

**DEPARTMENT OF HEALTH
DRUG OFFICE
DRUG REGISTRATION AND IMPORT/EXPORT CONTROL DIVISION**

Guidance Notes for Registration of Biosimilar Products

Introduction

1. According to the Pharmacy and Poisons Regulations, all pharmaceutical products must satisfy the criteria of safety, quality, and efficacy before they can be registered with the Pharmacy and Poisons Board and be sold in Hong Kong. The applicants will be required to comply with conditions (if any) as imposed on the Certificates of Drug/Product Registration when the applications are approved for registration. Pharmaceutical products may include chemical or '*biological*' materials as active ingredients or substances.

2. According to the World Health Organization (WHO), biological products are distinguished from other products by being derived from living organisms and frequently have complex molecular structures. They require special quality consideration because of the biological nature of the starting materials, the manufacturing processes, and/or the test methods needed to characterize batches of the products.

3. The expiration of patents and/or data protection for the originator's¹ biological products lead to the development of copy versions of the originator products, using the same approach of generics for the chemical products, i.e. to take advantage of the experience gained by the originator and submit only an abridged application dossier with reduced data on safety and efficacy profile of the copy product. However, in the context of biological products and having due consideration of the specificities mentioned in paragraph 2, these copy products cannot be considered as identical but merely '*similar*' to the originator products because of the inevitable differences in molecular structures and quality attributes arising from their different manufacturing processes. They will be referred as '*biosimilar*' products hereafter. In line with international practice and scientific consensus, the registration of biosimilar products cannot rely only on bioequivalence and quality data, they will need additional safety and efficacy information in comparison with the profile obtained by the originator products.

Purpose and Scope

4. The purpose of this document entails the special considerations for registration of biosimilar products. The applicants should also read in conjunction with the "Guidance Notes for Registration of Pharmaceutical Products/Substances" on the requirements for new biological products, where applicable. Because of the complexity of biological products including biosimilar, the applicants may be required to provide additional information on top

¹ A medicine which has been licensed by the national regulatory authorities on the basis of a full registration dossier; i.e. the approved indication(s) for use were granted on the basis of full safety, quality and efficacy data.

of the requirements stated in the guidance notes to allow evaluation of safety, quality, and efficacy of the products applying for registration.

5. The scope of this document is confined to biological products that are highly purified and can be thoroughly characterised (such as many biotechnology-derived products). For other biological products, similar principles in this document could also apply where a copy product is intended to be developed and submitted for registration in Hong Kong. However, vaccines, blood or plasma-derived products and their recombinant analogues, other biological products such as allergen products, gene or cell products for advanced therapy, cells and tissues for human applications are of complex nature and their applications as biosimilar products will not be considered at this stage.

General Requirements

6. Biosimilar product must be proven to be similar to a registered originator product (i.e. *reference product*) in terms of safety and efficacy. The applicant must provide evidence to support all aspects of the application, starting with characterization and evaluation of quality attributes followed by non-clinical and clinical studies of the product. Comprehensive characterization and comparison at the quality level provide the basis for possible data reduction of non-clinical and clinical studies.

7. If differences between the biosimilar and reference products are found during the above characterization and comparison studies, the reasons for the differences should be explained and justified; and additional data may be required to further document the possible impact of those differences on the similarity profile.

8. In order to register a biosimilar product with reduced non-clinical and clinical data, it depends on proof of its biosimilarity to a reference product through the comparability exercise using sensitive and specific analytical methods to detect potential differences between the biosimilar and reference products. The applicant should submit a full quality dossier with the application that includes a complete characterization of the biosimilar product and its production and purification processes. The comparability exercise between the biosimilar and reference products in the quality part represents an additional element to the traditional full quality dossier for pharmaceutical products containing chemical or biological materials as active ingredients or substances.

9. The comparability exercise at quality level described in the above paragraph 8 is the basis for reducing the non-clinical and clinical data requirements, which should indicate that the biosimilar product has highly similar quality attributes to the reference product. The comparability data at quality level is an additional set of data over that which is normally required for an originator product and may be presented as a separate section in the quality dossier. The comparability exercise should be completed by non-clinical and clinical studies to provide an integrated set of comparative data.

10. The biosimilar product should have been granted marketing authorisation(s) by at least one of the following reference agencies: (i) the US's Food and Drug Administration, (ii) European Medicines Agency, (iii) Japan's Ministry of Health, Labour and Welfare, (iv) Australia's Therapeutic Goods Administration, and (v) Health Canada. Otherwise, the

application cannot be accepted for registration as a biosimilar product, and will be considered as an application of pharmaceutical product containing new biological material as active substance; and will be required to submit the documents as stated in the “Guidance Notes for Registration of Pharmaceutical Products/Substances”.

11. The active substance(s) must be similar in molecular and biological terms between the biosimilar and reference products.

12. The dose form, strength, and route of administration should be the same between the biosimilar and reference products.

13. The proposed indication(s) of the biosimilar product must fall within the clinical indication(s) granted to the reference product in Hong Kong.

Reference Product

14. The reference product must have been registered in Hong Kong for over 8 years. Otherwise, the application cannot be accepted for registration as a biosimilar product. In addition, a registered biosimilar product cannot be chosen as the reference product in a new application for registration as a biosimilar product.

15. To support registration of the biosimilar product, similarity of the biosimilar and reference products should be demonstrated through “head-to-head” comparisons. The same reference product should be used throughout the entire comparability exercise to substantiate similarity in terms of safety, quality, and efficacy between the biosimilar and reference products.

Specific Requirements

Quality Documents

16. A full quality dossier should be submitted with information on (i) extensive characterization studies of both the active substance and the finished product; and (ii) the development, manufacturing process, and quality control of both the active substance and the finished product.

17. A separate section in the quality dossier on comparability exercise between the biosimilar and reference products on both the active substances and the finished products should be submitted. Where applicable, the applicant may refer to the WHO “Guidelines on Evaluation of Similar Biotherapeutic Products” for details of the study requirements.

18. It is acknowledged that the quality data of the biosimilar and reference products will not be identical and so, the applicant should provide justification(s) for any observed differences with regard to their potential impact on safety and efficacy.

19. The differences of the quality data may affect the requirements for the amount of non-clinical and clinical data, and will be considered with a case-by-case approach. If sufficient similarities between the biosimilar and reference products cannot be established based on the

submitted quality data, it is very likely that reduced non-clinical and clinical data will not be sufficient to confirm the similarity profile and so, the application may not be accepted for registration as a biosimilar product.

Non-Clinical Documents

20. The applicant should submit non-clinical data of the biosimilar product including: (i) *in vitro* studies (e.g. assays like receptor-binding studies or cell-based assays) to establish comparability in reactivity of the products; (ii) *in vivo* studies (e.g. animal studies on the biological or pharmacodynamic activity relevant to the clinical application; non-clinical toxicity as determined in at least one repeat dose toxicity study including toxicokinetic measurements) when necessary; and (iii) other toxicological studies when necessary (see below).

21. In general, routine toxicological studies such as safety pharmacology, reproductive toxicology, mutagenicity, and carcinogenicity are not required for non-clinical testing of biosimilar products, unless triggered by differences identified at the quality level and/or the results of the repeat dose toxicity study(ies) or known toxicological properties of the biosimilar or reference products.

22. Non-clinical studies constitute part of the overall comparability exercise. These studies should be comparative in nature and designed to detect differences in response between the biosimilar and reference products and not just the response to the products alone. Any deviation from this approach should be justified.

Clinical Documents

23. The applicant should submit clinical data of the biosimilar product including the following comparative studies to enable the detection of potential differences between the biosimilar and reference products: (i) pharmacokinetic (PK) studies; (ii) pharmacodynamics (PD) studies; and (iii) clinical efficacy and safety trial(s).

24. In general, clinical studies are required to demonstrate clinical comparability between the biosimilar and reference products. In certain cases, comparative PK/PD studies may be sufficient, provided that all of the following conditions are met:

- the PK and PD properties of the reference product are well characterized;
- at least one PD marker is accepted as a surrogate marker for efficacy;
- the relationship between dose/exposure, relevant PD marker(s) and response/efficacy of the reference product is sufficiently characterized.

25. In the efficacy/equivalence clinical studies, the study population and dosage should be sensitive to detect potential differences between the biosimilar and reference products. The clinical comparability margins should be pre-specified and justified, primary on clinical grounds.

26. If the reference product has more than one registered indication, the efficacy and safety of the biosimilar product for each proposed indication should be demonstrated separately.

When biosimilar comparability has been demonstrated thoroughly in one indication, extrapolation of clinical data to other indications of the reference product could be acceptable, but needs to be scientifically justified. In case it is unclear whether the safety and efficacy confirmed in one indication would be relevant for another indication, additional data will be required. Besides, immunogenicity is related to multiple factors including route of administration, dosing regimen, patient-related factors, and disease-related factors. Thus, immunogenicity could differ among indications. Extrapolation of immunogenicity from the studied indication or route of administration to other uses of the reference product should be justified (*Note: Please also see paragraph 29 below*).

Immunogenicity Studies

27. As animal studies may not be able to predict the immune response of biosimilar product in humans, immunogenicity of the biosimilar product should always be investigated in humans (in a comparative way) before the biosimilar product can be approved for registration, even if efficacy clinical studies would not be conducted in some circumstances.

28. The applicant should submit immunogenicity data of the biosimilar product including: (i) antibody testing strategy; (ii) characterisation of the observed immune response; (iii) evaluation of the relationship between antibody formation and PK or PD profile, relevant for clinical safety and efficacy in all aspects; and (iv) consideration on the risk of immunogenicity in different therapeutic indications or patient populations separately.

29. If the applicant intends to extrapolate efficacy and safety data of one indication to other indications of the reference product, care should be taken to ensure that immunogenicity is investigated in the patient population with the highest risk of an immune response and immune-related adverse events. This strategy should be justified.

Pharmacovigilance Requirements

30. The applicant is required to comply with the following pharmacovigilance requirements before registration of the biosimilar product is approved:

(i) Reporting of local suspected serious or unexpected adverse drug reactions (ADR) related to the biosimilar product as soon as possible and within 15 calendar days of receipt of the information. Follow-up reports with additional information will be submitted as necessary. The registration certificate holder will be required to conduct evaluation of the ADR and to submit the findings of the frequency and causality of the ADR to the Department of Health. For details on how to report the ADR, the applicant should refer to the Department of Health Drug Office's Guidance for Pharmaceutical Industry - Adverse Drug Reaction Reporting Requirements.

(ii) Submission of Periodic Safety Update Reports (PSURs) of the biosimilar product every 6 months for the first 2 years, and then annually for the following 3 years after the registration is approved. Periodic benefit-risk evaluation report to serve the above purpose is also accepted.

(iii) Providing information on the Risk Management Plan and/or Risk Evaluation and Mitigation Strategy for the biosimilar product as required by the reference agency(ies) if applicable, and any proposed local risk management plan activities and risk mitigation strategies. These activities and strategies should take into account the identified and potential risks associated with the use of the reference product and, if applicable, additional potential risks identified during the development of the biosimilar product, and should provide details on how these issues will be addressed in the post-marketing follow-up. If applicable, the registration certificate holder may be required to implement additional pharmacovigilance measures.

(iv) Preparation of educational materials for healthcare professionals on the specific risks of the biosimilar product and measures to reduce them; and package inserts for patients on the potential risks of the biosimilar product; and the signs and symptoms that they should beware for reporting to their healthcare professionals.

Labelling Requirements

31. The biosimilar product should be labelled to provide information relevant to the safe use of the product by healthcare professionals and patients.

32. The information on the label of a biosimilar product should include: (i) a statement on the nature as a biosimilar product; (ii) product name, manufacturer's name and invented, common or scientific name of the active substance; (iii) registered indication(s) of the biosimilar product; and clinical studies that have been performed with the biosimilar product; and (iv) warning statement on the risk of substitution of reference product with biosimilar product.

33. As biosimilar product is similar but not identical to the reference product, claims for any bioequivalence or clinical equivalence between the biosimilar and reference products will not be allowed.

Remarks

34. For additional reference materials on biosimilar product registration, applicants may also refer to biosimilar guidelines issued by the aforesaid reference agencies including the US Food and Drug Administration and European Medicines Agency.

35. After the biosimilar product registration is approved, the registration certificate holder is responsible for ensuring that the product imported for local sale and supply is identical, in all aspects, to that approved by the Pharmacy and Poisons Board. The registration certificate holder should notify Drug Office of any major variations (such as change of manufacturing site and change in manufacturing process) and obtain approval before implementation as stipulated in the *Guidance Notes on Change of Registered Particulars of Registered Pharmaceutical Products*.

Disclaimer

36. As biosimilar product is similar but not identical to the reference product, approval for registration of a biosimilar product does not imply bioequivalence or clinical equivalence between the biosimilar and reference products. The Department of Health does not endorse the substitution of reference product with biosimilar product. Healthcare professionals should rely on his/her professional judgement and inform their patients if necessary regarding the risk of substitution of reference product with biosimilar product.