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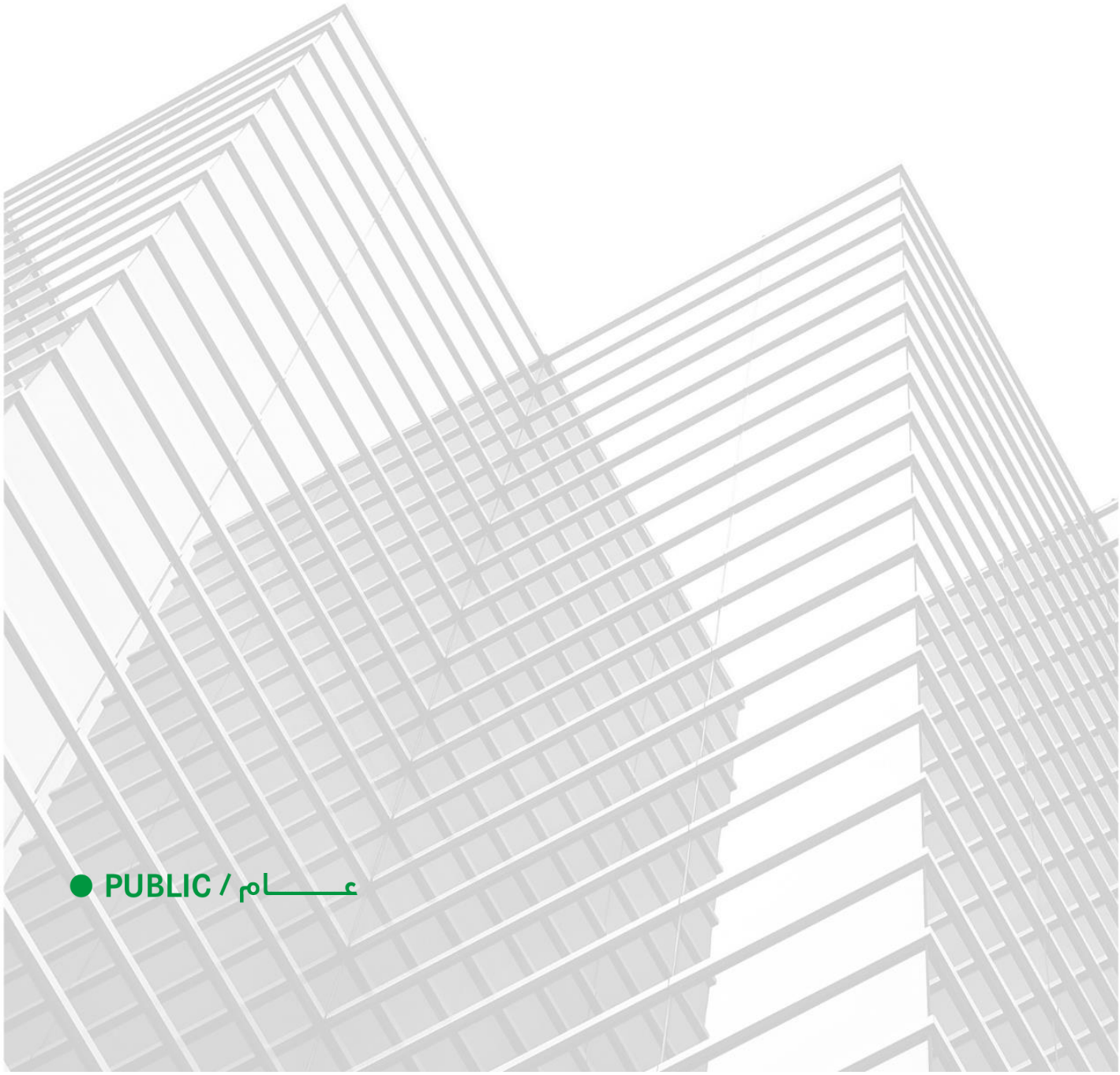
DEPARTMENT OF HEALTH

Guide to Biosimilars for Healthcare



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1.Guideline Purpose and Brief

This guideline aims to provide guidance for healthcare professionals with the purpose of:

- Informing and assisting their decision-making processes when prescribing, dispensing, or administering biosimilars.
- Clarifying the differences between a 'reference biological medicine' and a 'biosimilar', the requirements for biosimilars to achieve marketing authorization (regulatory approval) and how this takes account of the specific nature of these medicines.
- Addressing issues surrounding the pharmacovigilance of biosimilars in the context of the UAE marketplace.
- Defining the roles and responsibilities of different healthcare professionals, the scope of implementation, patient education and recommended monitoring and evaluation for any adverse drug reaction.

2. Definitions and Abbreviations

No.	Term / Abbreviation	Definition
2.1	ADRs	Adverse Drug Reactions; a response to a medicine which is noxious and unintended.
2.2	MOHAP	Ministry of Health and Prevention- UAE
2.3	FDA	Food and Drug Administration – US
2.4	EMA	The European Medicines Agency
2.5	DoH	Department of Health – Abu Dhabi
2.6	INN	International Non-Propriety Name is a unique name given to an active substance which is globally recognized and is public property. The INN is used to facilitate the identification of active substances and the INN system is managed by the World Health Organization (WHO).
2.7	Biological medicine	A medicine that contains an active substance made by a biological process or derived from a biological source.
2.8	Biosimilar	EMA Definition : A biosimilar is a biological medicine highly similar to another biological medicine already approved in the EU (called 'reference medicine') in terms of structure, biological activity and efficacy, safety and immunogenicity profile (the intrinsic ability of proteins and other biological medicines to cause an immune response). FDA Definition is a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product.

2.9	Interchangeability	Refers to the possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect. This could mean replacing a reference medicine with a biosimilar (or vice versa) or replacing one biosimilar with another.
2.10	Reference medicine	A medicine which has already been authorized by health authority and is used as the basis for a generic or biosimilar medicine. The reference medicine must be at the end of its market exclusivity period before a generic or biosimilar version can be marketed
2.11	Marketing authorization Holder	The company that markets the medicine in UAE and licensed by MOHAP
2.12	Switching	Switching is when a prescriber decides to exchange one medicine for another medicine with the same therapeutic intent.
2.13	Pharmacovigilance	Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem.
2.14	Pharmacy & Therapeutic Committee PTC	It is a committee comprised of clinical experts at provider level (Hospital) with the aim of ensuring safe, appropriate, and cost-effective use of pharmaceuticals. One of their main responsibilities is to manage drug formularies with authorization and restriction of the use of new drugs in the clinical environment.

3.Guideline Content

3.1. Biological medicine:

3.1.1 Most biological medicines are produced from cell cultures of living organisms, such as mammalian cells, bacterial or yeast cells, which have been engineered to produce a specific therapeutic molecule or group of molecules, usually protein(s).

3.1.2. There are many types of biological medicines, which range in complexity, diversity, and innovation. Examples of biological medicines include:

- recombinant proteins such as insulin, epoetin (erythropoeitin) and follicle stimulating hormone (FSH);

- enzymes, such as agalsidase, which are used in enzyme replacement therapy;

- monoclonal antibodies, which are highly targeted engineered antibodies used to treat a wide variety of conditions such as cancer and arthritis;

- blood-derived products such as clotting factors;

- vaccines;

- gene therapy

- animal-derived products such as heparin.

3.1.3. Biological medicines contain larger and more complex active substances than chemically synthesized molecules and in general tend to be more targeted in their therapeutic activity. As biological active substances are produced by living organisms, there is an inherent natural variability, which is not present with chemical entities.

3.1.4. Biological medicines, often produced using living cells, can exhibit inherited variability between manufacturing batches, this variability arise form factors such cell lines, culture conditions and manufacturing processes. Due to this complexity ensuring identical copies of biologic medicine from batch to batch is challenging., quality control measures are crucial in the production of these medicines to maintain consistency within acceptable limits and ensure safety and efficacy.

3.2. Biosimilar:

3.2.1 Biosimilars should be registered by Ministry of Health and Prevention (MOHAP) and approved by Department of Health DoH.

3.2.2. All biosimilar products must comply with the accepted standards of quality, safety and efficacy as laid down in European legislation and guidance or the US FDA.

3.2.3. Biosimilars have the same primary structure (e.g., identical amino acid sequence for proteins), and they will have a high degree of similarity in molecular and biological terms to reference medicine.

However, the manufacturing process and the raw materials used in the manufacturing of the biosimilar will differ from those used by the manufacturer of the reference medicine. Coupled with the natural variability and micro-heterogeneity of biological medicines, this means that unlike chemical generic medicines, manufacturing an exact copy of the reference medicine is not technically possible. Therefore, biosimilars are similar but not identical versions of their reference biological medicine.

3.2.4. The key principle on which a biosimilar is approved for use is that any differences between it and the reference medicine have been shown not to affect its safety or efficacy in a clinically significant way. Biosimilars generally have the same strength, and are used at the same dose, to treat the same medical conditions (if approved) and usually have the same route of administration as the reference medicine. However, in some cases there may be differences in pharmaceutical form, formulation, excipients or presentation; a biosimilar may also use different administration devices.

3.2.5 Using biosimilars in healthcare systems offers added value as it increases patient access to biological products, ensures system sustainability, helps prevent drug shortages, and allows resources to be used for other treatments.

3.3 Interchangeability, Switching, Prescribing and Dispensing:

3.3.1 Interchangeability

3.3.1.1. Biosimilars can be prescribed interchangeably with the reference medicine or with other biosimilars of that reference medicine, only by the physician and in consultation with the patient.

3.3.1.2. With this guidance, DoH directs physicians with the initiation of therapy of naïve patients using biosimilars that are listed in Appendix 1.

3.3.1.3. DoH will update healthcare professionals on any change in the listed biosimilars.

3.3.2. Switching

3.3.2.1 Only the physician can exchange one medicine for another with the same therapeutic intent; this process should be done with appropriate supervision and monitoring.

3.3.2.2 Decisions to switch a patient's medicine should be carried out in line with agreed hospital protocols or local policies developed by DoH.

3.3.2.3 In the cases of medicines intended for administration by patients or caregivers, necessary training on devices is required.

3.3.3 Prescribing & Dispensing

3.3.3.1 Any biological medicine prescribed, dispensed, or sold should be clearly identifiable by brand name or, as appropriate, INN accompanied by the brand or the Market Authorization Holder (MAH) names.

3.3.3.2 It is important to highlight that under this guidance, biological medicines are specifically excluded from being added to interchangeable medicine lists. As such, they cannot be subjected to pharmacy substitution.

3.3.3.3 Traceability systems must be in place to make sure that adverse reactions (ADRs) can be attributed to the correct medicine.

3.3.3.4 In order to facilitate accurate reporting in the event of an ADR, the batch number should also be recorded.

3.4 Extrapolation of Indications

3.4.1 The reference biological medicine may be authorized in more than one clinical indication and clinical trials will have been conducted with the reference medicine to demonstrate efficacy in each indication for

which it is approved.

3.4.2 It should be noted that a biosimilar might not be authorized for use in all indications approved for the reference medicine, therefore it is important for healthcare professionals to review the package leaflet in order to be aware of the approved indications.

3.4.3 Clinical efficacy studies in biosimilars are normally carried out in a single indication, which represents the most sensitive patient population with the most sensitive clinical endpoints. Once biosimilarity has been demonstrated in one indication, extrapolation to other approved indications could be permissible.

3.4.4 The demonstration of biosimilarity through the combination of analytical testing and relevant non-clinical and clinical studies forms a scientific bridge between the biosimilar and the reference medicine that allows for the extrapolation of safety and efficacy information from the reference medicine to the biosimilar. However, the decision to allow indication extrapolation is made for each biosimilar on a case-by-case basis.

3.4.5 The quality and pre-clinical comparability data provide a foundation upon which indication extrapolation can be approved. Extrapolation is based on the overall evidence of comparability and sound scientific justification.

3.4.6 For extrapolation to be approved by regulator, the scientific justification must include assurance that the mechanism of action of the medicine in terms of achieving the therapeutic effect is the same across each indication. Where this is not the case, additional clinical studies and/or analytical studies may be required.

3.4.7 It is imperative that the method of action is well understood in each indication and that evidence is sought/provided that will demonstrate the biosimilar's clinical and immunogenic effect.

3.5 Pharmacovigilance and ADRs Reporting

3.5.1 DoH Standard on Reporting Suspected Adverse Drug Reactions and Adverse Events Following Immunization sets out the requirements for recording and reporting of suspected adverse reactions, an online reporting form is accessible through the E-notification tool which is available at DoH website via the link in the reference section.

3.5.2 As is the case for all biological medicines, the clinical safety of biosimilars must be monitored closely on an ongoing basis during the post-approval phase.

3.5.3 Any specific safety monitoring imposed on the reference medicine or medicine class will also apply to the biosimilar.

3.5.4 As for all medicines, healthcare professionals are asked to report any suspected adverse reactions associated with medicines. Reporting of suspected adverse reactions is mandatory in accordance with this standard.

3.5.5 Clear identification and traceability of medicines is important when reporting suspected adverse reactions and in particular for biological medicines, given their particular characteristics.

3.5.6 For identifying and tracing biological medicines in UAE, medicines have to be distinguished by the tradename and batch number and this is particularly important in cases where more than one medicine with the same INN exists on the market. This ensures that, in line with the requirements for ADR reporting, the medicine can be correctly identified if any product-specific safety or immunogenicity concern arises.

3.5.7 Biological medicines should be clearly identifiable throughout the prescribing, dispensing and pharmacovigilance processes; recording of the name and batch number of the medicine is the key to this crucial point.

3.6 Patient Education

3.6.1 Physicians, nurses, pharmacists, should join forces when educating patients.

3.6.2 Patient education should address the patients concerns about safety, efficacy, extrapolation of indication, and the societal benefits of biosimilars.

3.6.2 The provided information should be consistent, in a clear manner and in line with this guideline.

3.7 Roles and Responsibilities

Health care professionals can play a vital role in disseminating information supporting the use of biologics and support the safety of their use by reporting any adverse reactions to DoH.

3.7.1 Physicians
3.7.1.1 Comply with biosimilar medication guidelines.
3.7.1.2 Prescribe biosimilar drugs that are listed in this guideline for new patients,
3.7.1.3 Pay attention to changes and updates in the biosimilars list that is recommended by DoH.
3.7.1.4 Discuss biosimilar treatment options with patients and provide the necessary education and counselling.
3.7.1.5 Report ADRs to DoH through the E-notification tool.
3.7.1.6 Participate in establishing switching protocols at your facility.

3.7.2 Pharmacists
3.7.2.1 Comply with biosimilar medication guidelines.
3.7.2.2 Ensure that appropriate biosimilar or biologic drug is dispensed as per the physician order.
3.7.2.3 Report ADRs to DoH through the E-notification tool.
3.7.2.4 Ensure patient's adherence through appropriate patient education and follow up.

3.7.3 Hospital PTC
3.7.3.1 Comply with biosimilar medication guidelines.
3.7.3.2 Review and approve biosimilar medications to be listed in hospital formulary.
3.7.3.3 Establish switching programs and identify key elements for monitoring.
3.7.3.4 Review ADRs reports and report to DoH through the E-notification tool.
3.7.3.5 Approve patient education materials related to biosimilar medications.

3.7.4 Drug suppliers/Drug Agent
3.7.4.1 Comply with biosimilar medication guidelines.
3.7.4.2 Ensure availability of Biosimilars that are registered with MOHAP under drug store's name.
3.7.4.3 Handle any recalls for biosimilar medication based on DoH recommendation.

4.Relevant References Documents			
No.	**Reference Date**	**Reference Name**	**Relation Explanation / Coding / Publication Links**
4.1	2023	EMA	Pharmacovigilance: Overview - European Medicines Agency. https://www.ema.europa.eu/en/human-regulatory/overview/pharmacovigilance-overview.
4.2	2023	FDA	Research, C. for D.E.A. (2023) Biosimilars. https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/biosimilars.
4.3	2023	EMA	Biosimilar medicines: Overview - European Medicines Agency. https://www.ema.europa.eu/en/human-regulatory/overview/biosimilar-medicines-overview.
4.4	2021	DoH	DoH standard on reporting suspected adverse drug reactions and adverse events following immunization
4.5	2012	Pharmacy and Therapeutics	Shulkin D. Reinventing the pharmacy and therapeutics committee. P T. 2012 Nov;37(11):623-49. PMID: 23204816; PMCID: PMC3498992.
4.6	2008	WHO	*TRS 948 - Annex 5: International Nonproprietary Names for biological and biotechnological substances: a review* (no date). https://www.who.int/publications/m/item/annex-5-trs-948.
4.7	N/A	E-notification tool	https://bpmweb.doh.gov.ae/usermanagement/login.aspx?Home=1

APPENDIX 1. List of biologics that have DOH approved biosimilar products

Based on the accompanying guidance, physicians are directed to the initiation of therapy of naïve patients using biosimilars for the below listed biological molecules.

1. Bevacizumab
2. Filgrastim
3. Etanercept
4. Trastuzumab
5. Adalimumab
6. Peg-filgrastim
7. Infliximab
8. Rituximab