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Biosimilar Registration Requirements in Malaysia

	
Krishna Mohan Raju .S*¹, S. B. Puranik²	
<i>¹Research scholar OPJS University, Churu, Rajasthan, India</i>	
<i>²Research Guide OPJS University, Churu, Rajasthan, India</i>	
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ABSTRACT

Biosimilar medicinal product is considered 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. A variety of terms, such as similar biological medicinal products, follow-on protein products, subsequent-entry biologics or biogenerics have been coined by different jurisdictions. For the purpose of this document “biosimilar” is used which is a short designation for a similar biological medicinal product. Biosimilars are an important issue for all parties concerned from patients to generic and innovative industries, to healthcare authorities. However, delivering these medicines to the patients involve complex technical and regulatory challenges, as well as experience with these medicines, is limited. Through this, we summarised the registration procedure for Biosimilars in Malaysia.



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INTRODUCTION

Biopharmaceuticals are protein molecules derived from biotechnology methods or other cutting-edge technologies. They were introduced on the market in the early 1980s, setting new milestones in modern pharmaceutical therapy that improve quality of life for many patients with life-threatening, serious, chronic and debilitating diseases. Today, the so-called similar biological medicinal products (also known as biosimilars), their first-generation successors, are poised to go into the medical application.

Biologics are large, highly complex molecular entities manufactured using living cells and are inherently variable. The manufacturing process is highly complex and critical in defining the characteristics of the final product. Maintaining batch-to-batch consistency is a challenge. Subtle variations in the production or even transport or storage conditions may potentially result in an altered safety and efficacy profile of the final product in some cases. Hence, the dogma .the process is the product is often used in reference to biologics.

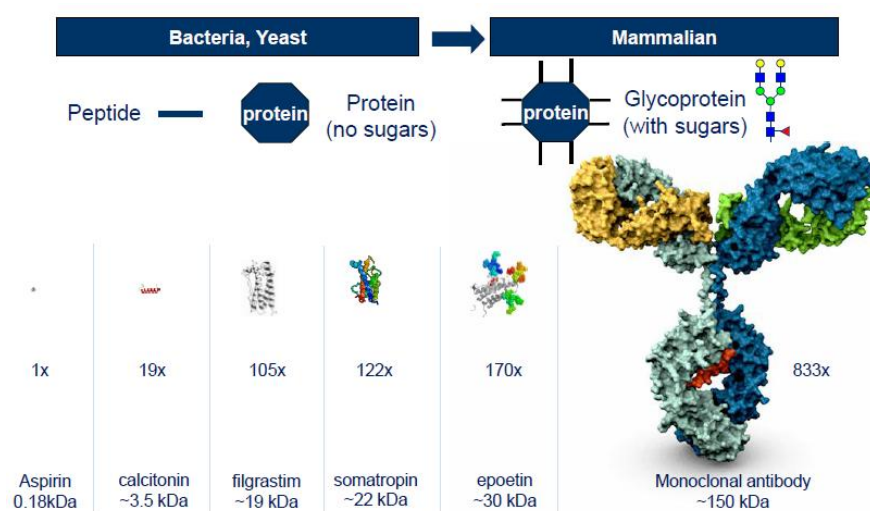


Figure 1: Biologics are more complex than small molecules

Based on the current analytical techniques, two biologics produced by different manufacturing processes cannot be shown to be identical, but similar at best. Therefore, the term “biosimilar” is appropriate and conversely “biogeneric” is felt by many National Regulatory Authorities ¹⁻²(NRAs) to be misleading in this context. Immunogenicity of biotherapeutics is of concern from clinical and safety aspects. Clinical trials and robust post-marketing pharmacovigilance are essential to guarantee the product's safety and efficacy over time.

Regulatory Body

The Control of Drugs and Cosmetics Regulations (CDCR) 1984 were promulgated under the Sale of Drugs Act 1952. The Authority (known as Drug Control Authority, DCA) established under these Regulations, is tasked with ensuring the quality, safety, and efficacy of medicinal products through the registration, including quality control, inspection & licensing and post-registration activities. The National Pharmaceutical Regulatory Agency (NPRA) acts as the secretariat to the Authority and undertakes the responsibility for registration of drugs, biologicals, GMP inspection, and post-registration monitoring activities.

History of NPRA:

The National Pharmaceutical Regulatory Agency (NPRA)³, formerly known as the National Pharmaceutical Control Bureau (NPCB), was set up in October 1978 under the quality control activity of Pharmacy and Supply Programme. This institution was established to implement quality control of pharmaceutical products. The infrastructure and facilities were designed to meet the requirements for testing and quality control activities.

Beginning in 1985, NPRA was given the task of ensuring the quality, efficacy, and safety of pharmaceuticals through the registration and licensing scheme. This is achieved through the evaluation of scientific data and laboratory tests on all products before they are marketed. A system to monitor products in the market was set-up. Information on drugs to the medical profession and consumer was made available through a drug information service.

NPRA organogram:

Roles and Functions of NPRA:

- To implement the drug registration / cosmetic notification scheme through evaluation of technical data, laboratory analysis, research and information received from international agencies.
- To carry out analytical, pharmaceutical, microbiological and pharmacological tests on drugs and cosmetics to determine quality, efficacy, and safety of such products.
- To implement the regulatory scheme on quality of pharmaceutical products in the market through random sampling and carrying out analytical tests.

- To implement the licensing scheme for pharmaceutical manufacturers, importers and wholesalers including a licensing scheme for a clinical trial.
- To encourage and assist local pharmaceutical manufacturers to upgrade manufacturing standards to levels equivalent to the requirements of Good Manufacturing Practice as recommended by the World Health Organisation (WHO).
- To manage the Adverse Drug Reaction Monitoring Program and participate in the WHO International Adverse Drug Reaction Monitoring Program.
- To manage the product recall scheme for pharmaceutical products which are found to be substandard or dangerous to consumers.
- To disseminate information on policies/news of the Drug Control Authority (DCA) via the newsletter "Berita Ubat-ubatan" as well as provide service in the aspect of explaining to the public on the process of online registration, information on registered products and other queries pertaining to NPCB.
- To carry out research on methodology and basic research for the purpose of evaluating the quality, efficacy, and safety of drugs/ cosmetics.
- To establish a reference standard system especially for use in this country generally and for neighboring countries through a scheme of cooperation in the field of pharmaceuticals among ASEAN countries.
- To carry out training for pharmaceutical officers, other professional officers and other semi-professional officers who are placed in this institution from time to time through local training scheme or international co-operational scheme.

Regulatory Framework^{4,5}

In Malaysia "DRUG REGISTRATION GUIDANCE DOCUMENT (DRGD)" will serve as the reference guide for the registration process including quality control, inspection & licensing and post-registration activities of medicinal products. The scope of this DRGD includes information relating to administrative requirements and procedures for;

- a) Submission of an application for the registration of medicinal products, which is based on the ASEAN Common Technical Dossier/ Requirements (ACTD/ ACTR), where applicable;
- b) Submission of an application for the licensing of manufacturers, importers, and wholesalers;
- c) Submission for amendments to a registered medicinal product; and
- d) Post-registration activities.

DRGD guidance in conjunction with the current laws and regulations together with other relevant legislation, where applicable, governing pharmaceutical and natural products for human use in Malaysia, which include but not limited to the following:

- a) Sale of Drugs Act 1952;
- b) Control of Drugs and Cosmetics Regulations 1984;
- c) Dangerous Drugs Act 1952;
- d) Poisons Act 1952;
- e) Medicines (Advertisement & Sale) Act 1956;
- f) Patents Act 1983;
- g) Wildlife Conservation Act 2010 (Laws of Malaysia Act 716); and
- h) International Trade in Endangered Species Act 2008 (Act 686).

The written laws shall take precedence over this guidance document in any event of a discrepancy.

The drug Registration process includes quality control, inspection & licensing as well as a post-registration process of medicinal products is illustrated in Figure below:

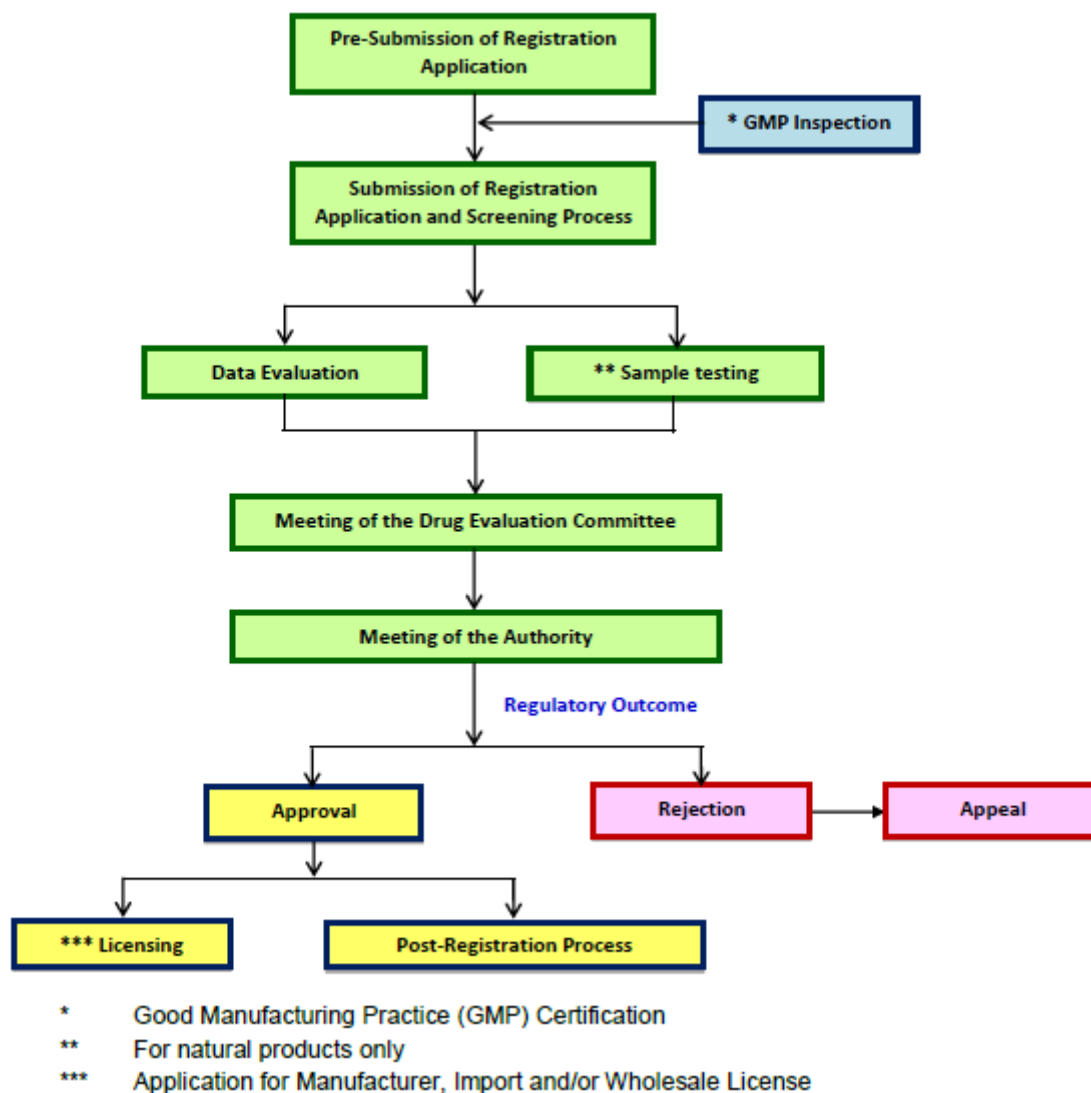


Figure 2: Product registration flowchart

REGISTRATION OF PRODUCTS IN MALAYSIA

Under the CDCR 1984, Regulation 2: “Product” means:

(a) a drug¹ in a dosage unit or otherwise, for use wholly or mainly by being administered to one or more human beings or animals for a medicinal purpose²; or

(b) a drug¹ to be used as an ingredient of preparation for a medicinal purpose².

Under Sales of Drug Act 1952, Section 2:

¹ “drug” includes any substance, product or article intended to be used or capable, or purported or claimed to be capable, of being used on humans or any animal, whether internally or externally, for a medicinal purpose.

² “medicinal purpose” means any of the following purposes:

- (a) Alleviating, treating, curing or preventing a disease or a pathological condition or symptoms of a disease;
- (b) Diagnosing a disease or ascertaining the existence, degree or extent of a physiological or pathological condition;
- (c) Contraception;
- (d) Inducing anesthesia;
- (e) Maintaining, modifying, preventing, restoring, or interfering with, the normal operation of a physiological function;
- (f) Controlling body weight;
- (g) General maintenance or promotion of health or wellbeing.



REGISTRABLE PRODUCTS

Any product as defined in section 1.1 of DRGD shall be registered with the Authority.

The products include, but not limited to the following:

- a) Pharmaceutical products containing scheduled poisons
- b) Pharmaceutical products containing non-scheduled poisons

(For examples: Medicated plaster with medicine, antiseptic/ disinfectants for use on the human body, diagnostic agents for human use (in-vivo) and health supplements such as probiotics and chitosan)

- c) Natural products

Includes herbal and traditional products

NON-REGISTRABLE PRODUCTS

i) Diagnostic agents and test kits for laboratory/ in-vitro use

Diagnostic agents/ test kits for laboratory use must be labeled „FOR LABORATORY USE ONLY“.

Medicinal products for registration are classified under the following categories:

NEW DRUG PRODUCTS

New Drug Products (NDP) is defined as any pharmaceutical products that have not been previously registered in accordance with the provisions of the CDCR 1984.

An NDP may be classified according to the following categories:

a) New Chemical Entity (NCE)/ Radiopharmaceutical Substance

A new pharmaceutical product containing any of the following:

i. New Chemical Entity (NCE)

Defined as an active moiety that has not been registered in any pharmaceutical product.

ii. Radiopharmaceutical substance

Defined as a radionucleotide, ligand or the coupling mechanism to link the molecule and the radionucleotide that has not been registered in any pharmaceutical product.

b) New Combination Product

A new pharmaceutical product containing two or more drugs that are physical, chemically or otherwise combined or mixed and produced as a single pharmaceutical product, in a combination that has not been registered in any other pharmaceutical product. This includes any of the following:

i. Combination of New Chemical Entities;

ii. Combination of registered chemical entity(s) AND New Chemical Entity(s);

iii. Combination of registered chemical entities;

- iv. Combination of registered chemical entities in a new chemical form;
- v. Combination of registered chemical entity(s) in new chemical form(s) AND New Chemical Entity(s);
- vi. Combination of registered chemical entity(s) in new chemical form(s) AND registered chemical entity(s).

c) Supplemental Product

A new pharmaceutical product containing a drug that has been previously registered as a pharmaceutical product but differing in properties with regards to safety and/or efficacy from the product that has been previously registered.

This includes any of the following:

- i. Registered chemical entity in a new chemical form;
- ii. Registered chemical entity in a new dosage form;
- iii. Registered chemical entity in a new dosage strength with a change in dosing/ posology;
- iv. Registered chemical entity for use by a new route of administration;
- v. Registered chemical entity for new indication(s), dosage recommendation(s) and/or patient population(s).

BIOLOGICS

The term „biopharmaceutical“ was coined in the 80“s to define proteins that were made by recombinant DNA technology [which includes hybridoma technology for monoclonal antibody (mAb) production].

Biologics include a wide range of products such as:

- Vaccines;
- Blood products;
- Monoclonal antibodies (therapeutics);

- Recombinant proteins:

GENERICIS

A generic product is a product that is essentially similar to a currently registered product in Malaysia. However, the term generic is not applicable to Biologics.

Generics may be further classified into two groups:

- Scheduled Poison (Known as Controlled Medicine/ Controlled Poison): Products containing poisons as listed in the First Schedule under Poisons Act 1952.
- Non-scheduled Poison (Known as Non-Poison or “Over-the-Counter”, OTC)

BIOSIMILAR REGISTRATION IN MALAYSIA⁵⁻⁶

European Union (EU) through the European Medicines Agency (EMA) has the most well developed regulatory framework for biosimilars and which is supported by specific guidelines.

NPRA has released the guidance for “Biosimilar Registration in Malaysia” in August 2008. The information in the guidance was adopted from the EMA guidelines, in particular, the Guidelines on similar biological medicinal products containing biotechnology-derived proteins as active substances, with some adaptations for Malaysian application.

The purpose of the guidance document is:

- To introduce the concept of biosimilars;
- To outline the basic principles to be applied;
- To provide applicants with a user guide for the relevant scientific information, in order to substantiate the claim of similarity.

The registration applications need to be submitted to the “Biotechnology Section” under the Centre for Product Registration, National Pharmaceutical Regulatory Agency, and Ministry of Health Malaysia.

As part of implementing this guidance document, all the relevant Guidelines on biological products containing biotechnology-derived proteins as active substance and the Guidelines on similar biological medicinal products (also known as biosimilars), will be used as the basis for defining the registration requirements and/or process for registration of biosimilars in Malaysia by NPRA.

Scope and application

The concept of a biosimilar applies to biological drug submission in which the manufacturer would, based on demonstrated similarity to a reference medicinal product, rely in part on publicly available information from a previously approved biologic drug in order to present a reduced non-clinical and clinical package as part of the submission.

The demonstration of similarity depends upon detailed and comprehensive product characterization, therefore, information requirements outlined within this document apply to biologic drugs that contain, as the active substances, well-characterized proteins derived through modern biotechnological methods such as recombinant DNA, into microbial or cell culture.

Conversely, the biosimilar approach is more difficult to apply to other types of biologics which by their nature are more complex, more difficult to characterize or to those for which little clinical regulatory experience has been gained so far. Therefore, it does not cover complex biologics such as blood-derived products, vaccines, immunological and gene, and cell therapy products.

Whether a product would be acceptable using the biosimilar paradigm depends on the state-of-the-art of analytical procedures, the manufacturing process employed, as well as clinical and regulatory experiences.

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

- The principles within the existing regulatory framework for biologics, biotechnology drugs, and generic pharmaceutical drugs shall be the basis of the regulatory framework for biosimilars.

- Biosimilars are not generic biologics/biogenics. Thus, the classic generic paradigm (i.e. demonstration of bioequivalence of the generic drug with the reference product is usually appropriate to infer therapeutic equivalence) and many characteristics associated with approval process used for generic drugs do not apply to biosimilars.
- 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 substitutability with the reference product shall be based on science and clinical data.
- A biosimilar product cannot be used as a reference product by another manufacturer because a reference product has to be approved on the basis of a complete/full quality and clinical data package.
- 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.
- The manufacturer must conduct a direct and extensive comparability exercise between its product and the reference product, in order to demonstrate that the two products have a similar profile in terms of quality, safety, and efficacy. Only one reference product is allowed throughout this exercise. The rationale for the choice of a reference product should be provided by the manufacturer to the NRA.
- Non-clinical and clinical requirements outlined for biosimilar submission in this guidance document are applicable to biosimilars that have demonstrated to be similar to the reference product, based on results of the comparability exercises from chemistry, manufacturing, and control (CMC) perspectives. When similarity of a biosimilar cannot be adequately established, the submission of such a product should be as a stand-alone biotechnological product with complete non-clinical and clinical data.
- Non-clinical and clinical issues of specific products are further elaborated in the Committee for Medicinal Products for Human Use (CHMP) product- class-specific guidelines which appears as Annexes to the general non-clinical and clinical guidelines for a biosimilar.

- 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 patient should be clearly identified.
- It was acknowledged that although International Non-proprietary 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 the interchangeability of biologicals in particular biosimilars.
- For a biosimilar manufacturer from countries that is not from Pharmaceutical Inspection Convention/Scheme (PIC/S) Member Countries or from the 8 Reference Countries, a Good Manufacturing Practice (GMP) on-site audit of the manufacturing facilities is required.

Harmonization with other international regulators:

It is NPRA intention to harmonize as much as possible with other competent regulators and international organizations such as the World Health Organisation (WHO) and the International Conference of Harmonization (ICH). This is with the expectation that guidance on scientific principles that should be involved in evaluating biosimilars, this would help harmonize requirements worldwide and lead to greater ease and speed of approval and greater assurance of the quality, safety, and efficacy of these products worldwide.

Implementation Guidance:

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

The quality part of a biosimilar, like all other biologics, should comply with established scientific and regulatory standards.

A biosimilar product is derived from a separate and independent master cell bank, using independent manufacturing and control method, and should meet the same quality standards as required for innovator products. A full quality dossier is always required.

In addition, the biosimilar manufacturer is required to submit extensive data focussed on the similarity, including comprehensive side-by-side physicochemical and biological characterization of the biosimilar and the reference product.

The base requirement for a biosimilar is that it is demonstrated to be highly similar” to the reference product. Due to the heterogeneous nature of therapeutic proteins, the limitations of analytical techniques and the unpredictable nature of clinical consequences to structure/biophysical differences, it is not possible to define the exact degree of biophysical similarity that would be considered sufficiently similar to be regarded as biosimilar, and this has to be judged for each product independently.

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

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

Comparability exercise:

- Comparability exercise is to ascertain if the biosimilar and the reference products are similar in terms of quality, safety, and efficacy.
- Comparability program/exercise to demonstrate similarity should involve all aspects of development, full analytical comparability of quality, and abridged studies for the non-clinical and clinical components
- The same reference product to be used throughout the comparability program.

- Comparability with the chosen reference product should be addressed for both the active substance and drug product.
- It is not expected that the quality attributes in the biosimilar and the reference product will be identical. For example, minor structural differences in the active substance such as variability in post-translational modifications may be acceptable, however, should be justified.
- Quality differences may impact the amount of non-clinical and clinical data needed and will be a case by case approach.
- If the reference drug substance used for characterization is isolated from a formulated reference drug product additional studies should be carried out to demonstrate that the isolation process does not affect the important attributes of the drug substance/moiety.

Biosimilar Manufacturing process⁷⁻⁸:

- The biosimilar product is defined by its own specific manufacturing process for both active substance and finished product.
- The process should be developed and optimized taking into account state-of-the-art science and technology on manufacturing processes and consequences on product characteristics.
- A well-defined manufacturing process with its associated process controls assures that an acceptable product is produced on a consistent basis.
- A separate comparability exercise, as described in ICHQ5E, should be conducted whenever a change is introduced into the manufacturing process during development.

Reference product:

- Appropriate comparative tests at the level of the isolated active substance from the formulated reference product are generally needed, except in some cases when quality attributes of the active substance can be tested on the finished product.
- The manufacturer should demonstrate that the active substance used in the comparability studies is representative of the active substance of the reference product.

- Comparisons of the active substance in the biosimilar product made against public domain information e.g. pharmacopoeial monographs are not sufficient to demonstrate similarity. Reference standards are not appropriate for use as a reference product.
- The same reference product should be used for all three parts of the dossier (i.e Quality, Safety, and Efficacy)
- The chosen reference product should have a suitable duration and volume of marketed use such that the demonstration of similarity will bring into relevance a substantial body of acceptable data dealing with safety and efficacy.
- The brand name, pharmaceutical form, formulation and strength of the reference product used in the comparability exercise should be clearly identified.
- The shelf life of the reference product and its effect on the quality profile adequately addressed, where appropriate.

Analytical procedure/techniques:

- Extensive state-of-the-art analytical methods should be applied to maximize the potential for detecting is light differences in all relevant quality attributes.
- Methods used in both the characterization studies and comparability studies should be appropriately qualified and validated [as in ICH Q2(R1)].
- If available, standards and international reference materials [e.g. from European Pharmacopeia (Ph. Eur.), WHO etc.] should be used for method qualification and validation.

Characterizations considerations:

- Characterizations of a biotechnological/biological product by appropriate techniques, as described in ICH Q6B, includes the determination of physicochemical properties, biological activity, immunochemical properties (if any), purity, impurities, contaminants, and quantity.
- Key points in the conduct of characterization program/exercise:
- Physicochemical properties: determination of composition, physical properties and should consider the concept of the desired product (and its variants) as defined in ICH Q6B. The

complexity of the molecular entity with respect to the degree of molecular heterogeneity should also be considered and properly identified.

- Biological activity includes an assessment of the biological properties towards confirmation of product quality attributes that are useful for characterization and batch analysis, and in some cases, serve as a link to clinical activity.
- Limitations of biological assays could prevent detection of differences. A set of relevant functional assays should be considered to evaluate the range of activities.
- Immunochemical properties: When immunochemical properties are part of characterization, the manufacturer should confirm that the biosimilar product is comparable to the reference product in terms of specific properties.
- Purity, impurities, and contaminants: Should be assessed both qualitatively and quantitatively using state-of-the-art technologies and firm conclusion on the purity and impurity profiles be made.
- A complete side-by-side characterizations are generally warranted to directly compare the biosimilar and the reference product. However, additional characterizations may be indicated in some cases.
- Accelerated stability studies of the reference and of the biosimilar product can be used to further define and compare the degradation pathways/stability profiles.
- Process-related impurities are expected, but their impact should be confirmed by appropriate studies (including non-clinical and/or clinical studies).
- Measurement of quality attributes in characterization studies does not necessarily entail the use of validated assays, but the assay should be scientifically sound and provide results that are reliable. Those methods used to measure quality attributes for batch release should be validated in accordance with ICH guidelines (ICH Q2A, Q2B, Q5C, Q6B), as appropriate.

Specifications Setting:

- The analytical procedures chosen to define drug substance or drug product specifications alone are not considered adequate to assess product differences since they are chosen to

confirm the routine quality of the product rather than to fully characterize it. The manufacturer should confirm that the specifications chosen are appropriate to ensure product quality.

- Specification limits: should not be wider than the range of variability of the reference product.

Stability considerations:

- Proteins are frequently sensitive to changes, such as those made to buffer composition, processing and holding conditions, and the use of organic solvents.
- Accelerated and stress stability studies are useful tools to establish degradation profiles and can, therefore, contribute to a direct comparison of biosimilar and the reference product. Appropriate studies should be considered to confirm that storage conditions and controls are selected.
- ICH Q5C and Q 1A(R2) should be consulted to determine the conditions for stability studies that provide relevant data to be compared before and after a change.
- For a biosimilar approach, it would be worth comparing a biosimilar with reference product by accelerated stability studies as these studies at elevated temperature may provide complementary supporting evidence for the comparable degradation profile.

Non-clinical requirements

- Biosimilars should undergo appropriate non-clinical testing sufficient to justify the conduct of clinical studies in healthy volunteers or patients. These studies should be comparative and aim to detect differences between the biosimilar and the reference product and not just response per se.
- Ongoing consideration should be given to the use of emerging technologies (For e.g In vitro techniques such as e.g real-time binding assays may prove useful. In vivo, the developing genomic/proteomic microarray sciences may, in the future, present opportunities to detect minor changes in biological response to pharmacologically active substances).

✓ ***In-vitro* studies:**

- Receptor-binding studies or cell-based assay (e.g cell-proliferation assay) should be conducted.

✓ ***In-vivo* studies:**

- Animal pharmacodynamic study where appropriate, relevant to clinical use.

- At least one repeat-dose toxicity study, including toxicokinetic measurements, should be conducted in relevant species.

- Relevant safety observations (for e.g local tolerance) can be made during the same toxicity study.

The rationale for the request of antibody measurements in the context of the repeat dose toxicity study:

○ Generally, the predictive value of animal models for immunogenicity in humans is considered low. Nevertheless, antibody measurements (e.g antibody titers, neutralizing capacity, cross-reactivity) as part of repeated dose toxicity studies is required to aid in the interpretation of the toxicokinetic data and to help assess, as part of the comparability exercise, if structural differences exist between the biosimilar and the reference product.

Other toxicological studies, including safety pharmacology, reproductive toxicology, mutagenicity and carcinogenicity studies are not required for biosimilar unless warranted by the results from repeated toxicological studies.

Clinical requirements⁷⁻⁹

Pharmacokinetic (PK) studies

✓ Comparative pharmacokinetic studies should be conducted to demonstrate the similarities in pharmacokinetic (PK) characteristics between the biosimilar and the reference product.

✓ If appropriate from an ethical point of view, healthy volunteers will in most cases represent a sufficiently sensitive and homologous model for such comparative PK studies.

- ✓ Choice of designs must be justified and should consider factors such as clearance and terminal half-life, the linearity of PK parameters, where applicable the endogenous level and diurnal variations of the protein under study, production of neutralizing antibody, conditions, and diseases to be treated.
- ✓ The acceptance range/equivalence margin to conclude clinical comparability should be defined prior to the initiation of the study, taking into consideration known PK parameters and their variations, assay methodologies, safety and efficacy of the reference product.
- ✓ Other PK studies such as interaction studies or other special populations (e.g children, elderly, patients with renal or hepatic insufficiency) are usually not required.

Pharmacodynamic (PD) studies

- ✓ Parameters should be clinically relevant or a surrogate marker which is clinically validated. The PD study may be combined with a PK study and the PK/PD relationship can be characterized. PD studies should be comparative in nature.

Confirmatory Pharmacokinetic/Pharmacodynamic (PK/PD) studies

Comparative PK/PD studies may be sufficient to demonstrate comparable clinical efficacy, provided all the followings are met (however, cases, when approval on the basis of PK/PD data might be acceptable, are highly limited):

- ✓ PK and PD properties of the reference product are well characterized.
- ✓ Sufficient knowledge of PD parameters is available.
- ✓ At least one PD marker is accepted as a surrogate marker for efficacy.
- ✓ Dose-response is sufficiently characterized (ICH E10).
- ✓ Equivalence margin is pre-defined and appropriately justified.

Clinical efficacy trials

- ✓ Comparative clinical trials (head-to-head adequately powered, randomized, parallel group clinical trials, so-called equivalence trials are required to demonstrate the similarity in

efficacy and safety profiles between the biosimilar and the reference product. The design of the studies is important. Assay sensitivity must be ensured (ICH E10).

- ✓ Equivalence margins should be pre-specified, adequately justified on clinical grounds.
- ✓ Equivalent rather than non-inferior efficacy should be shown in order for the biosimilar to adopt the posology of the reference product and to open the possibility of extrapolation to other indications, which may include different dosages.

Clinical safety and Immunogenicity

- ✓ The safety of biosimilar should be demonstrated to be similar to the reference product in terms of nature, seriousness, and frequency of adverse events. Thus data from a sufficient number of patients and sufficient study duration with sufficient statistical power to detect major safety differences are needed.
- ✓ For products intended for administration for longer than 6 months, the size of the safety database should typically conform to the recommendations of ICH E1 on the extent of population exposure to assess clinical safety.
- ✓ Data from pre-approval studies are insufficient to identify all differences in safety. Therefore, safety monitoring on an ongoing basis after approval including continued benefit-risk assessment is mandatory.
- ✓ A written rationale on the strategy for testing immunogenicity should be provided. State-of-the-art methods should be used, validated and able to characterize antibody content (concentration or titer), neutralizing antibody and cross-reactivity.
- ✓ Special attention should be paid to the possibility that the immune response seriously affects the endogenous protein and its unique biological function.

Pharmacovigilance Plan/Risk Management Plan (RMP)

Any post-market Risk Management Plan (RMP) should include detailed information on a systematic testing plan for monitoring immunogenicity of the biosimilar post-market.

The RMP should include:

- ✓ Risk Identification and characterization (e.g case definitions, antibody assays);

- ✓ Risk Monitoring (e.g specific framework to associate risk with a product);
- ✓ Risk Minimization and Mitigation strategies (e.g plans to restrict to intravenous use where necessary, actions proposed in response to detected risk etc.);
- ✓ Risk communication (e.g minimizing and mitigation messages for patients and physicians)
- ✓ Monitoring activities to ensure the effectiveness of risk minimization.

POSTMARKET REQUIREMENTS¹⁰⁻¹²

- ✓ The pharmacovigilance plan must be approved prior to approval of the product and the system must be in place to conduct monitoring.
- ✓ The pharmacovigilance plan should be designed to monitor and detect both known inherent safety concerns and potentially unknown safety problems that may have resulted from the impurity profiles of a biosimilar.
- ✓ The pharmacovigilance, as part of a comprehensive RMP, should include regular testing for consistent manufacturing of the bio similar.
- ✓ The pharmacovigilance plan should be able to distinguish between and tracking different products and manufacturers of products in the same class of medicinal products (e.g epoetins, insulins, interferons). Such capability is essential to help ensure adverse events are properly attributed to the relevant medicinal product (i.e traceability).
- ✓ Traceability of the product should involve product identification defined in terms of the product name, brand name, pharmaceutical form, formulation,
- ✓ Strength, manufacturers name and batch number(s).
- ✓ Periodic Safety Update Reports (PSURs) of bio similars should be submitted and evaluation of benefit/risk of the biosimilar post-market should be discussed. Such systems should include provisions for passive pharmacovigilance and active evaluations such as registries and post-marketing clinical studies.

DOSSIER

✓ The data for submission is organized according to the ASEAN Common Technical Dossier (ACTD), with full quality data plus comparability exercise and abridged studies of the non-clinical and clinical components.

INTERCHANGEABILITY SUBSTITUTION¹³⁻¹⁴

Biosimilars are not generic products and cannot be identical to the reference products. Further, the formulations may be different and these can have profound effect on the clinical behaviour. In addition, biosimilars do not necessarily have the same indications or clinical use as the reference products. Therefore, given current science, they cannot be considered interchangeable with the reference product or products of the same class. Automatic substitution (i.e the practice by which a different product to that specified on the prescription is dispensed to the patient without the prior informed consent of the treating physician) and active substance-based prescription cannot apply to biologicals, including biosimilars. Such an approach ensures that treating physicians can make informed decisions about treatments is in the interest of patient's safety.

REFERENCES:

1. Drug Registration Guidance Document Jan 2018 Revision
2. Guideline for Submission of Analytical Method Validation Documents
3. Malaysian Guidelines for the Conduct of Bioavailability and Bioequivalence Studies September 2000
4. Guidance for Application for Registration of Biotechnology/Biological Products
5. Malaysian Guidelines on Good Clinical Practice
6. Guidelines for Application for Variation of Registered Products
7. Guidance on GMP Audit of a Foreign Manufacturer
8. Guidelines for Application of Clinical Trial Import Licence and Clinical Trial Exemption
9. Malaysian Guidelines for the Adverse Drug Reactions Reporting and Monitoring
10. ASEAN Guidance on ACTD.
11. National Pharmaceutical Control Bureau Ministry of Health Malaysia Petaling Jaya Drug Registration Guidance Document.
12. Guidelines for Application for Registration of Biological/ Biotechnology Product Application To Market A New Or Abbreviated New Drug Or Biologic For Human Use (Title 21, Code of Federal Regulations, Parts 314 & 6.
13. Prescription Drug User Fee Rates for Fiscal Year 2013.
14. NPCB Guidance Documents <http://npra.moh.gov.my>