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Position Statements on the Use of Biosimilars in the Ministry of Health, Malaysia Healthcare Facilities

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MINISTRY OF HEALTH MALAYSIA

PHARMACEUTICAL SERVICES PROGRAMME

Position Statements on the Use of Biosimilars in the Ministry of Health, Malaysia Healthcare Facilities

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Pharmaceutical Services Programme
Ministry of Health Malaysia
Lot 36, Jalan Profesor Diraja Ungku Aziz,
46200 Petaling Jaya,
Selangor, Malaysia.
Tel: +603-7841 3200 Fax: +603-7968 2222
Website: www.pharmacy.gov.my

FOREWORD BY THE DIRECTOR GENERAL OF HEALTH MALAYSIA

Biological medicines have transformed the outlook for patients with many chronic and often disabling conditions. An increasing number of biological medicines now have 'biosimilars', i.e. a biotherapeutic product which is highly similar in terms of quality, safety and efficacy to an already approved biological medicine (also known as the reference product). Introducing biosimilars to the market has created new opportunities and the need for changes in practice within healthcare institutions. Today, biosimilars are an integral part of the effective biological therapies available in Malaysia and worldwide.

This Position Statement has therefore been prepared to guide the use of biosimilars in the Ministry of Health facilities. A thorough understanding of the differences between a biosimilar and the biological reference product is vital because, unlike generics, complex biological molecules are not considered identical chemical copies as minor differences in molecular structure, and inactive compounds may exist. Understanding the pharmacodynamics and pharmacokinetics of the biosimilars will assist healthcare practitioners in optimising medicines-use practices involving biosimilars.

As healthcare professionals at the forefront of patient care, we must be augmented with reliable information on biologics and biosimilars: what they are and what scientific principles support their clinical development, approval and safety monitoring. Therefore, training and education are paramount to ensuring the safe and effective use of biosimilars within healthcare facilities.

Finally, I congratulate the Pharmaceutical Services Programme, the Ministry of Health Malaysia and all relevant stakeholders. Their contributions to developing this Position Statement are apt and timely. I fervently hope that this Position Statement will significantly encourage the use and guide biosimilars' prescribing and dispensing practices in the Ministry of Health facilities.

Thank you

Tan Sri Dato' Seri Dr. Noor Hisham Abdullah

Director General of Health, Malaysia

FOREWORD BY THE SENIOR DIRECTOR OF PHARMACEUTICAL SERVICES

In tandem with the progressive development and use of biological medicines in the Ministry of Health (MOH) facilities including biosimilars, suitable guidance is needed to ensure safe and appropriate prescribing and dispensing practices. This has prompted the development of the first edition of the "Position Statements on the Use of Biosimilars in the Ministry of Health Malaysia Healthcare Facilities".

The MOH supports the use of biosimilars as we understand that biosimilars offer a viable, safe, and cost-effective alternative to the innovator biopharmaceutical products currently used in the treatment of several diseases. This Position Statement represents the collective views of key stakeholders from the MOH. The 10 position statements in this document cover the principles and practical issues around biosimilar use as well as the requirement for ongoing pharmacovigilance and outcome monitoring.

We hope this document will provide valuable information to support therapeutic decisions related to the use of biosimilars that can help in maximizing the clinical benefit for our patients in the MOH facilities.

I would like to take this opportunity to congratulate and express my appreciation to the Task Force for Biosimilar Position Statement and all relevant stakeholders for their efforts in producing this important guide.

Thank you

Norhaliza Binti A. Halim

Senior Director of Pharmaceutical Services

Ministry of Health Malaysia

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ADVISORS

Mdm. Fuziah bt Abdul Rashid
Director
Pharmacy Practice and Development Division
Pharmaceutical Services Programme

Dr. Nur Sufiza bt Ahmad
Deputy Director
Pharmacy Practice and Development Division
Pharmaceutical Services Programme

TASKFORCE MEMBERS

Mdm. Haarathi Chandriah
Senior Principal Assistant Director
Pharmacy Practice & Development Division
Pharmaceutical Services Programme

Mdm. Nazatul Syima bt Idrus
Senior Principal Assistant Director
Pharmacy Practice & Development Division
Pharmaceutical Services Programme

Mdm. Rosliza bt Lajis
Senior Principal Assistant Director
Centre of Product & Cosmetic Evaluation
National Pharmaceutical Regulatory Agency

Ms. Sarahfarina bt Abd Rahim
Pharmacist
National Cancer Institute, Putrajaya

Mdm. Noraisyah bt Mohd Sani
Senior Principal Assistant Director
Centre of Product & Cosmetic Evaluation
National Pharmaceutical Regulatory Agency

Ms. Coleen Choo Siew Bee
Senior Principal Assistant Director
Pharmacy Practice & Development Division
Pharmaceutical Services Programme

Mdm. Norhayati bt Musa
Senior Principal Assistant Director
Pharmaceutical Services Division
Selangor State Health Department

Mdm. Sharon Ong Chin Wen
Senior Principal Assistant Director
Pharmacy Practice & Development Division
Pharmaceutical Services Programme

Dr. Vidhya Hariraj
Senior Principal Assistant Director
Centre of Compliance & Quality Control
National Pharmaceutical Regulatory Agency

Mdm. Nurulmaya bt Ahmad Sa'ad
Senior Principal Assistant Director
Pharmacy Practice & Development Division
Pharmaceutical Services Programme

Mdm. Chua Hui Ming
Senior Principal Assistant Director
Centre of Product & Cosmetic Evaluation
National Pharmaceutical Regulatory Agency

Mdm. Siti Hajar bt Mahamad Dom
Senior Principal Assistant Director
Office of the Senior Director of Pharmaceutical Services
Pharmaceutical Services Programme

Ms. Yong Yee Vern
Senior Principal Assistant Director
Pharmacy Practice & Development Division
Pharmaceutical Services Programme

Mdm. Ong Su Hua
Pharmacist
Klinik Kesihatan Putrajaya Presint 9, Putrajaya

Mdm. Nur Syazana bt Amir
Senior Principal Assistant Director
Kuala Lumpur & Putrajaya Health Department

Ms. Nabila bt Abdul Rahman
Principal Assistant Director
Pharmacy Practice & Development Division
Pharmaceutical Services Programme

Ms. Ng Sin Yee
Principal Assistant Director
Pharmacy Practice & Development Division
Pharmaceutical Services Programme

Ms. Mastura bt Abu Samad
Senior Assistant Director
Pharmacy Practice & Development Division
Pharmaceutical Services Programme

REVIEWERS (IN ALPHABETICAL ORDER)

Mr. Ahmad Syafiq bin Ahmad Izani
Pharmacist
Hospital Pulau Pinang, Pulau Pinang

Datin Dr. Asmahan bt Mohamed Ismail
Consultant Rheumatologist
Hospital Raja Perempuan Zainab II, Kelantan

Dr. Azizah bt Ab Ghani
Senior Principal Assistant Director
Centre of Product & Cosmetic Evaluation
National Pharmaceutical Regulatory Agency

Dr. Azuana bt Ramli
Senior Principal Assistant Director
Centre of Compliance & Quality Control
National Pharmaceutical Regulatory Agency

Mdm. Chew Lan Sim
Pharmacist
Hospital Raja Permaisuri Bainun, Perak

Ms. Ching Shan Lii
Pharmacist
Hospital Kuala Lumpur, Kuala Lumpur

Ms. Daphne Gima
Pharmacist
Hospital Putrajaya, Putrajaya

Dato’ Dr. Fazir bin Mohamad
Senior Consultant Orthopaedic Surgeon
Hospital Kuala Lumpur, Kuala Lumpur

Dr. Gerard Lim Chin Chye
Senior Consultant Clinical Oncologist (Former)
National Cancer Institute, Putrajaya

Dato’ Dr. Goh Ai Sim
Senior Consultant Haematologist
Hospital Pulau Pinang, Pulau Pinang

Dato' Dr. Gun Suk Chyn
Senior Consultant Rheumatologist
Hospital Tuanku Ja’afar, Negeri Sembilan

Dr. Hasenah bt Ali
Director (Former)
National Pharmaceutical Regulatory Agency

Dr. Hung Liang Choo
Senior Consultant Paediatric Cardiologist
Hospital Kuala Lumpur, Kuala Lumpur

Dr. Irfhan Ali bin Hyder Ali
Consultant Respiratory Physician
Hospital Pulau Pinang, Pulau Pinang

Dr. Jameela bt P.N.A Sathar
Senior Consultant Haematologist (Former)
Hospital Ampang, Selangor

Dato’ Dr. Kavita M. Bhojwani
Senior Consultant Anaesthesiologist & Intensive Care Physician
Hospital Raja Permaisuri Bainun, Perak

Dr. G. Letchuman a/l Ramanathan
Senior Consultant Physician (Former)
Hospital Raja Permaisuri Bainun, Perak

Dr. Mahathar bin Abd. Wahab
Senior Consultant Emergency Physician
Hospital Kuala Lumpur, Kuala Lumpur

Dato' Seri Dr. Mohamed Yusof bin Hj. Abdul Wahab
Senior Consultant General Surgeon
Hospital Tengku Ampuan Rahimah, Selangor

Dr. Mollyza bt Mohd Zain
Senior Consultant Rheumatologist
Hospital Selayang, Selangor

Dato' Dr. Muhammad Radzi bin Abu Hassan
Senior Consultant Gastroenterologist/ Hepatologist
Hospital Sultanah Bahiyah, Kedah

Mdm. Munira bt Muhammad
Deputy Director
Pharmacy Practice & Development Division
Pharmaceutical Services Programme

Dr. Ng Chen Siew
Senior Consultant Nuclear Physician
Hospital Sultanah Aminah, Johor

Ms. Nik Nuradlina binti Nik Adnan
Pharmacist
Institut Kanser Negara, Putrajaya

Dr. Nor Fariza bt Ngah
Senior Consultant Ophthalmologist
Hospital Shah Alam, Selangor

Mdm. Norhuda bt Mohd Tajuddin
Deputy Director
Pharmacy Practice & Development Division
Pharmaceutical Services Programme

Mdm. Nurul Suhaida Badarudin
Pharmacist
National Cancer Institute, Putrajaya

Datin Shantini a/p Thevendran
Senior Principal Assistant Director
Public Health Pharmacy Sector
Public Health Development Division

Mdm. Kong Su Shan
Pharmacist
Hospital Ampang, Selangor

Dato' Dr. Ong Loke Meng
Senior Consultant Nephrologist
Hospital Pulau Pinang, Pulau Pinang

Mdm. Poh Wei Yoon
Pharmacist
Hospital Selayang, Selangor

Dr. Richard Lim Boon Leong
Consultant Palliative Medicine Physician
Hospital Selayang, Selangor

Mdm. Rohana bt Hassan
Deputy Director
Pharmacy Practice & Development Division
Pharmaceutical Services Programme

Dr. Ros Suzanna bt Ahmad Bustamam
Consultant Clinical Oncologist
Hospital Kuala Lumpur, Kuala Lumpur

Dr. Roshayati bt Mohamad Sani
Director
National Pharmaceutical Regulatory Agency

Mdm. Rosilawati bt Ahmad
Deputy Director
Centre of Product & Cosmetic Evaluation
National Pharmaceutical Regulatory Agency

Cik Salmi Abdul Razak
Pharmacist
Hospital Tuanku Ja'afar, Negeri Sembilan

Dr. Santhi a/p Datuk Puvanarajah
Senior Consultant Physician & Neurologist
Hospital Kuala Lumpur, Kuala Lumpur

Dr. Shamala Retnasabapathy
Senior Consultant Ophthalmologist
Hospital Sungai Buloh, Selangor

Dr. Tan Soek Siam
Senior Consultant Gastroenterologist/ Hepatologist
Hospital Selayang, Selangor

Mdm. Siti Rabiatul Adawiyah
Pharmacist
Hospital Tuanku Ja'afar, Negeri Sembilan

Dato' Dr. Siti Sabzah bt Mohd Hashim
Senior Consultant Otorhinolaryngologist
Hospital Sultanah Bahiyah, Kedah

Dr. Suganthi a/p Thevarajah
Senior Consultant Dermatologist
Hospital Kuala Lumpur, Kuala Lumpur

Dr. Suhana bt Yusak
Consultant Clinical Oncologist
Institut Kanser Negara, Putrajaya

Dr. Wong Hin Seng
Senior Consultant Nephrologist
Hospital Selayang, Selangor

Dr. Yau Weng Keong
Senior Consultant Physician & Geriatrician
Hospital Kuala Lumpur, Kuala Lumpur

Mdm. Yeo Yee Ling
Pharmacist
Hospital Raja Permaisuri Bainun, Perak

Dr. Yusniza bt Mohd Yusof
Senior Consultant Rehabilitation Physician
Hospital Rehabilitasi Cheras, Kuala Lumpur

KEY TERMS

The following are the definition to some key terms used in this document:

TERM	DEFINITION
Biologics	Biologics include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources - human, animal, or microorganism - and may be produced by biotechnology methods and other cutting-edge technologies. They often are at the forefront of biomedical research and may be used to treat a variety of medical conditions for which no other better treatment option is available (1).
Biosimilars	A new biological medicinal product developed to be similar in terms of quality, safety and efficacy to an already registered (approved), well-established, biologic medicinal product (reference product) (2).
Reference product	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 chosen reference medicinal product should be used throughout the development program for quality, safety and efficacy studies during the development of a biosimilar product (2).
Interchangeability	Medical practice of exchanging two medicines that are therapeutically equivalent and can be safely exchanged in clinical practice (3,4). This includes the action of replacing a reference product with a biosimilar or vice versa, or replacing one biosimilar with another. Replacement may be done by: i. Switching, ii. Automatic substitution
Switching	An informed decision between the treating physician and the patient to exchange one medicine for another medicine with the same therapeutic intent (4).
Automatic substitution	The act of replacing one medicine with another medicine (containing the same active ingredient) at the pharmacy level whether in a hospital or primary care setting, without the consent from the treating physician (4).
Extrapolation of data	Extending information and conclusions available from studies in one or more subgroups of the patient population (source population), or in related conditions or with related medicinal products, to make inferences for another subgroup of the population (target population), or condition or product, thus reducing the need to generate additional information (types of studies, design modifications, number of patients required) to reach conclusions for the target population, or condition or medicinal product (5).

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1. Introduction

Biologics are large, highly complex, heterogeneous molecules that are directly derived from living cells or engineered using biotechnology methods in living cells (3). These range from simple proteins such as insulin to highly complex proteins such as monoclonal antibodies (2,4). The manufacturing process of biologics is highly complex and is critical in defining the characteristics of the final product (2). Since its introduction in the early 1980s, biologics have revolutionised the treatment of many chronic diseases such as cancer, diabetes and autoimmune disorders. However, the high treatment cost of biologics has added considerable strain onto the limited healthcare budgets worldwide. In recent years, the patent for a majority of innovator biologics (termed as reference products) have begun to expire. This has led to the development of follow-on biologics (or biosimilars) which are expected to be marketed at a lower price and hence, providing a cost-saving alternative to their respective reference products. This is definitely advantageous as the potential savings will help to expand patients' access to treatment.

In Malaysia, a biosimilar is defined as a new biologic product developed to be highly similar in terms of quality, safety and efficacy to an already registered, well established reference product (2). Unlike generic medicines, a biosimilar is not identical to its reference product. Hence, biosimilars cannot be regarded as a generic to the reference product. The term 'generic medicine' refers to chemically-derived products which are identical and therapeutically equivalent to the innovator product. For generics, demonstration of bioequivalence with the innovator product is usually adequate to infer therapeutic equivalence. However, it is unlikely that biosimilars can follow this standard approach for generics because of their large and complex molecular structures, which are more difficult to adequately characterise in the laboratory. For these reasons, the standard generic approach is scientifically not applicable to the development of biosimilar products and a new regulatory paradigm for biosimilars is required (2).

2. International consensus and Malaysia's regulatory framework for biosimilars

The National Pharmaceutical Regulatory Agency (NPRA), was established as a secretariat to the Drug Control Authority (DCA), the regulatory authority entrusted with regulating pharmaceutical products in Malaysia. Established under the Control of Drugs and Cosmetics Regulation of 1984 (6), its main task is to ensure the quality, safety and efficacy of pharmaceutical products (including cosmetics) that are to be marketed and sold in Malaysia.

Malaysia is one of the earliest countries in the world to establish a regulatory pathway to control biosimilar products. The regulation on biosimilars in Malaysia started with the publication of its regulatory guidelines, Guidance Document and Guideline for Registration of Biosimilars in Malaysia in 2008. It is in accordance with the principles of product comparability against reference product which was a concept pioneered and issued by the European Medicines Agency (EMA) in their 2005 guideline.

The approval of biosimilars is based on a stepwise comparability and totality of evidence approach which supports the claim of biosimilarity. This means the similarity against reference product must be established at quality level (physicochemical properties, biological activity, immunochemical properties, purity and impurities) before embarking on pre-clinical and clinical investigations. The demonstration of similarity at the quality level will allow a reduction of the non-clinical and clinical data requirement compared to a full dossier. Demonstration of similarity may also allow extrapolation of efficacy and safety data to other indications of the reference product.

3. Scope

This position statement is a guidance to the use and handling of biosimilars in healthcare facilities under the purview of the Ministry of Health (MOH), Malaysia. It should also be read along with the Guidance Document and Guidelines for Registration of Biosimilars in Malaysia, 2008.

However, this Position Statement does not cover regulatory policies governing the registration of biosimilars in Malaysia. Readers are advised to refer to the relevant guidelines published by the NPRA for information pertaining to registration of biologics and biosimilars in Malaysia.

The following section outlines the MOH Malaysia's position on the use and handling of biosimilars.

4. Position Statements on the Use of Biosimilars in MOH, Malaysia Healthcare Facilities

A. Interchangeability, Drug Selection, Switching and Automatic Substitution

Position Statement 1

As the standard generic approach is not applicable to biosimilars, prescribing practice and interchangeability between reference products and biosimilars or among biosimilars need to be carefully considered.

Interchangeability is defined as the medical practice of exchanging two medicines that are therapeutically equivalent and can be safely exchanged in clinical practice (4). This includes the action of replacing a reference product with a biosimilar or vice versa or replacing one biosimilar with another.

Biosimilars are protein molecules that may have inherent degrees of variability and may have different formulations when compared to their respective reference product. Hence, they are by no means identical to their reference product.

Interchangeability between biosimilars and reference products is an ongoing area of debate among the regulators, health professionals, pharmaceutical companies and policy makers. As such, interchangeability between biosimilars and reference products or vice versa or among biosimilars will need to be carefully considered.

Position Statement 2

In treatment-naïve patients, the use of a reference product or biosimilar with greater cost-savings is encouraged, taking into consideration the patient's risk-benefit profile.

Treatment-naïve is referring to patients with no previous therapeutic exposure to the reference product or patients with previous exposure but with an adequately long wash-out period based on the judgment of the treating physician (7). The selection of product (either reference product or biosimilar) to be initiated should be balanced between cost and clinical reasons (8,9) after weighing the risks and benefits for the eligible patient.

Position Statement 3

The decision to switch a patient from reference product to biosimilar, vice versa or among biosimilars can only be performed by the treating physician in consultation with the patient.

Switching means an informed decision between the treating physician and the patient to exchange one product to another with the same approved therapeutic indication and route of administration that is expected to achieve the same clinical effect in a given clinical setting (4).

Switching may occur in the following situations (10):

- Switching from reference product to biosimilar
- Switching from biosimilar to reference product
- Switching from a biosimilar to another biosimilar based on the same reference product

Switching can only be done by the treating physician and should involve discussion between the prescriber, patient, and pharmacist. The treating physician will be responsible for providing sufficient information to the patient pertaining to the switch especially on the justification for the switch and possible safety concerns. The patient should also be closely monitored for potential immunogenic reactions (Kindly refer to Position Statement 9).

Switching should also be due to medical/clinical reason(s) rather than based solely on non-clinical reason(s) such as cost. If a switch has to be made due to a non-medical reason, the patient should be informed and provided with an explanation on the reason(s).

Multiple back and forth switching between a reference product and a biosimilar or vice versa, or replacing one biosimilar with another is not recommended as evidence on the impact of this practice is limited (11). It is important to note that antibodies to biologics can develop in less than 28 weeks (12). Hence, a switch within 6 months due to non-medical reason(s) is not advisable (13).

Position Statement 4

Automatic substitution of biologics at pharmacy level is NOT allowed.

Automatic substitution is defined as the act of replacing one medicine with another medicine (containing the same active ingredient) at the pharmacy level whether in a hospital or primary care setting, without the consent from the treating physician (4).

Automatic substitution is not allowed for biologics. This is to ensure treatment decision using reference product or biosimilar is made based on the professional, informed judgement and is under the responsibility of the treating physician for the benefit of the patient.

B. Extrapolation

Position Statement 5

Biosimilars should only be used for indications approved and registered by the Malaysian Drug Control Authority (DCA).

Extrapolation may be generally defined as extending information and conclusions from studies in one or more population, condition or product, to make inferences for the target population, condition or product. Extrapolation of data is not a new concept but a well-established scientific principle that has been used for many years. It has also been used for reference products cases when their manufacturing processes undergo major changes (14).

A biosimilar may be approved for some of or all the indications held by the reference product without having been studied in each patient population. The decision to approve an indication for a particular biosimilar is made by the DCA when a convincing demonstration of biosimilarity to the reference product is shown based on the totality of evidence from a comprehensive comparability exercise (2,15). The exercise takes into account the mechanism of action of the active substance in both the initial and the extrapolated indications (15), as well as efficacy, safety and immunogenicity of the product. The comparability exercise is carried out in a sensitive and relevant population in which potential differences in clinical performance can be detected (4).

As the process of approving an extrapolation of indication is robust and involves comprehensive evaluation of data by the Malaysian DCA, physicians and healthcare professionals should be aware that a biosimilar may not be registered for similar use in certain indication(s) approved for the reference product. Hence, it is important that the package insert (PI) be read carefully to ensure that the biologic (biosimilar or reference product) is used only for its approved indication(s) in Malaysia before prescribing and dispensing to the patient (15,16).

The following position statements in Sections C, D & E are applicable to ALL biologics (reference products and biosimilars).

C. Naming and Labelling

Position Statement 6

For formulary listing purpose, all biologics will be listed according to their International Non-proprietary Name (INN).

As mentioned above, a biosimilar is not identical to its reference product and hence, interchangeability will require careful consideration. Any switching must be done by the physician who is acting in the best interest of the patient. However, for administrative purposes as well as to facilitate efficient stock management and procurement processes, biologics (including biosimilars) will be listed in the Ministry of Health Medicines Formulary (MOHMF) according to their INN (e.g. Rituximab 100mg Injection).

If biosimilars are available for biologics listed in the MOHMF, a list of these biosimilars will be made accessible by the Pharmaceutical Services Programme to healthcare professionals for their reference.

For healthcare facilities that are procuring biologics, an updated list of biologics (including biosimilars) available in their facilities should be maintained periodically for quick referencing.

Position Statement 7

Prescription for biologics should be written in international non-proprietary name (INN) *along with* their brand name.

The use of INN along with brand name when prescribing biologics will allow for tracing of the specific product prescribed and dispensed to a particular patient. This is important to avoid accidental automatic substitution and to ensure traceability of the product during post-marketing activities. The similar way of prescribing should be maintained when writing repeat prescriptions, in patient's record and when reporting adverse drug reactions (ADR) related to biologics (2). When using electronic prescribing, the prescribing system should allow prescribers to clearly state the brand name of the intended biosimilar product along with the INN (11). A pop-up message to highlight that the item is a biosimilar is highly recommended. Patients should be encouraged to keep the original packaging or a photograph of the actual medicine dispensed to them and to bring this along to every consultation and also during collection of medication at the pharmacy (11).

Position Statement 8

Biologics dispensed to patients should be labelled with the international non-proprietary name (INN) AND brand name to ease traceability and surveillance.

Biologics are dispensed to patients directly from the outpatient pharmacy or indirectly in the inpatient wards. Labelling of biologics should include the INN and brand name [e.g. ABC 100 mg Injection (Brand Name®)] to ensure the product received by the patient corresponds to the product prescribed. Proper labelling will ensure transparency and traceability, reduce the risk of automatic substitution, prevent confusion as well as increase the accuracy of ADR reporting (8). The same method of labelling should be applied regardless of whether a facility uses an electronic or manual dispensing system.

D. Pharmacovigilance

Position Statement 9

For effective pharmacovigilance monitoring, traceability of biologics (including biosimilars) is important for the monitoring of adverse effect(s) and safety issue(s).

In accordance with Regulation 28: Reporting adverse reaction under Control of Drugs and Cosmetics Regulations 1984, Sale of Drugs Act 1952 (amendment 2006), the product registration holders or any person who possesses any registered product shall inform immediately the Director of Pharmaceutical Services of any adverse reaction(s) arising from the use of the registered product.

Thus, safety monitoring of biosimilars follows the same requirements that apply to all biologic products (17). However, biologics (including biosimilars) have the potential of immunogenicity-related issues and needs to be correctly identified should there be any product-specific concern.

Immunogenic adverse reactions (e.g. infusion-related reactions or injection-site reactions) are normally not severe. In rare cases, an immune reaction could be serious and life-threatening.

Reporting of adverse drug reaction (ADR) is the main activity in pharmacovigilance for safety monitoring of biologics and signal detection of safety issues (18). Please refer to the latest Malaysian Pharmacovigilance Guidelines for further information on ADR reporting (Available at: www.npra.gov.my).

Healthcare professionals play a crucial role in contributing to the risk-benefit assessment of a registered product once it is used by patients. Thus, it is important that healthcare professionals report ADR of biosimilar products even if they are the same as the effects seen with their reference product. Sometimes, antibodies from patients directed against the biological product (‘anti-drug antibodies’ or ADAs) may neutralise the biologic medicine’s activity and reduce its efficacy (4). Healthcare professionals are encouraged to report immunogenicity testing results (if available) using the same ADR reporting mechanism with the relevant supporting documents.

To ensure traceability, all healthcare professionals need to **clearly identify** the product when reporting a suspected ADR by providing the following **critical** information:

i) brand name
ii) active ingredient (or INN)
iii) Malaysian product registration number (MAL number)
iv) batch number

E. Procurement

Position Statement 10

At both the central and local level, procurement of a reference product/alternative biosimilar product must take into account a range of factors, including clinical and cost-related factors, and has to be done with the consensus from all relevant disciplines.

The procurement process of biologic products is conducted via a tender process at the central level or through local purchase by individual facilities.

For biologics procured through a central tender, expert opinions from all the relevant disciplines must be obtained during the preparation of the tender specification, technical evaluation and selection of tender offers. For procurement through local purchase, pharmacists will have to discuss and obtain the consensus from all relevant consultants/specialists. It is important to ensure that the DCA approved indication(s) and route of administration of the biologic product procured is in line with the formulary indication(s).

The pharmacist is responsible for informing all physicians at their facility of any change of brand for a particular biologic product, be it procured via central tender or through local purchase. If there is a need to keep more than one brands of the same biologic product, criteria on brand selection for a specific group of patients will have to be discussed and made available for reference to all healthcare professionals within that institution to avoid confusion and error.

5. Appendix: Glossary of terms

NO	TERM	DEFINITION
1.	**Active ingredient (interchangeable with active pharmaceutical ingredient, API)**	Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when used so, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body (3).
2.	**Adverse drug reaction (ADR)**	A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function (18).
3.	**Anti-drug antibody**	Antibodies produced by the body's immune system against an active substance (particularly a large molecule, such as a protein). ADAs against a medicine can result in loss of efficacy or in immunological reactions (4).
4.	**Batch number**	A distinctive combination of numbers and/or letters which specifically identifies a batch on the labels, the batch records, and the certificates of analysis, etc (19).
5.	**Bioequivalence**	The absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives become available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study (20).
6.	**Biosimilarity**	Two or more biological medicinal products that have high similarity in terms of structure, biological activity and efficacy, safety and immunogenicity profile (4).

NO	TERM	DEFINITION
7.	**Biotherapeutic**	Therapeutic biological products, some of which are produced by recombinant DNA technology (2).
8.	**Brand name**	A word, name, symbol, etc., especially one legally registered as a trademark, used by a manufacturer to identify its products distinctively from others of the same type (21).
9.	**Central tender**	National tender for procurement values exceeding RM500,000 annually for each product (22).
10.	**Comparability studies**	The activities, including study design, conduct of studies, and evaluation of data, that are designed to investigate whether the products are comparable (23).
11.	**Generic medicines**	A medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the innovator medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies (24).
12.	**Immunogenic reactions**	Unwanted immune response after being triggered by more than one single factor (immunogen). This immunological response is complex and, in addition to antibody formation, other events such as T cell activation or innate immune response activation could contribute to potential adverse responses (25).
13.	**Immunogenicity**	The ability of a substance to trigger an immune response in a particular organism (2).
14.	**Innovator product**	Same as originator product which is defined as the product for which a marketing authorization is granted to a given marketing authorization holder (MAH) for a given active substance based upon a complete dossier (3).

NO	TERM	DEFINITION
15.	**International Non-proprietary Name (INN)**	International Nonproprietary Names (INN) identify pharmaceutical substances or active pharmaceutical ingredients. Each INN is a unique name that is globally recognized and is public property. A nonproprietary name is also known as a generic name (26).
16.	**Local Purchase**	Procurement at local level via direct purchase (annual value <RM50,000) or quotation (annual value RM50,000 to RM500,000) for each medicine (27).
17.	**Malaysian product registration number**	All pharmaceutical products including health supplements and traditional preparations must be registered with the Drug Control Authority (DCA) of Malaysia before being marketed in Malaysia. The registration number starts with 'MAL', followed by eight numbers, and ending with the letter T, A, X or N (3).
18.	**Monoclonal antibodies**	Monoclonal antibodies (mAbs) are a major class of recombinant deoxyribonucleic acid (rDNA) technology derived biotherapeutic products and as such have achieved outstanding success in treating many life-threatening and chronic diseases (28).
19.	**Pharmacovigilance**	Science and activities relating to the detection, assessment, understanding and prevention of medicine-related problem (18).
20.	**Package insert**	An insert containing information for the user, which accompanies the medicinal product (18).
21.	**Treatment naïve**	Referring to patient(s) with no previous therapeutic exposure to the reference product or patients with previous exposure but with a washout period of time adequately long based on the judgment of the treating physician (7).

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