

**APPENDIX 15      *GUIDANCE ON REGISTRATION OF BIOSIMILAR PRODUCTS***

**TABLE OF CONTENTS**

1	INTRODUCTION .....	2
1.1	Scope.....	2
1.2	Purpose.....	3
1.3	Definition .....	3
2	BASIC PRINCIPLES.....	3
2.1	Biosimilar Product Approach .....	3
2.2	Choice of Reference Product .....	4
3	SUBMISSION PROCEDURE.....	5
4	DOCUMENTARY REQUIREMENTS .....	6
4.1	Quality Documentation.....	6
4.2	Non-clinical Documentation.....	8
4.3	Clinical Documentation .....	9
5	INTERCHANGEABILITY & SUBSTITUTABILITY .....	12
6	VIGILANCE REQUIREMENTS .....	12
6.1	ADVERSE REACTION (AR) REPORTING .....	13
6.2	ROUTINE SUBMISSION OF PRODUCT BENEFIT-RISK EVALUATION REPORT (PBRERs) .....	14
6.3	RISK MANAGEMENT PLANS (RMPs) .....	14
6.4	EDUCATIONAL MATERIALS AND DISTRIBUTION RECORDS.....	15
6.5	PRODUCT SALES DATA .....	17

## 1 INTRODUCTION

Biological medicines are produced using a living system or organism. They are different from traditional chemical medicines in many ways. The manufacturing process of a biological medicine is highly complex and is a determining factor in the development of a biological medicine. The definition of “process” includes the type or identity of the source material and the individual process steps in cell fermentation, protein purification, sterile filling and drug product formulation. Even very small process changes can result in significant differences in the clinical properties of the biological medicines.

The expiration of the patents on many biological products has prompted the development of these products as similar biological products, or biosimilar products. A biosimilar product would have an abbreviated non-clinical and clinical development programme leveraging on the existing information of the original product and focusing on demonstration of similarity with the original product. While the launch of such biosimilar products would provide patients with potentially cheaper alternatives, it is also prudent to ensure that the quality, safety and efficacy of such products are not compromised.

### 1.1 Scope

This guidance document describes the basic principles of a biosimilar product, as well as the procedures and requirements for registration of a biosimilar product.

Applicants are expected to comply with the procedures and requirements laid out in this guidance. However, alternative approaches to the specified procedures and requirements may be accepted, provided there is adequate scientific evidence and justification. Any alternative approach should be discussed with HSA and agreed upon in advance in order to avoid rejection of the application. Conversely, HSA may request for information or specify conditions not described in this document but deemed necessary to adequately assess the safety, efficacy and quality of the product under evaluation.

## 1.2 Purpose

This guidance document is intended to:

- Introduce the concept of biosimilar products;
- Outline the basic principles to be applied for biosimilar products;
- Describe the procedure and documentary requirements for submitting a biosimilar product application; and
- Describe the vigilance requirements for biosimilar products.

This guidance document is adapted mainly from the EMA ([biosimilars](#), [biologicals: drug substance](#)) and [WHO](#) guidelines on biosimilar products, taking into consideration Singapore's local regulatory environment.

## 1.3 Definition

A biosimilar product is a biological therapeutic product demonstrated to be similar, in physicochemical characteristics, biological activity, safety and efficacy to an existing registered biological product.

Applicants are advised to refer to Chapter A of this guidance for details on data protection, data exclusivity and patent linkage.

## 2 BASIC PRINCIPLES

### 2.1 Biosimilar Product Approach

The standard generic approach applied to chemically-derived therapeutic products (demonstration of structural similarities and bioequivalence of the generic product with the reference product using appropriate bioavailability studies) is scientifically not appropriate for biological/biotechnology-derived products. This is due to the complexity of biological molecules which pose challenges in characterisation to demonstrate the similarity of the products. Hence, the licensing of a biosimilar product

should be based on the biosimilar product approach where similarity to reference product in quality, non-clinical and clinical parameters is demonstrated via comparability exercise.

A biosimilar product is intended to be similar in terms of quality, safety and efficacy to a registered biological product (reference biological product) for which there is substantial evidence of safety and efficacy. The comparability exercise for a biosimilar product is designed to show that the biosimilar product has highly similar quality attributes when compared to the reference biological product. Demonstration of similarity of a biosimilar product to a reference product in terms of quality is a prerequisite for determining the non-clinical and clinical data set required for registration.

Significant differences between the biosimilar product and the chosen reference biological product detected during the comparability exercise would be an indication that the products are not similar and more extensive non-clinical and clinical data may be required to support the application for licensing. If relevant differences are found in the quality, non-clinical, or clinical data, the product is unlikely to qualify as a biosimilar product.

Comparability exercises to demonstrate similarity are more likely to be applied to highly purified products, which can be thoroughly characterised (such as some biotechnology-derived therapeutic products). Vaccines, blood or plasma-derived products and their recombinant alternatives, and other types of biological therapeutic products, such as gene or cell products used for advanced therapy, and human tissues or cells intended for human application, are of a complex nature and applications based on biosimilarity for such products will not be considered at the present moment.

## **2.2 Choice of Reference Biological Product**

The chosen reference therapeutic biological product must be a therapeutic biological product registered in Singapore. A biosimilar product cannot be used as a reference product.

The same chosen reference biological product should be used throughout the comparability assessment for quality, safety and efficacy studies during the development of a biosimilar product in order to allow for the generation of coherent data and conclusions.

The active substance of a biosimilar product must be similar, in molecular and biological terms, to the active substance of the reference therapeutic biological product.

The pharmaceutical form, strength, and the route of administration of the biosimilar product should be the same as that of the Singapore reference biological product (SRBP). Any deviations from or differences between the biosimilar product and the SRBP will have to be justified by appropriate studies.

If the comparative studies are performed with a reference biological product (RBP) from a non-Singapore registered manufacturing source, the manufacturer needs to demonstrate that the RBP is comparable to the SRBP and hence suitable to support the application for marketing authorisation of a biosimilar product by providing an additional bridging study. The type of bridging data needed will typically include data from analytical studies (e.g. structural and functional data) that compare all three products (the proposed biosimilar product, the SRBP and the RBP), and may also include clinical PK and/or PD bridging studies data for all three products. All comparisons should meet the target acceptance criteria for analytical and PK/PD similarity which will be determined on a case-by-case/product-type basis. A final determination regarding the adequacy of the scientific justification and bridging data will be made during the evaluation of the application.

### **3 SUBMISSION PROCEDURE**

Prospective applicants are encouraged to discuss the submission and documentary requirements in a pre-submission consultation prior to the submission of a biosimilar product application. The request for a consultation should be made in writing, with the purpose and agenda for the consult stated, via email to [HSA\\_TP\\_Enquiry@hsa.gov.sg](mailto:HSA_TP_Enquiry@hsa.gov.sg).

The application for a biosimilar product is to be submitted as a new drug application (NDA) via the abridged evaluation route. The timelines and fees applicable for a NDA via the abridged evaluation route apply. The administrative requirements are as per those required for an NDA via the abridged evaluation route.

Applicants are advised to refer to the Chapter C of this guidance for details on the general procedures and requirements for submitting a NDA.

The biosimilar product must have been evaluated and approved by at least one of HSA's reference agencies, namely Australia TGA, Health Canada, EMA and US FDA. If not, the application is to be submitted with the complete dataset as for a new biological product.

Applications for a biosimilar product do not qualify for evaluation via the verification evaluation route.

## **4 DOCUMENTARY REQUIREMENTS**

### **4.1 Quality Documentation**

The quality documentation requirements are adapted from the [CHMP Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues \(EMA/CHMP/BWP/247713/2012\)](#), and [WHO Guidelines on Evaluation of Similar Biotherapeutic Products \(SBPs\)](#).

The complete quality dossier, including all relevant documents, as required for a new biological product submitted via the abridged dossier evaluation route should be submitted.

The biosimilar product shall, with regards to the quality data, fulfill all technical content requirements for Module 3 of the ICH CTD or Part 2 of the ACTD, and satisfy the technical requirements of the monographs of pharmacopoeia and any additional requirements, as defined by HSA and ICH guidelines. Complete information on the

development, manufacture and control of both the active drug substance and the drug product should be provided.

The RBP used in the biosimilar product comparability exercise at the quality level must be clearly identified (e.g. brand name, pharmaceutical form, cell substrate, formulation, strength, manufacturing site of the reference medicinal product, number of batches, lot number, age of batches used).

Comparability data between the biosimilar product and the reference biological product (in terms of quality) must be included in the quality dossier. The extent of the comparability studies and the assessment criteria should take into consideration:

- the complexity of the molecular structure;
- the capability of the methods used to demonstrate comparability; and
- their impact on quality, safety and efficacy.

For the development of a biosimilar product, the quality target product profile (QTPP) should be established based on the data obtained from the extensive characterisation of the reference biological product in order to relate the biosimilar product to the reference biological product in terms of molecular characteristics and quality attributes. This QTPP should be considered as a development tool through which some target ranges may evolve during development, as further information on the reference therapeutic biological product becomes available.

For robust comparability analysis, a representative quality profile of the reference biological product should be generated from multiple different batches of the reference biological product when establishing the QTPP for the biosimilar product. Quantitative ranges should be established for the biosimilar comparability exercise based primarily on the measured quality attribute ranges of the reference therapeutic biological product and should not be wider than the range of variability of the representative reference therapeutic biological product batches, unless otherwise justified.

An extensive comparability exercise is essential to demonstrate that the biosimilar product has a highly similar quality profile when compared to the reference therapeutic biological product. The manufacturer must carefully design the comparability exercise

based upon full knowledge of the molecular structure and its relevance to the mode of action. The result is a series of physicochemical tests, along or in combination with such biological tests as *in vitro* and *in vivo* bioassays, and receptor binding studies. These tests are applied to the biosimilar product and the selected reference biological product to demonstrate similarities and differences between the two products. These analyses should include side-by-side comparative studies to demonstrate the similarities and differences between the two products. Where comparability testing cannot establish similarity or where differences arise, the differences detected in the quality attributes will have to be appropriately justified with regard to their potential impact on safety and efficacy.

Extensive state-of-the-art characterisation studies should be applied to the biosimilar and reference therapeutic biological products in parallel, to demonstrate with a high level of assurance that the quality of the biosimilar product is comparable to the reference therapeutic biological product. Methods used in the characterisation studies form an integral part of the quality data package. The selected methods should be appropriately qualified for the purpose of comparability and demonstrate that the methods are of acceptable sensitivity and capable to detect slight differences in all aspects pertinent to the evaluation of quality (e.g. ability to detect relevant variants with high sensitivity).

For the process changes during the development of the biosimilar product, comparability exercise(s) for process changes introduced during development should be clearly identified and addressed separately from the comparability exercise performed against the reference biological product. It is strongly recommended to generate the required quality, safety and efficacy data using the biosimilar product manufactured with the commercial manufacturing process (representing the quality profile of the batches to be commercialised) in the comparability exercise for the demonstration of biosimilarity against the reference biological product.

#### **4.2 Non-clinical Documentation**

The non-clinical documentation requirements are adopted from the [CHMP Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-clinical and Clinical Issues \(CHMP/42832/05\)](#).



Before initiating clinical development, non-clinical studies should be performed. These studies should be comparative in nature and should be designed to detect differences in response between the biosimilar product and the reference biological products and not just the response *per se*. Available product specific guidelines should be referenced when appropriate. Relevant international guidelines should be referred to in the design of an appropriate non-clinical study programme.

The requirements for the non-clinical documentation include:

- *In vitro* studies: Assays like receptor-binding studies or cell-based assays should normally be undertaken in order to establish comparability in reactivity and the likely causative factor(s) if comparability cannot be established; and
- Animal studies should be performed to investigate the pharmacodynamic effect/activity relevant to the clinical application, non-clinical toxicity as determined in at least one repeat dose toxicity study, including toxicokinetic measurements, and specific safety concerns.

Normally other routine toxicological studies such as safety pharmacology, reproduction toxicology, mutagenicity and carcinogenicity studies are not required for biosimilar products, unless indicated by the results of repeat-dose studies.

### 4.3 Clinical Documentation

The clinical documentation requirements are adopted from the [CHMP Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-clinical and Clinical Issues \(CHMP/42832/05\)](#).

The requirements depend on the existing knowledge of the reference biological therapeutic product and the claimed therapeutic indication(s). Available product/disease specific guidelines should be followed when appropriate. Relevant international guidelines should be referred to in the design of an appropriate clinical study programme for biosimilar products.

The required clinical data for the comparability study should be generated with the test product produced with the final manufacturing process and therefore representing the quality profile of the batches to be commercialised. Any deviation from this is to be justified and supported by adequate additional data.

The clinical comparability exercise should begin with pharmacokinetic (PK) and pharmacodynamic (PD) studies followed by clinical efficacy and safety studies.

Comparative PK studies designed to demonstrate clinical comparability between the biosimilar product and the reference biological product with regard to key PK parameters are required. PD parameters are to be studied whenever feasible and the PD markers should be selected based on their clinical relevance.

Normally comparative clinical studies are required for the demonstration of clinical comparability. In certain cases however, comparative PK/PD studies between the biosimilar product and the reference biological product may be sufficient to demonstrate clinical comparability, provided that all the following conditions are met:

- The PK profile of the reference biological product is well characterised.
- There is sufficient knowledge of the PD properties of the reference biological product, including the binding to its target receptor(s) and intrinsic activity. Sometimes, the mechanism of action of the biological product will be disease-specific.
- The relationship between dose/exposure and response/efficacy of the reference biological product is sufficiently characterised.
- At least one PD marker is accepted as a surrogate marker for efficacy, and the relationship between dose/exposure to the product and this surrogate marker is well known.

For comparative clinical studies to demonstrate clinical comparability between the biosimilar product and the reference product, clinical comparability margins should be pre-specified and justified, primarily on clinical grounds.

The conditions of use for the biosimilar product must fall within the directions for use including indication(s), dosing regimen(s) and patient group(s) for the SRBP. Potential differences between the biosimilar product and the SRBP should be investigated in a sensitive clinical model.

In case the SRBP has more than one indication, the efficacy and safety of the biosimilar product 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 SRBP. Justification of extrapolation to other indications will depend on various factors, which include the sensitivity of the clinical study population, clinical experience, available literature data, mechanisms of action, target receptors, pattern of molecular signalling upon binding to the receptor, PK in different patient populations, PD parameters, patient-related factors, etc. Possible safety issues in different subpopulations should also be addressed.

### **Immunogenicity**

The ability to predict immunogenicity of a protein product, particularly the more complex proteins, is extremely limited. Animal studies may not be able to predict how a protein is likely to behave in humans as immunogenic response is species-dependent. The development of antibodies in some instances is a benign effect causing few, if any, undesirable symptoms in patients receiving therapy. In other instances, the induction of antibodies is associated with undesirable consequences, which manifest themselves as mild to severe anaphylactoid reactions. Efficacy may be diminished by the induction of neutralising antibodies or binding antibodies, which may affect PK.

The immunogenicity of a biosimilar product must always be investigated. The extent of independent testing needed depends on a variety of scientific factors such as the indication, whether the product is to be administered chronically, the overall assessment of the product's immunogenic potential, and whether there is the possibility of generating a cross-reaction with an important endogenous molecule.

The assessment of immunogenicity requires an optimal antibody testing strategy, characterisation of the observed immune response, as well as evaluation of the correlation between antibodies and PK or PD, relevant for clinical safety and efficacy in all aspects. It is important to consider the risk of immunogenicity in different therapeutic indications separately.

Reference is to be made to the [CHMP Guideline on Immunogenicity Assessment of Biotechnology-Derived Therapeutic Proteins \(CHMP/BMWP/14327/06\)](#).

## **5 INTERCHANGEABILITY**

Unlike generic chemical drugs, whereby the chemical structure is identical to that of the reference chemical product, a biosimilar product does not usually have an identical structure to the reference biological product. Therefore, even though a biosimilar product may be approved to be similar in terms of quality, safety and efficacy to the reference biological product, immunogenicity may preclude switching between products.

A warning statement on the risks associated with the switching of products during treatment is to be included in the package insert of the biosimilar product.

## **6 VIGILANCE REQUIREMENTS**

During the clinical development of a therapeutic product, the patient sample size is relatively small and the patient population recruited into clinical trials are quite homogenous due to the inclusion and exclusion criteria in the protocol for enrolment into the study. As such, the safety and efficacy experience at the point of market approval of a therapeutic product is usually limited. In spite of rigorous reviews prior to market entry, new safety issues (especially rare ones) may be discovered and characterised with increased usage of the product following marketing authorisation.

In addition to the above concerns, biosimilar products may also potentially bring about unwanted immune responses in treated patients. This potential immunological response is partly a reflection of the complexities in the manufacturing, safety and efficacy controls of biosimilar products when compared to their small-molecule generic chemical counterparts. With manufacturing protocols being proprietary knowledge of the originator company, it is impossible for a biosimilar product manufacturer to duplicate these processes. This invariably leads to structural differences in the final biosimilar product, potentially giving rise to differences in efficacy and adverse events, such as the triggering of patient's immune responses, which could have serious consequences.

The current systems of detecting safety issues relating to therapeutic products are applicable for biosimilar products. In view of the inherent potential of biologics to provoke immunologic reactions, special care in the reporting and assessment of adverse reactions should also be taken for biosimilar products.

The post-marketing vigilance requirements outlined below are required for biosimilar products seeking product approval in Singapore:

## **6.1 SERIOUS ADVERSE REACTIONS (SARs) REPORTING**

Upon becoming aware of any SAR, the company must report the event to the Vigilance and Compliance Branch as soon as possible within 15 calendar days. The regulatory reporting time clock starts as soon as any personnel of the company is aware of the SAR.

All spontaneous reports of SARs must be reported. This includes reports where the company does not agree with the reporter/ reporting healthcare professional's assessment of a possible causal association and reports where the reporter/ reporting healthcare professional has not provided a causality assessment.

SARs which are not suspected of being product-related by the healthcare professional attending to the patient should not be reported unless the company has reasons to suspect a causal association.

When submitting the SAR report, the brand name and batch and/or lot number of the biosimilar product should also be provided. The product registrant should follow up on the information if they are not available in the initial report.

## **6.2 SUBMISSION OF PRODUCT BENEFIT-RISK EVALUATION REPORT (PBRERs)**

HSA may require any registrant of a biosimilar product to submit, within the timelines specified by the Authority, a benefit-risk evaluation report relating to the product should significant safety concerns be identified during pre- and post-marketing of the product and assessed to require further close monitoring. PBRERs may be submitted to the Therapeutic Products Branch via [HSA\\_TP\\_Enquiry@hsa.gov.sg](mailto:HSA_TP_Enquiry@hsa.gov.sg).

The registrant of a biosimilar product must submit the benefit-risk evaluation report —

- a) for an initial period of 2 years, at intervals of 6 months commencing from either the date of registration of the biosimilar product, or its international birth date; and
- b) annually, for the next 3 years.

After the initial 5 years of registration approval, HSA may request in writing for PBRERs to be continued to be submitted if there are reasons to continue the safety monitoring of the biosimilar product in the market. Each PBRER should cover the period of time since the last updated report and must be submitted within 70 days (for PBRER covering up to 12 months) or 90 days (for PBRERs covering more than 12 months) from the data lock point.

## **6.3 RISK MANAGEMENT PLANS (RMPs)**

The submission of RMP documents in support of all biosimilar product applications is mandatory. RMP documents should be provided as part of the application dossier at the point of application submission and should include the following:

- (a) Singapore-Specific Annex (SSA)
- (b) Latest version of the approved EU-RMP and/or US REMS (where available)
- (c) Proposed local RMP materials (e.g. draft educational materials, if any).

During HSA's review of the application, if an updated version of the EU-RMP and/or US REMS becomes available, it should be submitted to HSA. Submission of the updated EU-RMP and/or US REMS to HSA should be made as soon as possible upon receipt of the updated documents to facilitate the timely review of the application. The relevant updates to the EU-RMP and/or US REMS should be highlighted to HSA in a cover letter.

It is not necessary to submit updated versions of the EU-RMP and/or US REMS after the product applications have been approved, unless otherwise requested by HSA.

The required RMP documents should be attached in PRISM, Section 7 (Supporting Attachments) under *Other Supporting Documents*. The submission of the documents in hardcopy is not required.

Please refer to Appendix 16 - *Guideline on the Submission of Risk Management Plan Documents* for further details on the risk management requirements for biosimilar product applications.

## **6.4 EDUCATIONAL MATERIALS AND DISTRIBUTION RECORDS**

### **6.4.1 Educational Materials for Physicians and/or Patients**

Educational materials for physicians and/or patients (e.g. physician educational material, patient medication guide) may be requested as part of risk management plan for biosimilar products during risk assessment at either pre- or post-marketing phases. The objective of such materials is to inform physicians and/or patients of the potential risks associated with the use of these products and to educate them on the early detection and management of adverse events.

For physician educational materials, there should also be a generic paragraph to remind physicians of the following:

- Information regarding interchangeability;

- The importance of keeping good records of patients prescribed the biosimilar product (including the batch number) for traceability purposes in the event of safety/ quality concerns; and
- To report SARs (including brand name and batch and/or lot number) associated with the biosimilar product to the product registrant and HSA.

Where the applicant considers educational materials as part of the local risk minimisation activities, the draft educational materials should be submitted together as part of RMP documents at the point of application for biosimilar product registration. The draft educational materials will be reviewed during application evaluation and approved at the point of product registration.

Post-approval revisions affecting the clinical use and/or safety content of the educational materials should be submitted for review and approval by HSA prior to distribution to the healthcare professionals. However, for revisions that do not affect the clinical use and/or safety content of the educational materials (e.g. editorial changes, administrative changes, corrections of typographical errors, and changes in address), a notification of the soft copy of the revised materials to HSA will be sufficient (i.e. approval from HSA is not needed). The revised materials may be distributed following the notification to HSA. All revised educational materials should be submitted via email to [HSA\\_TP\\_Enquiry@hsa.gov.sg](mailto:HSA_TP_Enquiry@hsa.gov.sg).

Please refer to the '*Guidance for Industry – Post-marketing Vigilance Requirements for Therapeutic Products*' for further details on the requirements for educational materials.

#### 6.4.2 Distribution Records

The product registrant should ensure that all healthcare professionals who will be prescribing the biosimilar product are provided with a copy of the latest HSA-approved physician educational materials (where applicable). Copies of the latest approved patient educational materials and medication guides, where applicable, should also be made available to healthcare professionals for distribution to all patients who will be supplied with the biosimilar product.



The product registrant should keep records of the distribution of the educational materials to healthcare professionals. The distribution records must include:

- Names of the healthcare institutions/clinics/pharmacies receiving the educational material(s); and
- Date of distribution of the educational material(s).

The distribution records must be submitted to HSA when requested.

## 6.5 PRODUCT SALES DATA

The product registrant may be required to provide sales data of the biosimilar product, in terms of the number of units of product sold and the buyer categories (e.g. restructured hospitals, private hospitals, specialist clinics, general practitioner clinics) to HSA when requested. When requested by HSA, the product registrant will be required to provide the list of buyers for their biosimilar product. These data will be used to estimate the local exposure to the product.

Please refer to Appendix 16 Guideline on the Submission of Risk Management Plan Documents and the '*Guidance for Industry – Post-marketing Vigilance Requirements for Therapeutic Products*' for further details regarding the above vigilance requirements.

---

## REVISION HISTORY

Guidance Version (Publish Date)

TPB-GN-016-000 (uploaded 31 October 2016)