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REGULATORY GUIDANCE

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**GUIDANCE ON
REGISTRATION OF
SIMILAR BIOLOGICAL PRODUCTS
IN SINGAPORE**



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ABBREVIATIONS AND ACRONYMS

| | |
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| ACTD | ASEAN Common Technical Document |
| ADR | Adverse Drug Reaction |
| CHMP | Committee for Medicinal Products for Human Use (formerly Committee for Proprietary Medicinal Products) (EU) |
| cGMP | Current Good Manufacturing Practice |
| CTD | Common Technical Documents |
| DNA | Deoxyribonucleic Acid |
| EMA | European Medicines Agency (formerly the European Agency for the Evaluation of Medicinal Products) (EU) |
| FDA | Food and Drug Administration (US) |
| GLP | Good Laboratory Practice |
| HSA | Health Sciences Authority (Singapore) |
| ICH | International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use) |
| NDA | New Drug Application |
| PD | Pharmacodynamics |
| PK | Pharmacokinetics |
| PSUR | Periodic Safety Update Report |
| QOS | Quality Overall Summary |
| TGA | Therapeutics Goods Administration (Australia) |
| UK | United Kingdom |
| US | United States |

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. A similar biological 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 similar biological 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 similar biological product, as well as the procedures and requirements for registration of a similar biological 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 similar biological products
- Outline the basic principles to be applied for similar biological products
- Describe the procedure and documentary requirements for submitting an application for a similar biological product
- Describe the pharmacovigilance requirements for similar biological products
- Describe the post-approval batch release requirements for similar biological products

This guidance document is adapted mainly from the EMEA guidelines on similar biological products¹, with consideration of Singapore’s local regulatory environment.

1.3 DEFINITION

A similar biological (biosimilar) product is a biological medicinal product referring to an existing registered product, submitted for medicinal product registration by an independent applicant, and is subject to all applicable data protection periods and/or intellectual property rights for the original product.

¹ <http://www.emea.europa.eu/htms/human/humanguidelines/multidiscipline.htm>

Applicants are advised to refer to sections 11 & 12 in the Guidance on Medicinal Product Registration in Singapore² for details on *Data Protection, Data Exclusivity and Patent Linkage*.

2 BASIC PRINCIPLES

2.1 BIOSIMILAR PRODUCT APPROACH

In principle, the concept of a “similar biological medicinal product” is applicable to any biological medicinal product. However, in practice, the success of such a development approach will depend on the ability to characterise the product and therefore to demonstrate the similar nature of the concerned products.

Biological medicinal products are usually more difficult to characterise than chemically derived medicinal products. In addition, there is a spectrum of molecular complexity among the various products (recombinant DNA, blood or plasma-derived, immunologicals, gene and cell-therapy, etc.). Moreover, parameters such as the three-dimensional structure, the amount of acido-basic variants or post-translational modifications such as the glycosylation profile can be significantly altered by changes, which may initially be considered to be ‘minor’ in the manufacturing process. Thus, the safety/efficacy profile of these products is highly dependent on the robustness and the monitoring of quality aspects.

The standard generic approach (demonstration of bioequivalence with a reference medicinal product by appropriate bioavailability studies) is normally applied to chemically derived medicinal products. Due to the complexity of biological/biotechnology-derived products, the generic approach is scientifically not appropriate for these products. The biosimilar product approach, based on a comparability exercise (demonstration of similarity), will then have to be followed.

Current technologies, such as peptide mapping, protein sequencing, and mass spectroscopy enable manufacturers to determine, with certainty, the amino acid sequence of a recombinant protein. However, the amino acid sequence is the most rudimentary characteristic of a protein. Conclusive analysis of other aspects of a protein's structure requires much more sophisticated technologies and is fraught with uncertainties that are proportional to the size and complexity of the protein itself. Therefore, the ability to predict the clinical comparability of two products depends on our understanding of the relationship between the structural characteristics of the protein and its function, as well as on our ability to demonstrate structural similarity between the biosimilar product and the reference product. Although this may be currently possible for some relatively simple protein products, technology is not yet sufficiently advanced to allow this type of comparison for more complex protein products. Similarity will therefore need to be confirmed via non-clinical and clinical studies.

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 medicinal products).

The biosimilar product approach is more difficult to apply to other types of biological medicinal products, which by their nature are more difficult to characterise, or which have little clinical and regulatory experience in their evaluation. Whether a medicinal product would be acceptable using the biosimilar product approach depends on the state of the art of

² http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/western_medicines/guidelines.html

analytical procedures, the manufacturing processes employed, as well as clinical and regulatory experience.

Vaccines, blood or plasma-derived products & their recombinant alternatives, and other types of biological medicinal 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 for biosimilar products for such products will not be considered at the present moment.

Products employing clearly different approaches to manufacture than the reference product (e.g., use of transgenic organisms versus cell culture, or use of eukaryotic versus prokaryotic host cell), or any use of a non-analogous host cell line or change to the culture conditions (e.g. cell monolayer versus suspension), would require a strong rationale in order to be considered eligible as a biosimilar product.

2.2 CHOICE OF REFERENCE PRODUCT

The chosen reference medicinal product must be a medicinal product registered in Singapore. A biosimilar product cannot be used as a reference product. Data generated from comparability studies with medicinal products registered in other countries may only provide supportive information.

The same chosen reference 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 the generation of coherent data and conclusions. The chosen reference product used should be of the corresponding strength and from the Singapore registered drug product manufacturing source.

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

The pharmaceutical form, strength, and route of administration of the similar biological medicinal product should be the same as that of the reference medicinal product. When the pharmaceutical form, the strength or the route of administration is not the same, additional data in the context of the comparability exercise should be provided. Any differences between the similar biological medicinal product and the reference medicinal product will have to be justified by appropriate studies on a case-by-case basis.

3 SUBMISSION PROCEDURE

Applicants are encouraged to discuss the submission and documentary requirements in a pre-submission consultation prior to submission of a biosimilar product. The request for a consultation should be made in writing, with the purpose and agenda for the consult stated, via email to HSA_MedProd_Registration@hsa.gov.sg.

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

Applicants are advised to refer to the Guidance on Medicinal Product Registration in Singapore³ for details on the general procedures and requirements for submitting a NDA.

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

Application for a biosimilar product would not qualify for evaluation via the verification evaluation route as with all biological products.

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 (CHMP/49348/05)⁴, and CHMP Guideline on Comparability of Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues (CHMP/BWP/3207/00 Rev. 1)⁵.

The complete quality dossier as required for a new biological product submitted via the abridged dossier evaluation route is to be submitted, including the Singapore Quality Overall Summary (QOS).

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, such 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.

Comparability data between the biosimilar product and the reference product (in terms of quality) must be submitted in the quality dossier. The extent of the comparability studies and the assessment criteria depends on the complexity of the product and the capability of the methods used to demonstrate comparability. The comparability exercise should entail evaluation of both drug substance and drug product. Comparability study must take into consideration:

- the complexity of the molecular structure,
- the type of changes introduced in the manufacturing process during development, and
- their impact on quality, safety and efficacy.

For the purposes of clarity, any comparability exercise(s) for process changes introduced during development should be clearly identified and addressed separately from the comparability exercise versus the reference product.

Comparability is essential to establish an overall development package for biosimilars. 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 and

³ http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/western_medicines/guidelines.html

⁴ <http://www.emea.europa.eu/pdfs/human/biosimilar/4934805en.pdf>

⁵ <http://www.emea.europa.eu/pdfs/human/bwp/320700en.pdf>

the selected reference product to demonstrate similarities and differences between the two products. Where comparability testing cannot establish similarity or where differences arise, the outstanding issues must be addressed through supporting preclinical and/or clinical work.

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)⁶.

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 similar biological product and the reference medicinal product and not just the response *per se*. Relevant international guidelines should be referred to in the design of an appropriate non-clinical study programme.

The requirements for the non-clinical documentation would 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.
- Animal studies should be performed to investigate 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)⁷.

The requirements depend on the existing knowledge about the reference medicinal 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.

⁶ <http://www.emea.europa.eu/pdfs/human/biosimilar/4283205en.pdf>

⁷ <http://www.emea.europa.eu/pdfs/human/biosimilar/4283205en.pdf>

Comparative PK studies designed to demonstrate clinical comparability between the biosimilar product and the reference product with regard to key PK parameters are required. Pharmacodynamic studies to demonstrate therapeutic efficacy of the product is required.

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 product may be sufficient to demonstrate clinical comparability, provided that all the following conditions are met:

- The PK of the reference product are well characterised.
- There is sufficient knowledge of the PD properties of the reference product, including 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 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 Singapore reference product.

In case the reference medicinal product 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 reference medicinal product. Justification will depend on e.g., clinical experience, available literature data, whether or not the same mechanisms of action or the same receptor(s) are involved in all indications. 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. Development of antibodies in some instances is a benign effect causing few, if any, undesirable symptoms in patients receiving therapy. In other instances, induction of antibodies is associated with undesirable consequences, which manifest themselves as mild to severe anaphylactoid reactions. The efficacy may be diminished by induction of neutralising antibodies.

The immunogenicity of a biosimilar product must always be investigated. The extent of independent testing needed will again depend 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 pharmacokinetics or pharmacodynamics, 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)⁸.

5 INTERCHANGEABILITY & SUBSTITUTABILITY

A product is interchangeable with another if both products are approved for the same indication, and can be used for the said indication. Two products are substitutable with each other if they can both be used in lieu of the other during the same treatment period. For interchangeable products, one or the other can be used (prescribed) but these products cannot be substituted with one another during a treatment period. Interchangeability does not imply substitutability.

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 product, immunogenicity may preclude switching between products.

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

6 PHARMACOVIGILANCE REQUIREMENTS

At the time of market approval for a medicinal product, information on the safety of the product is relatively limited. There are some potential risks which may not have been identified at the time of market authorization due to several factors like small numbers of subjects in clinical trials, small study population with specific inclusion criteria and short duration of exposure. However, when the medicinal product is used more widely in the postmarket setting, new and unidentified risks associated with the product may emerge. In addition to the above concerns with medicinal products on the whole, biosimilars may induce unwanted immune response in treated patients.

This potential immunological response is partly a reflection of the complexities of manufacturing, and safety and efficacy controls of biosimilars 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's manufacturer to duplicate the process. This invariably leads to structural differences in the final products, resulting in differences in efficacy and adverse events such as triggering of patient's immune responses, which could have serious consequences.

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

The following activities are required in addition to current pharmacovigilance activities for medicinal products:

⁸ <http://www.emea.europa.eu/pdfs/human/biosimilar/1432706enfin.pdf>

(i) Adverse drug reaction (ADR) reporting by product licence holders

In the current framework for medicinal products, the product licence holder has to report suspected serious ADRs occurring in Singapore to the Pharmacovigilance Branch no later than 15 days from the first receipt of the reports. For biosimilar products, this reporting by product licence holder will extend to include the reporting of non-serious adverse reactions that do not appear in the product label occurring in Singapore as well. This is to enable the Pharmacovigilance Branch to capture cluster effects of both serious and non-serious ADRs.

(ii) Reviewing of periodic safety update reports (PSURs) for biosimilar products

The product licence holder is required to submit the global PSURs to HSA every 6 months for the first 2 years, followed by yearly for the following 3 years for a biosimilar product that is newly registered in Singapore. In addition, the product licence holder will be required to submit the line listings of all the serious and non-serious adverse events in Microsoft Excel format to the Pharmacovigilance Branch to aid in assessments and reviews, when requested.

(iii) Risk management plans for biosimilar products

For all biosimilar products, additional monitoring activities need to be in place to address the safety concerns which these products may bring about, on top of routine pharmacovigilance activities. The product licence holder is required to submit a risk management plan for the biosimilar product at the time of application for product licensure. The plan must be with the intention to mitigate potential risks associated to the biosimilar product.

(iv) Educational materials

The product licence holder should provide additional educational materials to the physicians to provide them with information on the specific risks of the biosimilar product and measures on how to reduce them.

Patient's information leaflets should be prepared by the product licence holder to provide patients with relevant information on what are the potential risks of the product and what are the signs and symptoms which they should alert their healthcare providers on.

(v) Product Sales Data

The product licence holder is required to supply the Pharmacovigilance Branch with the sales data, in terms of number of units of product sold and the buyer categories (e.g. restructured hospitals, private hospitals, specialist clinics, general practitioner clinics) of their biosimilar product on a quarterly basis. These data will be used for an estimation of the number of local exposures to the product. When requested by HSA, the product licence holder will be required to provide buyer list of their biosimilar product.

7 POST-APPROVAL BATCH RELEASE REQUIREMENTS

Biosimilar products are subjected to a risk-based post-approval batch release programme.

The product licence holder is to submit the following documents prior to import and sale of each batch of the biosimilar product:

- Manufacturer's batch release data and certificate of analysis

- A letter of commitment to provide yearly stability data on annual stability batch

HSA may choose to request for the following additional documents:

- Batch release certification from one of HSA's reference agencies namely, Australia TGA, Health Canada, EMEA, UK Medicines and Healthcare Products Regulatory Agency (MHRA) and US FDA
- Certificates of analysis from a laboratory in one of HSA's reference agencies or other accredited biologics testing laboratory⁹

HSA may also choose to carry out independent batch testing of selected batches based on the following factors:

- No batch release certificate from one of HSA's reference agencies
- Unsatisfactory result(s) in the certificate of analysis from a laboratory in one of HSA's reference agencies or other accredited biologics testing laboratory¹⁰
- Unsatisfactory inspection history
- Unsatisfactory testing history
- Unsatisfactory stability data
- Post-marketing experience e.g., adverse drug reaction

⁹ Laboratory in compliance with the latest recommendations from the US FDA, ICH, CHMP and all assays performed under full compliance with GLP and cGMP standards

¹⁰ Laboratory in compliance with the latest recommendations from the US FDA, ICH, CHMP and all assays performed under full compliance with GLP and cGMP standards

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