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.

### 4.6.10 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 the determination of shelf-life as the time associated with the last measurement within the specification whilst the second method involve 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 PBSL 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 temperature may provide complementary supporting evidence for the comparable degradation profile.

### 4.7 Non-clinical and clinical guidelines

#### 4.7.1 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 non- clinical 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.

### 4.7.2 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 assay) 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 titers, neutralizing capacity, cross reactivity) as part of repeated dose toxicity studies is required to aid in the interpretation of the toxicokinetic 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 base 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)

### 4.7.3 Clinical requirements

The applicant of the biosimilar product must include in its submission to the PBSL, information demonstrating that there are no clinically meaningful differences between the biological product and the reference product in term 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 .The scope of the study will be based on the magnitude of uncertainty about the biosimilarity of similar biological medicinal product 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.

### 4.7.3.1. 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.

### 4.7.3.2. Pharmacodynamics (PD) studies

Chosen parameters should be clinically relevant. A surrogate marker which is clinically validated maybe 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.

### 4.7.3.3. 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.

### 4.7.3.4. 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.

### 4.7.3.5 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 the a comparative safety and effectiveness data is made available to the PBSL upon submission. The applicant may provide a 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.

Applicant should provide a 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.

The 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 PBSL.

### 4.7.3.6 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 PBSL 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 other indications, 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 the 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 PBSL 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

### 4.7.3.7 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 PBSL guideline for reporting adverse reactions(www.pharmacyboard.gov.sl)
- ❖ Educational materials;
  - ▪ the product license 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.
  - ▪ patients 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.

- ❖ product sales data

The applicant is required to provide the PBSL with information on the sales data, in terms of

Number of units of product sold and the buyer categories (e.g. Restructured hospitals, private hospital specialist clinics, general

practitioner clinics) of the biosimilar product on a quarterly basis. These data will be used to estimate the number of local exposures to the product. When requested by PBSL, the applicant will be required to provide a buyers list of their biosimilar product.

### 4.8 Post-market requirements

A robust and comprehensive post market safety monitoring is a crucial component in ensuring the safety, and effectiveness of biological product, including biosimilars. Due to the product-specific nature of some aspects of post-marketing safety monitoring, it is recommended that applicant consult with PBSL 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 PBSL 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, manufacturers 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.pharmacyboard.gov.sl for more information about the preparation of a RMP for Sierra Leone)

### 4.9 Organization 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.

### 4.9.1 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.

Prescription should be by the brand name. 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.

### 4.9.2 Labeling / package insert

Product labelling

The text proposed for the primary label, the secondary label or exterior packaging, and the

Package insert should be included.

### 4.9.3 Primary package label

Submit the label proposed for the biosimilar product's primary package or container, which should provide the following information as a minimum:

- proprietary, commercial or trade name
- non-proprietary name or common name.

- a clear indication that the medicine is a biosimilar of a specific stated reference product
- dosage form
- concentration, potency
- content/volume
- volume/dose
- number of doses per vial (for multidose presentations)
- route of administration
- storage temperature (if the size of the package so permits)
- warnings
- lot number
- expiry date
- Manufacturer
- registration number in country of origin

### 4.9.4 Secondary package label

Include the text proposed or the biological product secondary packaging which should provide the following information as a minimum:

- proprietary, commercial or trade name

- non-proprietary name or common name
- dosage form
- concentration ,potency
- content/volume
- volume/dose
- number of doses per vial (for multidose presentations)
- composition
- Excipients
- product storage
- route of administration
- instructions for preparation
- mode of use
- warnings (for hospital use only, keep out of reach and sight of children, and any warning specific to the product)
- distribution level
- identification marks (where applicable)
- lot number
- date of manufacture
- date of expiry
- name and address of the manufacturer of the finished product
- name and address of the company responsible for packaging
- name and address of the owner, representative, or distributor

- name of the professional in charge
- registration number from country of origin

### 4.9.5 Package inserts

Include the text proposed for the package insert, which should contain the following
Information as a minimum:

- a clear indication that the medicine is a biosimilar of a specific reference product.
- the proprietary name and common or scientific name
- clinical data for the biosimilar describing the clinical similarity (i.e. Safety and efficacy) to the reference product and in which indication(s)
- interchangeability and substitution advice- this should clearly and prominently state that the Biosimilar is not interchangeable or substitutable with the reference product unless otherwise Prescribed by a treating physician/clinician
- pharmaceutical form
- concentration, potency

- content/volume
- volume/dose
- number of doses per vial (for multidose presentations)
- composition
- Excipients
- cell substrate
- route of administration
- Indications
- proper use
- precautions
- warnings
- adverse events
- contraindications
- use during pregnancy and breast feeding
- storage conditions
- name and address of the manufacturer of the finished product
- name and address of the company responsible for packaging
- name and address of the local agent
- date of publication review

### 4.9.6 Final packaging

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

### 4.9.7 Monograph for health professionals

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

### 4.9.8 Occupational health and safety

Potential occupational health and safety risks associated with the manufacture and use of the product must be addressed in the application. These may include the following:

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

### 4.9.9 Environment

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

### 4.9.10 Outline of the evaluation of application

4.12.1 The authority, in considering an application:

- shall satisfy itself that there is a need to have the drug registered in Sierra Leone.
- shall request the applicant to submit a manufacturers 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 reach a decision on the application.

4.12.2 An appeal for the review of an application may be made in writing to the authority within 60 (sixty) days of receipt of the rejection notice.

4.12.3 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.

4.12.4 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.

4.12.5 The authority, shall from time to time, publish a notice in the gazette notifying the registration of a drug under these regulations.

4.12.6 No information given in this application shall be disclosed by the pharmacy board of Sierra Leone to a third party, except:

- with the written consent of the license holder
- in accordance with the directive of the board of directors of the PBSL

4.13 Sanctions

4.13.1 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; or
- 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.

4.13.2 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.

## 6.0 REFERENCES

Where specific guidelines are unavailable, the PBSL 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 Harmonisation (ICH) guidelines: http://www.ich.org

Guidelines on biological products containing biotechnology-derived proteins as active substances. While developing a biosimilar product and carrying out the comparability exercise to demonstrate that the product is similar to the reference product, some existing biotechnological product guidelines may be relevant and should therefore be taken into account. For example:

- CPMP/BWP/328/99 development pharmaceutics for biotechnological and biological products -Annex to note of guidance on development pharmaceutics (CPMP/QWP/155/96)

- topic Q5A, step 4 note for guidance on quality of biotechnological products: viral safety evaluation of biotechnological products derived from cell lines of human or animal origin (CPMP/ICH/295/95)

- topic Q5B note for guidance on quality of biotechnological products: analysis of the expression construct in cell lines used for production of R-DNA derived protein products. (CPMP/ICH/139/95).

- topic Q5C, step 4 note for guidance on quality of biotechnological products: stability testing of biotechnological/biological products (CPMP/ICH/138/95).

- topic Q5D, step 4 notes for guidance on quality of biotechnological products: derivation and characterisation of cell substrates used for production of biotechnological/biological products (CPMP/ICH/294/95).

- topic Q5D, step 4 notes for guidance on biotechnological/biological products subject to changes in their manufacturing process (CPMP/ICH/5721/103).

- topic Q6B, step 4 notes for guidance on specifications: test procedures and acceptance criteria for biotechnological/biological products (CPMP/ICH/365/96).

- 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 product will be made progressively available.

- guideline on similar biological medicinal products (EMEA/CHMP/437/04)

- guideline on similar biological medicinal products containing biotechnology-derived proteins as active substances: quality issues (EMEA/CHMP/BWP/49348/2005).

- guideline on similar biological medicinal products containing biotechnology-derived proteins as active substances: non-clinical and clinical issues (EMEA/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 (EMEA/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 (EMEA/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. (EMEA/CHMP/31329/2005).

- guideline on immunogenicity assessment of biotechnology-derived.

- therapeutic proteins (EMEA/CHMP /14327/2006).

- guideline on risk management systems for medicinal products for human use (EMEA/CHMP /96268/2005)

## 7.0 APPENDICES

### 7.1 Appendix I:

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

Guidance document, please ensure that the information below is included in the dossier submitted for the registration of the biological products.

- evidence of payment for evaluation and registration (a copy of payment receipt)
- covering letter (applicant)
- covering letter (local agent)
- table of contents
- application form (dated, stamped and signed)
- signed declaration
- manufacturing license
- contract agreement documents
- application overview

- full characterization of the host organism including the relevant genotypic and phenotypic properties
- certificate of analysis of master cell bank/master seed lot (protocol and report to qualify MCB/MSL)
- certificate of analysis of working cell bank/working seed lot (protocol and report to qualify WCB/WSL)
- certificate of analysis of the starting raw materials (cDNA, vector, expression system) (from Supplier)
- certificate of analysis of starting raw materials (cDNA, vector, expression system) (from Manufacturer)
- certificate of analysis of inactive raw materials (enzymes including restriction enzymes, phosphatase, polymerase, transcriptase, S1, etc, buffers constituents, growth media and additives, compressed gases, etc.)
- complete drug master file (DMF) containing development genetics, protein expression protocols, protein purification protocols, protein identification and characterization, formulation, etc
- map of empty expression vector/ map of expression construct
- report on genetic make-up of empty expression vector and expression system
- report on genetic material coding desired biological drug substance (API)

- relevant genotype and phenotype of the host organism
- report on the choice of host organism
- report of process validation
- evidence of purchase of reference product
- protocol and report for isolation of reference product drug substance (if applicable)
- certificate of analysis of biological drug substance
- protocol and report of analytical method of validation (AMV) for drug substance of reference Product (if applicable)
- protocol and report of analytical method validation (AMV) for reference product
- protocol and report of analytical method validation (AMV) for drug substance of the biological medicinal product
- protocol and report of analytical method validation (AMV) for finished biological medicinal product
- all comparability studies between the biological drug substance and the reference drug substance
- all comparability studies between the biological medicinal product and the reference product
- analytical control procedures
- BMR for finished biological medicinal product (should be recent and in english language)

- protocol and report of process validation
- certificate of pharmaceutical product/certificate of analysis of biological medicinal product
- batch release abstract and batch release document (completed, dated and signed)
- protocol and report for real time/long term stability studies
- protocol and report for accelerated stability studies
- protocol and report for stress stability studies
- protocol and report for non-clinical and clinical studies
- protocol and report for animal studies (if applicable)
- quantity and number of reference product received (client service, PBSL)
- quantity and number of samples (biological medicinal product) received (client service, PBSL)
- programme for post market surveillance/risk management plan/Pharmacovigilance
- report on substitution and interchangeability (if applicable)
- package insert

7.2 **Appendix II:**

Relevant PBSL guidance documents (refer to; www.pharmacyboard.gov.sl)

i. Guidelines for registration of biological products
ii. Guidelines for safety monitoring
iii. Guidelines for conducting clinical trials of allopathic drugs, vaccines, and medical Devices
iv. Guidelines for requirements for labelling of products

**7.3 Appendix III:**

Abbreviations and acronyms

| | |
|---|---|
| CMC | Chemistry, Manufacturing and Control |
| DNA | Deoxyribonucleic Acid |
| GMP | Good Manufacturing Practice |
| ICH | International Conference of Harmonisation |
| INN | International Non-proprietary names |
| NCE | New Chemical Entity |
| NRA | National Regulatory Authority |
| PK/PD | Pharmacokinetic/Pharmacodynamics |
| PSUR | Periodic Safety Update Reports |
| RMP | Risk Management Plan |
| WHO | World Health Organisation |
| MOA | Mechanism of Action |

BMR Batch Manufacturing Records

**7.4 Appendix IV:**

Non-clinical study program for different types of registration applications

| Parameters | Innovator Biological Products | Biosimilar Products |
|---|---|---|
| Pharmacology | | |
| Pharmacodynamics (PD) | + | + |
| Safety Pharmacology | + | + |
| Pharmacodynamic drug interactions | + | + |
| Pharmacokinetics | | |
| Data | + | + |
| Toxicology | | |
| Acute toxicity | + | + |
| Repeat dose toxicity | + | + |
| Genotoxicity | + | + |

| | | |
|---|---|---|
| Carcinogenicity | + | + |
| Local tolerance | +** | +** |
| Antigenicity/Immunogenicity | + | + |
| Reproductive and Developmental toxicity | + | + |
| | | |

Including toxico-kinetics and antibody measurements

** if feasible, part of repeat dose toxicity

(+) only applicable in specific cases

| ***Prepared by*** | ***Reviewed by*** | ***Approved by*** |
|---|---|---|
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