Regulatory guidelines for biosimilars in Malaysia

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Abstract

The biosimilars sector continues to attract huge interest and controversy. Biosimilars are new biopharmaceuticals that are “similar” but not identical to the innovator product. Characteristics of biopharmaceuticals are closely related to the manufacturing process, which implies that the products cannot be exactly duplicated. Minuscule differences in the product’s structure and manufacturing process can result in different clinical outcome. This raises concerns over the safety, efficacy and even pharmacovigilance of biosimilars. Thus, biosimilars are unique -- they are not a true chemical generic and are regulated via a distinct regulatory framework. This report discusses the features of Malaysian regulatory oversight of biosimilars and experience acquired in the evaluation of some products from various countries. Ensuring regulatory position adequately reflects scientific advancement, expertise/resources is key. The regulatory situation is an evolving process. Various guidance documents are being prepared with the aim of developing a uniform global framework towards assuring the dual goal of lower costs and patient safety while expediting the availability of important biosimilar products.

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1. Introduction

Biopharmaceuticals are medicinal products consisting of (glyco)proteins and/or ‘nucleic acids’, developed by means of biotechnology processes such as recombinant DNA, controlled gene expression and other novel production methods. Biotherapeutics were introduced in the market in the early 1980s, setting new milestones in modern pharmaceutical therapy resulting in potentially life-saving medical treatments for some of the most serious diseases and offering improvements in quality of life of patients. Biopharmaceuticals are produced from living cells/systems. They are relatively large and complex molecules. They are almost impossible to replicate and minuscule differences in product’s structure and manufacturing process can result in different clinical outcome. Unlike a chemical generic, a biosimilar product is one that is ‘not identical’ but highly similar in physico-chemical and biological characteristics to an innovator product. The inherent differences between any two biopharmaceuticals have the potential to produce dissimilarities in pharmacological properties, clinical efficacy, safety and immunogenicity. These raise concerns over the safety/efficacy and even pharmacovigilance of biosimilars. Clearly, the generic approach is scientifically not appropriate to biosimilars and additional non-clinical and clinical data are usually required. Hence, a biosimilar approval pathway was developed in which comparability exercise(s) in terms of quality, efficacy and safety is required. This further avoids an inordinate impact of development costs in new biopharmaceuticals.

The regulatory situation is an evolving process. This document is intended to provide information on the guidance available in Malaysia for the development and requirements for biosimilars. The guidelines are intended to serve as a live document that will evolve with further progress of scientific knowledge, advances in analytics and more experience.

2. Legislation

The legislative basis for the registration and marketing authorization of pharmaceuticals including biopharmaceuticals in Malaysia is the Control Of Drugs And Cosmetics Regulations (CDCR 1984) promulgated under the Sale Of Drugs Act 1952 (ACT 368). Biosimilar products are considered new biological medicinal products and are therefore regulated under the same legislation. The National Regulatory Authority (NRA) for medicinal products is the National Pharmaceutical Control Bureau, Ministry Of Health, Malaysia [1].

Malaysia’s guidance document and guidelines for registration of biosimilars was finalized in August 2008. The information in the guidance was adopted from the European Medicines Agency (EMA) comprehensive scientific biosimilar guidelines (including the product specific and other guidelines relevant to biosimilars), with some adaptations for Malaysian applications [2].
All relevant International Conference of Harmonization (ICH) Guidelines on biological products containing biotechnology-derived proteins as an active substance, are used as the basis for defining the registration requirements. The document also includes a provision to align or harmonize the regulatory oversight of biosimilars with the global regulatory guideline including the World Health Organization (WHO) Guidelines On Evaluation Of Similar Biological Products containing biotechnology-derived proteins as an active substance [3].

3. Scope and guiding principles

A biosimilar is defined as a new biological medicinal product developed to be similar in terms of quality, safety and efficacy to an already registered, well-established medicinal product/innovator product. The aim of the biosimilar approach is to demonstrate close similarity of the biosimilar product in terms of quality, safety and efficacy to one chosen reference medicinal product. A high degree of similarity between the biosimilar and the reference product is the basis for a reduced non-clinical and clinical package [3,4].

The demonstration of similarity depends upon detailed and comprehensive product characterization, therefore, information requirements outlined within the guideline apply to well-established and well-characterized biopharmaceutical product such as recombinant DNA-derived therapeutic proteins. Biosimilar approach is not applicable to more complex biopharmaceuticals such as blood products, vaccines and other immunologicals.

4. Policy statements

The following policy statements outline the fundamental concepts and principles constituting the basis of the regulatory framework for biosimilars:

1. Biosimilars are not 'generic biologics' or 'biogenerics'. Conventional generics of chemical drugs are approved if pharmaceutical equivalence (i.e identical active substances) and bioequivalence (i.e comparable pharmacokinetics) compared with the innovator drug have been established. Thus, clinical efficacy and safety studies are not needed. This generic paradigm cannot be applied to therapeutic proteins.

2. Approval of a product through the biosimilar pathway is not an indication that the biosimilar may be automatically substituted with its reference product. The decision for interchangeability with the reference product shall be based on science and clinical data.

3. Eligibility for a biosimilar pathway hinges on the ability to demonstrate similarity to a reference product. Product employing clearly different approaches to manufacture than the reference product (for example use of transgenic organisms versus cell culture) will not be eligible for the regulatory pathway for biosimilars.

4. The biosimilar manufacturer must conduct a direct and extensive comparability exercise(s) 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. The rationale for the choice of reference product should be provided by the manufacturer to the NRA.

5. Non-clinical and clinical requirements outlined for biosimilar submission in the guidance document are applicable to biosimilars that have demonstrated similarity to the reference product, based on results of the comparability exercise(s) from chemistry, manufacturing and control (CMC) perspectives. When the similarity of a biosimilar cannot be adequately established, the submission of such a product should be as a 'stand-alone' biotechnological product.

6. It should be recognized that there may be subtle differences between biosimilars from different manufacturers or compared with reference products, which may not be fully apparent until greater experience in their use has been established. Therefore, in order to support pharmacovigilance monitoring, the specific biosimilar given to the patient should be clearly identified by explicit use of brand name, for example.

7. It was acknowledged that although International Nonproprietary Names (INNs) served as a useful tool in worldwide pharmacovigilance, for biologicals they could not be relied upon as the only means of product identification, nor as an indicator of interchangeability or substitution.

8. The prescribing information for a biosimilar should be as similar as possible to that of the reference product except for product-specific aspects such as different excipient(s), clinical studies performed, route of administration etc. This is particularly important and may affect the clinical behavior. Therefore, automatic substitution and active substance-based prescription cannot apply to biosimilars. Such an approach ensures that the treating physicians can make informed decisions about treatments in the interest of patient safety.

5. Malaysian biosimilar guidelines versus WHO similar biotherapeutic products guidelines

Generally the two guidelines are complementary as they are based on similar principles. However, it is noted that the WHO guidelines emphasize on the evaluation of SBPs, thus is very useful. However, the following are specific concepts in the Malaysian perspective:

5.1. Reference product

The reference product is defined as a medicinal product already approved/registered in Malaysia on the basis of a complete dossier (quality, safety and efficacy), chosen as a reference product by the biosimilar manufacturer. The same reference product should be used throughout the development program for quality, safety and efficacy studies and the comparability exercise(s). Alternatively, a medicinal product registered in the reference countries (Australia, Canada, EU (via centralized procedure), United Kingdom, France, Japan, Sweden, Switzerland, and the USA) is considered acceptable. The product should have suitable duration of registration (5 years) and volume of marketed use.

5.2. Interchangeability/switching and substitution

The WHO leaves the issue to the policy or practice of individual country. When biosimilars are approved, they will be considered comparable to the reference product, but this does not necessarily imply therapeutic equivalence. The inherent differences between any two biopharmaceuticals have the potential to produce dissimilarities in pharmacological properties, clinical efficacy, safety and immunogenicity. Switching from one biopharmaceutical to any other can be viewed as a change in clinical management and require appropriate monitoring. The pharmacovigilance program must be rigorous to build an accurate database establishing the clinical use of each product and may include patient registries and retrospective or prospective observational studies. Therefore, for a variety of reasons, automatic substitution is not allowed for biosimilar product [4–7].
5.3. Good manufacturing practice (GMP)

For a biosimilar manufacturer from a country that is not within the Pharmaceutical Inspection Convention/Scheme (PIC/S) member countries or from the eight Malaysian reference countries, a GMP on-site audit of the manufacturing facilities is mandatory.

5.4. Efficacy studies

To demonstrate the similarity in the efficacy profile of the biosimilar product and the reference product, an equivalence trial is advocated. However, the WHO Guidelines on SBPs provide an overview of the advantages and disadvantages of non-inferiority trials, with a caveat there is no experience with the non-inferiority trial to date.

6. Malaysian experience in registration of a biosimilar product and others

There is one biosimilar product approved recently (October 2010) in Malaysia. The product contains Somatropin, brand name is SciTropin A®, manufactured by Sandoz GmbH, Austria and was secondary packaged in Singapore. It is also known as Omnitrope® in many other countries.

SciTropin A®, was classified as a biosimilar as it complies with the requirements of a biosimilar. The approval process for SciTropin A® included a number of comparability studies to the reference product Genotropin®, including quality, pharmacokinetic and pharmacodynamic, clinical efficacy, safety and immunogenicity studies.

A key safety parameter of biotherapeutic products is immunogenicity, i.e., the ability of a substance to trigger an immune response in the patient. Clinical trials and a robust post marketing pharmacovigilance are essential to guarantee product safety and efficacy over time. Such pharmacovigilance plans need to be tailored to each product and a Risk Management Plan (RMP) approved prior to product approval [7,8]. The marketing authorization holders (MAH) of biosimilars should make sure that they have an appropriate system of pharmacovigilance in place to assure responsibility of their products on the market and to ensure that appropriate action can be taken, if necessary. The conclusion of biosimilarity for SciTropin A®, was provided by the totality of evidence in quality, safety and efficacy. It was given registration subject to post-approval commitments to provide follow-up safety assessments.

Our experience in evaluating several “intended copies” or “bio-copies” of biopharmaceuticals, although claimed to be biosimilar products (such as Interferon alpha-2a, Filgrastim and Erythropoietin) from countries considered to have less stringent regulatory standards than the EU and the USA highlighted many inadequacies and shortfalls of the dossiers. Typical shortfalls identified which resulted in non-approval of the products are listed below:

- There was a paucity of data in all aspects of product development, manufacture and control of drug substance and drug product.
- The reference product chosen was not justified and isolation process was not described and justified.
- No or minimal comparability exercise(s) was carried out. Specifications chosen were not clear, hence quality questionable.
- Description of the purification was limited and investigation of impurities was insufficient.
- Batch-to-batch consistency was not demonstrated.
- Validation of infectious agents, TSE assessment was not provided.
- Quality control: inadequate testing and non-orthogonal approach. Poor analytical characterization and validation.
- Although the analytical tools used for assessment of quality were those described in the pharmacopeial monographs, only limited data showing the physico-chemical and biochemical characteristics of the protein were provided. Consequently, the comparability data provided was insufficient to establish similarity of the reference and the copy product at the quality level.
- Stability studies data were limited and stability profiles could not be established.
- Minimalistic non-clinical studies, non-sensitive species were used.
- Inadequate clinical data with poor study designs, small number of subjects and short duration of studies, therefore inconclusive.
- Safety: lack of risk management strategies and no pharmacovigilance data.
- Immunogenicity of the product was not investigated and was not properly evaluated.
- Prescribing information and labeling was very minimal.

Based on the above, sufficient information showing the biosimilarity of the copy product to the reference product was clearly lacking. These copy products have been licensed following the national regulations on the basis of a reduced data package and presumably not advocating stringent demands on demonstrating similarity via comparability exercise(s) [9,10]. Nevertheless, these served as a good learning platform and provided a discriminating insight of the dossier and a challenge to our evaluation skills.

In this respect, since the scientific justification for the various approval pathways is not clear in all cases, the WHO has recognized a need for defining regulatory expectations for these products to promote global consensus on the regulation of biosimilars and thus enhance the availability of safe and effective biosimilar products worldwide.

7. Conclusion

Why biosimilars — and why now? As patents on earlier bio-pharmaceuticals have either expired or about to expire, this creates a clear market opportunity to non-innovator versions of these products called biosimilars. Secondly, the biopharmaceuticals are very expensive and thus, are unaffordable to many patients and cause concerns to ever increasing healthcare costs globally.

Understandably, there is a compelling need to make biosimilar more widely available and cheaper. In light of existing scientific evidence, the regulatory paradigm for biosimilars will have to go beyond mere cost-effectiveness to protect public health. Therefore, the other critical elements in the value equation namely — quality and patient safety — must be given equal importance. Lower cost at the expense of patient safety is no bargain.

The biotechnology sector is at an exciting stage in its life cycle. It can no longer be considered an emerging industry, but neither is it yet a mature industry. Likewise, the rapidly expanding field of biosimilars calls for awareness, alertness and education of all stakeholders. Given these complexities and many other emerging uncertainties, it is important for all stakeholders to work together to evolve a viable and pragmatic regulatory oversight framework and clinical utilization of biosimilars.

Regulation of biosimilars will be a major challenge for NRAs for years to come. Ensuring regulatory position adequately reflects that scientific advancement, expertise, resources and capacity building are essential. Accrued experience will then allow regulatory authorities to optimally match guidelines to the genuine risks and benefits.
associated with biosimilars. Clearly, this area of rapidly evolving regulatory science would benefit from better cooperation, information exchange and collaboration from different regulators internationally. Undoubtedly, squaring the circle will take some doing.

Conflict of interest
Author has disclosed no potential conflicts of interests.

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