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Biologics and Biosimilars

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LIST OF ABBREVIATIONS

ADA	**Anti-drug antibody**
ADR	**Adverse drug reaction**
AUC	**Area under the curve**
CHMP	**Committee for Medicinal Products for Human Use (EMA's scientific committee formed by EU experts who review and recommend marketing approval)**
EDA	**Egyptian Drug Authority**
EMA	**European Medicines Agency**
EU	**European Union**
FDA	**Food and Drug Administration (the US medicines regulatory authority)**
HCP	**Health Care Professional**
HIV	**Human Immunodeficiency Virus**
mAbs	**Mono clonal Antibodies**
MHC	**Major Histocompatibility Complex**
NO HARMe	**National Office for Handling and Reduction of Medication errors**
ORR	**Objective Response Rate**
OS	**Overall Survival**
pCR	**Pathological Complete Response**
PD	**Pharmacodynamics**
PFS	**Progression Free Survival**
PK	**Pharmacokinetics**
SBP	**Similar biotherapeutic products (WHO term for biosimilars)**
WHO	**World Health Organization**

GLOSSARY

Adverse drug reaction	**An unwanted medical event following the use of a medicine. Suspected ADRs are those that have been reported to authorities but are not necessarily caused by the medicine.**
Anti-drug antibody	**Antibodies are produced by the body's immune system against an active substance (particularly a large molecule, such as a protein). ADAs against medicine can result in loss of efficacy or immunological reactions.**
Bio-better	**Is a biologic compound aimed at the same target protein as the reference biologic, but is a step-wise improvement on it in terms of efficacy, safety, and duration of activity it is the 'next-generation biologic. Bio-better is considered a new entity, and as such it must follow the complete, not abbreviated regulatory pathway, but is awarded data- and market exclusivity periods.**
Bioequivalence	**When two medicines release the same active substance into the body at the same rate and to the same extent under similar conditions.**
Biological Products	**Medicinal Products made of substances extracted from or produced by living organisms or liquids and tissues extracted from various human or animal sources**
Biosimilarity	**Demonstration of high similarity to a reference biological medicine in terms of chemical structure, biological activity and efficacy, safety, andimmunogenicity profile, mainly based on comprehensive comparability studies.**
Biotechnology	**Technology relies on biological systems, living organisms, or components from living organisms to make a specific product. A medicine obtained by biotechnology often has been produced by inserting a gene into cells so that they can produce the desired protein.**
Comparability	**Head-to-head comparison of a biosimilar with its reference medicine to rule out any significant differences between them in terms of structure and function. This scientific principle is routinely used when a change is introducedto the manufacturing process of medicines made by biotechnology, to ensure that the change does not alter safety and efficacy.**
Equivalence Trial	**This is a trial with the primary objective of showing that the response to two or more treatments differs by a clinically unimportant amount. This is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence margin of clinically acceptable differences.**
Extrapolation	**Extension of the efficacy and safety data from a therapeutic indication for which the biosimilar has been clinically tested to another therapeutic indication for the reference medicine.**

Generic	**A copy of a medicinal product with chemical, small molecule drug substance(s) that is/are structurally and therapeutically equivalent to that/those of an originator pharmaceutical product.**
Head-to-head comparison	**Direct comparison of the properties of the Biosimilar with the Reference product in the same study.**
Immunogenicity	**The ability of a bio-therapeutic product to provoke a humoral and/or cell-mediated immune response in animals or humans upon administration.**
Interchangeability	**Refers to the possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect.**
Micro-heterogeneity	**Minor molecular variability among biological substances due to natural biological variability and slight alterations to production methods.**
Non-inferiority study	**A study that tests whether a new treatment is not worse than an active treatment it is being compared to.**
Pharmaco-dynamic studies	**Studies of the biochemical and physiological effects of a medicine in the body, including mechanism of action.**
Pharmaco-kinetic studies	**Studies of how medicine is processed by the body, including its absorption, distribution, biotransformation, and excretion.**
Pharmacovigilance	**The science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other medicine-related problems. Pharmacovigilance aims to enhance patient care and patient safety concerning the use of medicines. This process should occur continuously throughout the life cycle of medicine and for the duration, it remains in the pharmaceutical market.**
Post-translational modification	**Modification of a protein after its production, which involves the attachment of molecules or groups such as phosphates or carbohydrates (sugars).**
Product drift	**A change in the product or its characteristics can occur over time or suddenly, for example, as a result of manufacturing changes. If a reference product undergoes a formulation or manufacturing change, the same tests used to establish a biosimilar are used to ensure that after the change, the reference product is similar to its original version. No additional clinical testing is required.**

Reference medicine	**Biological medicine is chosen by a company developing a biosimilar as a reference for the head-to-head comparison of quality, safety, and efficacy.**
Substitution	**The practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber.**
Surrogate endpoints	**Surrogate endpoints include a shrinking tumor or lower biomarker levels. They may be used instead of stronger indicators, such as longer survival or improved quality of life because the results of the trial can be measured sooner.**
Switching	**When the prescriber decides to exchange one medicine for another medicine with the same therapeutic intent.**
Superiority Trial	**This is a trial with the primary objective of showing that the response to the investigational product is superior to a comparative agent.**

CHAPTER INTENTION

The current underuse of biosimilars in clinical practice could be attributed, at least in part, to a lack of awareness among patients and clinicians about the benefits and challenges of biosimilars. So, we have developed this chapter to:

1. Introduce the basic principles of biologics and biosimilars including the basic definitions of terms like a biological product, reference product, biosimilar, interchangeable; and other terms to facilitate understanding of the relationship between biosimilars and their reference products.
2. Meet up with today's needs on biosimilars, especially in oncology practice.
3. Present an overview of the rigorous standards any biosimilar must meet before approval.
4. Support the uptake of biosimilars through education and spreading the essential recommendations and policies for switching and substitution of biologic medicines.
5. Promote the idea that reporting medication errors is a crucial aspect of patient safety.
6. Raise awareness and build capacity about good pharmacovigilance practice.
7. Bring attention among healthcare providers to the key concepts of biologics and biosimilars in oncology practice because healthcare providers' perceptions of and confidence in biosimilars will affect adoption and clinical use in oncology.
8. Enable healthcare providers to make a critical appraisal of data to allow for best-informed decision-making when integrating biosimilars into practice.
9. Highlight the key roles of qualified oncology pharmacists in managing the introduction of biosimilars into healthcare systems.

Finally, the Egyptian Drug Authority (EDA) believes that training and education are crucial to ensure the safe and effective use of biologics within healthcare institutions.

I. INTRODUCTION

Despite breakthroughs in cancer treatment, the World Health Organization (WHO) expects that global cancer cases would rise by 60% over the next two decades, from 18.1 million in 2018 to 29.5 million by 2040. Spending on all cancer-related drugs reached about $150 billion in 2018 and is expected to reach nearly $240 billion by 2023, expanding at a rate of 9–12% per year.

Cost and accessibility barriers create disparities in cancer treatments and the resulting clinical outcomes. Many of the most promising and efficacious drugs in the oncology space are biologics, and they are expensive, which in turn may prohibit patients' access to effective biologic therapies. Based on 2019 sales, monoclonal antibody-based biologics, including pembrolizumab, nivolumab, rituximab, bevacizumab, and trastuzumab, ranked among the top-selling cancer drugs. These biological agents were expensive and, at least in part, contributed to the rising cost of cancer treatment. However, biosimilars are now available for some of these biologic agents and have contributed to decreases in treatment costs by bringing about price competition between the reference product and its biosimilar competitors.

The term "biosimilars" was first introduced in 2006 in the European Union (EU) to describe biological medicines developed as copies of innovative biologicals (or reference products) after the expiry of their data protection and patents. The patent expiry of several biologic mAbs for cancer treatment has recently expired (**See appendix 1**). This has initiated multiple biosimilar development programs and regulatory approval requests for newly developed biosimilar agents. There has been intense interest in developing biosimilar agents to introduce cost savings for healthcare systems and to widen global access to key biological therapies.

Biosimilars for rituximab and trastuzumab already have reached the market, and clinicians will eventually be faced with a choice to use biosimilars as an alternative to existing reference products. Unlike small-molecule generic drugs that are typically chemically synthesized and easy to replicate, it is impossible to make exact copies of reference products because biosimilars (as biologics) are large and highly complex molecules produced in living

cells. Structural differences to the reference product may arise due to variations in post-translational modification (such as glycosylation patterns), which could have an impact on drug efficacy or safety.

II. BIOLOGICAL MEDICINES

1. Background

Biological medicines (‘biologicals’) contain active substances from a biological source, such as living cells or organisms. Biological medicines are well established in clinical practice and many cases, they are crucial in the treatment of serious and chronic conditions. such as diabetes, autoimmune diseases, and cancers.

Most biological medicines in current clinical use contain active substances made of proteins. These can differ in size and structural complexity, from simple proteins like insulin or growth hormone to more complex ones such as coagulation factors or monoclonal antibodies (mAbs).

Biological medicines are made by living organisms, which are naturally variable. Thus, the active substance in the final biological medicine can have an inherent degree of minor variability (‘microheterogeneity).

This minor variability must fall within the acceptable range to ensure consistent safety and efficacy. This is done by adjusting the manufacturing process to guarantee that the active substance fits into the desired specifications range.

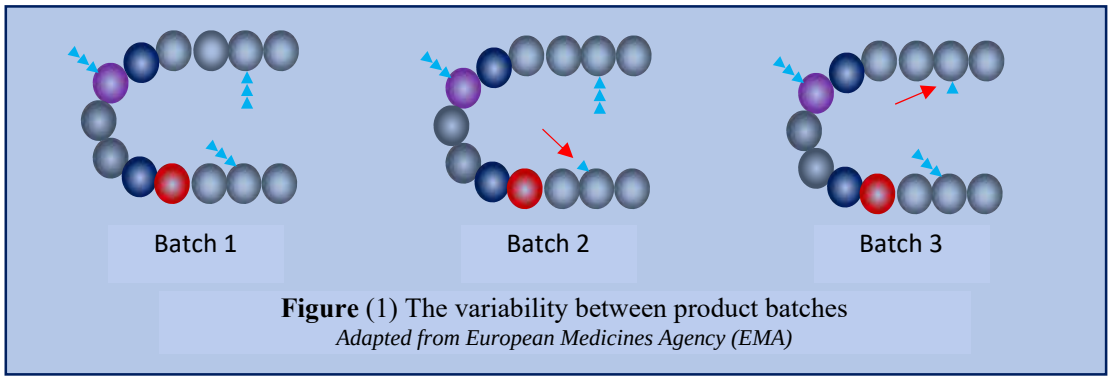
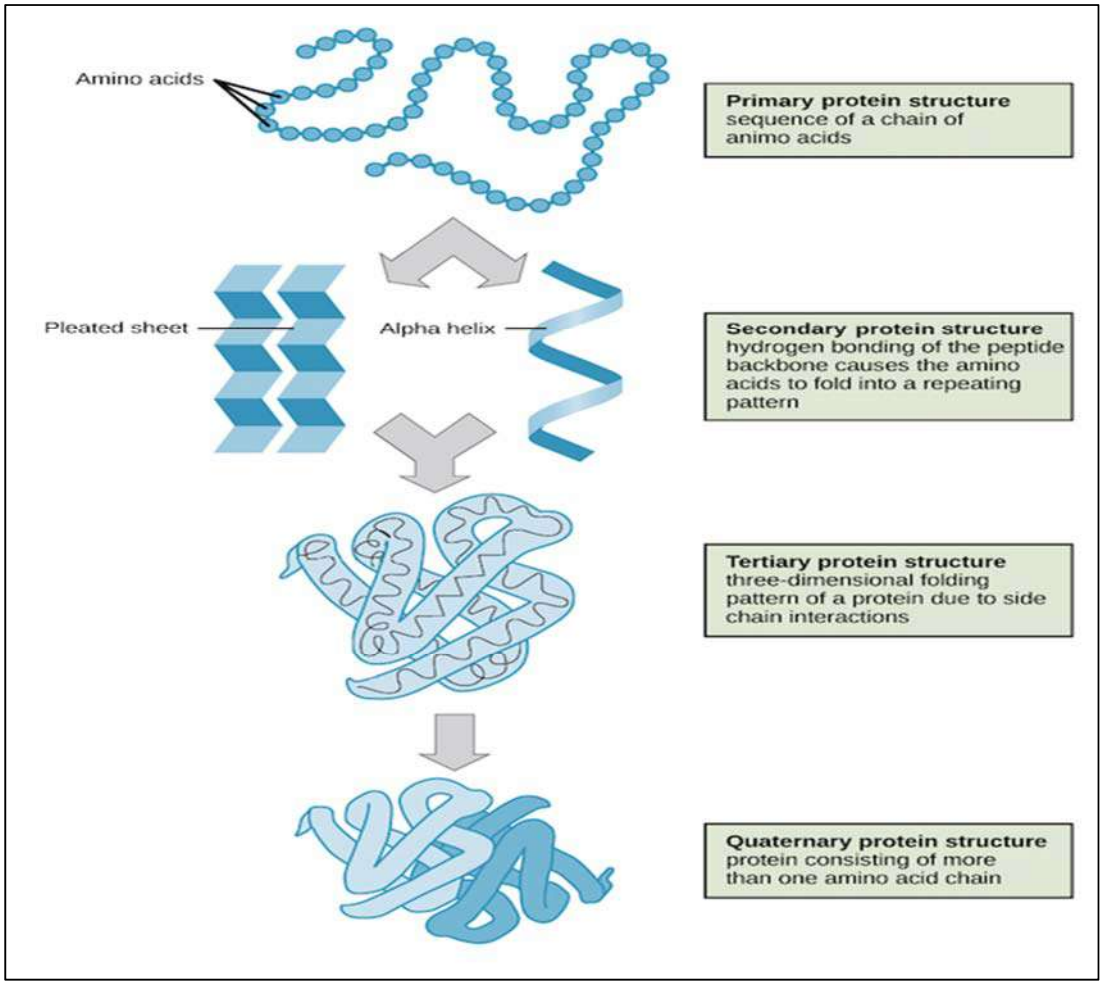


Figure (1) The variability between product batches
Adapted from European Medicines Agency (EMA)

This degree of minor variability can be present within or between batches of the same biological medicine (**figure1**), particularly when manufacturing processes are modified during the commercial life of the medicine (e.g. increasing production scale). Strict controls are always applied to ensure that, despite this variability, there is batch-to-batch consistency and that the differences do not affect safety or efficacy. In practice, variability (within a batch or batch-to-batch) is very low when using the same manufacturing process.

The biological activity of protein-based drugs depends on their:

- Amino acids sequence.
- Three-dimensional (3D) structure (folding of the protein), see **Figure (2)**



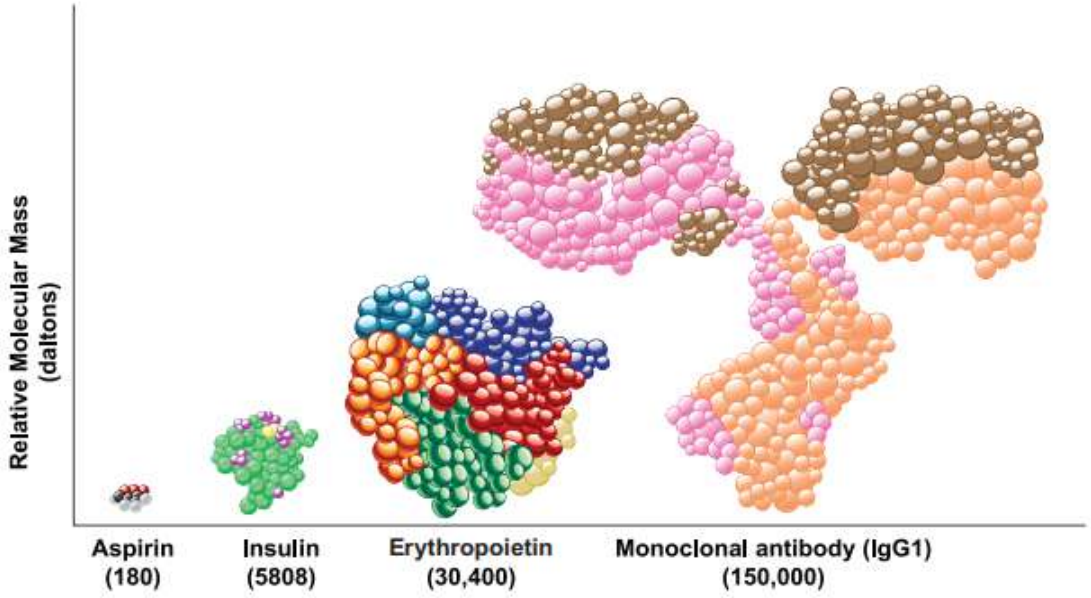


Figure (2) The order of protein structure
(Source: khanacademy.org/science/biology/macromolecules/proteins-and-amino-acids/a/orders-of-protein-structure)

Table 1: The main differences between small molecules and biologics:

Properties	Small molecules (chemically based drugs)	Biologics (protein-based drugs)
Manufacturing	Usually produced by chemical synthesis	Obtained from a biological source
Size	Mostly smaller molecules (low molecular weight)	In general, larger, structurally more complex molecules.
Characterization	Well-defined structure (easier to characterize)	Require multiple technologies for their characterization)
Stability	Stable.	More sensitive to storage and handling conditions.
Immunogenicity	Lower potential	Higher potential
Examples	Cyclophosphamide	Insulin, erythropoietin, and monoclonal antibodies (rituximab and trastuzumab)

Source: Håkan Mellstedt, Clinical considerations for biosimilar antibodies, European Journal of Cancer Supplements, Volume 11, Issue 3,2013

2. Biologics and immunogenicity

Because biologic products, including monoclonal antibodies, by their very nature are capable of evoking immune responses in humans, immunogenicity is a focus of safety assessments during development. An immune response may lead to altered efficacy or compromised safety.

2.1. Factors that may influence the development of an immune response against MAbs:

2.1.1. Patient- and disease-related factors:

- **Genetic factors modulating the immune response**

Genetic factors may influence immune responses to a therapeutic protein and lead to inter-patient variability. Genetic variation at the level of major histocompatibility complex molecules (MHC) and T-cell receptors will modify immune recognition whereas genetic variation at the level of the modulating factors, such as cytokines and cytokine receptors, may influence the evolution and the intensity of the response.

- **Age-related factors**

Data on immunogenicity from one age group cannot necessarily be projected to others, since the immune response to therapeutic proteins can be affected by patient age. Among the pediatric population, different levels of maturation of the immune system are seen depending on age, and discrepant immune responses to a biological product may be expected.

- **Disease-related factors**

A patient's underlying disease can be an important factor in the context of developing an unwanted immune response. Patients with activated immune systems (for example those suffering from chronic infections, allergies, and autoimmune/auto-inflammatory diseases), may be more susceptible to immune responses to therapeutic proteins. In other conditions (e.g. malnutrition, advanced malignant disease, advanced HIV disease, organ failure), an immune response might be less likely to occur due to an impaired immune system.

- **Concomitant treatment**

Concomitant therapies may either decrease or increase the risk of an immune response to a therapeutic protein. Typically, the immune reaction against a therapeutic protein is reduced when immunosuppressive agents are used concomitantly.

- **Treatment-related factors**

An immune response to a therapeutic protein may be influenced by dosage, dosing schedule, and route of administration.

- **Pre-existing antibodies**

Pre-existing antibodies are endogenous antibodies that are specific or cross-reactive for epitopes on proteins or glycans overlapping with therapeutic protein epitopes. Pre-Abs may result from previous exposure to similar or related proteins but are also found in treatment-naïve patients. The exact origin is most often not known.

2.1.2. Product-related factors

- Protein structure and post-translational modifications.
- Formulation and packaging.
- Aggregation and adduct formation.
- Impurities.

2.2. Potential clinical consequences of immunogenicity

The purpose of investigating the immunogenicity of therapeutic MAbs is to understand the clinical consequences; i.e. consequences for PK, PD, efficacy, and safety. Factors that determine whether antibodies to a therapeutic protein will have clinical consequences include, e.g., the epitope recognized by the antibody and the affinity and class of the antibody. In addition, the ability of immune complexes to activate complement may have an impact on the clinical outcome.

2.2.1. Consequences on Efficacy

- Anti-drug antibodies (ADAs) can affect the efficacy of a therapeutic protein either by interfering with the pharmacodynamic interaction between the therapeutic protein and its target or by altering its pharmacokinetic profile.
- When an ADA binds to or near the active site of a therapeutic protein or induces conformational changes, binding of the therapeutic protein to relevant receptors may be inhibited. These ADAs are usually designated as neutralizing antibodies.

- ADAs may change the exposure of the therapeutic protein by either increasing or decreasing the clearance of the therapeutic protein. When exposure is decreased due to enhanced clearance or increased, these ADAs are usually designated as clearing antibodies or sustaining antibodies, respectively. ADAs induced against a therapeutic protein may have both neutralizing and clearing or sustaining properties.
- The effects of ADAs on therapeutic proteins may vary from zero to complete loss of efficacy.
- Previous exposure to similar or related proteins resulting in pre-existing reactivity may modify the response to a new therapeutic protein (affect PK, efficacy, or safety).

2.2.2. Consequences on Safety

In general, most adverse effects of therapeutic proteins are related to their pharmacological effects. The main exception is that immune reactions may lead to adverse effects. Immune-based adverse effects may be both acute and delayed.

Less severe immune-based adverse effects include injection-site and infusion reactions. Non-allergic (not involving IgE-generation) infusion reactions are typically seen during the first infusions and can be mitigated by appropriate pre-medication.

- **Hyper-acute / acute reactions**

Acute infusion-related reactions including anaphylactic/anaphylactoid reactions (type I), may develop within seconds or during a few hours following infusion. All acute infusion reactions are potentially related to an immune response. Acute reactions can cause severe hypotension, bronchospasm, laryngeal or pharyngeal edema, wheezing, and/or urticaria. Pre-existing

immunity may modify the safety of a therapeutic protein; e.g., result in increased incidence and/ or severity of hypersensitivity reactions.

- **Delayed reactions**

In addition to acute reactions, delayed type (T cell-mediated) hypersensitivity and immune complex-mediated reactions have to be considered. The risk of such reactions may be higher with an increasing drug-free interval or when therapies are repeatedly switched among members of a product class. Delayed hypersensitivity reactions should be clearly distinguished from

infusion-related reactions. Clinical signs can include myalgia, arthralgia with fever, skin rash, and pruritus.

- **Autoimmunity: Cross-reactivity to an endogenous counterpart**

A possible life-threatening clinical consequence of ADA formation against a therapeutic protein is cross-reactivity with an endogenous protein when this protein has a non-redundant role in key physiological functions.

For example, ADAs cross-reacting with endogenous erythropoietin have caused pure red cell aplasia in epoetin alfa-treated patients with kidney failure.

2.3. Biologics in Oncology

- Biologics have revolutionized therapies for hard-to-treat diseases, including cancer. Biologics have improved clinical outcomes (including overall survival) and are integral for supportive care management of symptoms caused by cancer or chemotherapy.
- Biologics are essential in most guidelines, including breast, colorectal, oesophageal, gastric, head and neck, kidney, and non–small cell lung cancers, in addition to Hodgkin and non–Hodgkin's lymphoma
- Therapeutic oncology biologics include immunotherapies (e.g., immune checkpoint inhibitors, immune cell therapy, monoclonal antibodies, vaccines, immune-modulating agents) and targeted therapies (e.g., monoclonal antibodies). They are also vital in the treatment of cancer and chemotherapy-induced anaemia and neutropenia.
- As the use of biologics continues to grow and older biologics come off patent, and as patents for biologics expire, biosimilars can provide the same results more affordably. This means that more patients have a better chance of getting treatment, which could significantly improve their lives

III. BIOSIMILAR MEDICINES

1. Biosimilar definitions by global health agencies

World Health Organisation (WHO)

A bio-therapeutic product that is similar in terms of quality, safety, and efficacy to an already licensed reference bio-therapeutic product.

European Medicines Agency (EMA)

A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorized original biological medicinal product (reference medicinal product). A biosimilar demonstrates similarity to the reference product in terms of quality characteristics, biological activity, safety, and efficacy based on a comprehensive comparability exercise.

Food and Drug Administration (FDA)

A biological product that is highly similar to a United States licensed reference biological product not withstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.

2. Features of biosimilar medicines

2.1.Highly similar to the reference medicine

- The biosimilar has physical, chemical, and biological properties highly similar to the reference medicines. There may be minor differences from the reference medicine which are not clinically meaningful in terms of safety or efficacy.

2.2.No clinically meaningful differences compared with the reference medicine

- No differences are expected in clinical performance. Clinical studies that support the approval of a biosimilar confirm that any differences will not affect safety and efficacy.

2.3.Variability of biosimilars kept within strict limits

- Minor variability is only allowed when scientific evidence shows that it does not affect the safety and efficacy of the biosimilar. **The range of variability allowed for a biosimilar is the same as that allowed between batches of the reference medicine.** This is achieved with a robust manufacturing process to ensure that all batches of the medicine are of proven quality.

- Both the biosimilar and the reference medicine must contain the same protein (i.e. amino acid sequence) and the same '3D' structure (folding of the protein).
- Some differences may be allowed if they do not affect safety and efficacy - for example, differences in the formulation of the medicine (e.g. excipients), presentation (e.g. powder to be reconstituted versus solution ready for injection), and administration device (e.g. type of delivery pen).

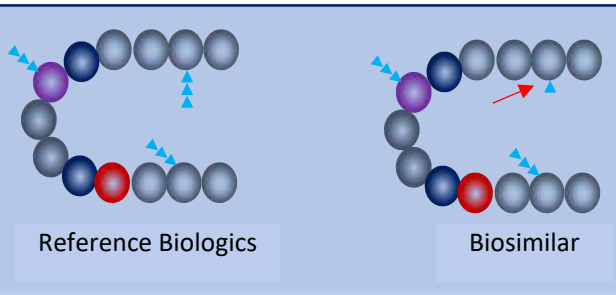


Figure (3) The variability between reference product and biosimilar
Adapted from European Medicines Agency (EMA)

3. Differences between generics and biosimilars

- Biosimilar drugs are often confused with generic drugs. Both are marketed as cheaper versions of costly name-brand drugs.
- Both are available when drug companies' exclusive patents on expensive new drugs expire. And both are designed to have the same clinical effect as their pricier counterparts.
- But the biosimilar is not regarded as a generic biological medicine. This is mostly because the natural variability and more complex manufacturing of biological medicines do not allow an exact replication of the molecular microheterogeneity. Consequently, more studies are needed for regulatory approval of biosimilars than for generics to ensure that minor differences do not affect safety or efficacy.

Table 2: **Differences between generics and biosimilars**

Generic medicine	Biosimilar medicine
Generally possible to obtain exactly the same molecule	Possible to reproduce the molecule to a high degree of similarity due to unique bio-manufacturing methods and natural biological variability
Full data requirements on pharmaceutical quality	Full data requirements on pharmaceutical quality, plus additional quality studies comparing the structure and biological activity of the biosimilar with the reference medicine
Development based on demonstration of bioequivalence (i.e. that the generic and the reference medicine release the active substance into the body at the same rate and to the same extent under similar conditions)	Development based on demonstration of biosimilarity using comparability studies (comprehensive head-to-head comparison of the biosimilar with the reference medicine to show high similarity in chemical structure, biological function, efficacy, safety, and immunogenicity)
Clinical data requirements are mainly pharmacokinetic bioequivalence studies	In addition to comparative pharmacokinetic and pharmacodynamics studies, safety and efficacy data may be required, particularly for more complex biological medicines
All indications approved for the reference medicine can be granted based on demonstrated bioequivalence, without the need for further clinical data	Efficacy and safety have to be justified in each indication. However, confirmatory clinical trials with the biosimilar are usually not needed in every indication that has been approved for the reference medicine. After the demonstration of biosimilarity, extrapolation of data to other indications is possible if the scientific evidence available addresses all specific aspects of these indications

4. Overview of the approval process for biosimilars

- The recommendation for regulatory approval is based on the "**totality of the evidence**", and includes a comprehensive data package from all stages of development (analytical, nonclinical, and clinical similarity assessment) that demonstrates biosimilarity to the originator biologic product
- The guiding principle of a biosimilar development program is to establish similarity between the biosimilar and the reference product by the best possible means, ensuring that the previously proven safety and efficacy of the reference medicinal product also apply to the biosimilar.
- A biosimilar should be highly similar to the reference medicinal product in physicochemical and biological terms. Any observed differences have to be properly justified concerning their potential impact on safety and efficacy.
- A stepwise approach is normally recommended throughout the development program, starting with a comprehensive physicochemical and biological characterization.
- The extent and nature of the non-clinical *in vivo* studies and clinical studies to be performed depend on the level of evidence obtained in the previous step(s) including the robustness of the physicochemical, biological, and non-clinical *in vitro* data.
- Generally, clinical data aim to address slight differences shown in previous steps and to confirm the comparable clinical performance of the biosimilar and the reference product.
- If the biosimilar comparability exercise indicates that there are relevant differences between the intended biosimilar and the reference medicinal product making it unlikely that biosimilarity will eventually be established, a stand-alone development to support a full marketing authorization application should be considered instead.

- In specific circumstances, a confirmatory clinical trial may not be necessary. This requires that similar efficacy and safety can clearly be deduced from the similarity of physicochemical characteristics, biological activity/potency, and PK and/or PD profiles of the biosimilar and the reference product.

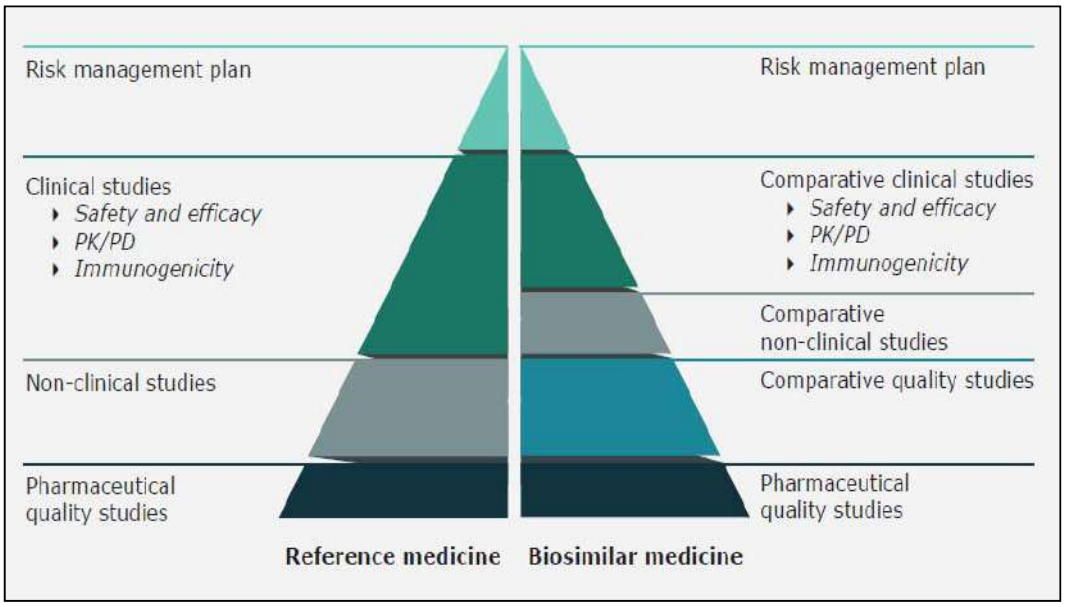


Figure (4) Comparison of data requirements for approval of a biosimilar versus the reference medicine.

Source: Biosimilars in the MENA Region: Regulatory Landscape

- In addition, it requires that the impurity profile and the nature of excipients of the biosimilar itself do not give rise to concern, you can see a comparison of data requirements for approval of a biosimilar versus the reference medicine in **Figure (4).**

5. Data required to demonstrate biosimilarity

5.1.Nonclinical in vitro studies

- The basis for establishing biosimilarity involves extensive physicochemical and biological characterization. Hence, the nonclinical in vitro program has to include robust analytical techniques along with sensitive biochemical and functional assays to detect any potential variability between the reference product and the biosimilar.
- These studies should include relevant assays on:

- Binding to target(s) (e.g. receptors, antigens, enzymes) known to be involved in the pharmaco-toxicological effects and/or pharmacokinetics of the reference product.

- Signal transduction and functional activity/viability of cells known to be of relevance for the pharmaco-toxicological effects of the reference product.

5.2. Nonclinical in vivo studies

- The nonclinical in vivo program follows a stepwise approach recommended by the EMA, FDA, and WHO. According to EMA guidelines, based on the outcome of the extensive structural and functional comparisons, a decision will be made to determine the need for in vivo studies in animals and, if so, the extent and focus of these studies. Animal studies may be needed to address remaining uncertainties about safety and to provide additional evidence before advancing to clinical studies in humans.
- However, if data from quality and in-vitro non-clinical data are deemed satisfactory and no issues are identified that would prevent direct entry into humans, in-vivo animal studies are usually not considered necessary.

5.3.Clinical studies

- The purpose of the clinical similarity study is to directly compare the biosimilar and reference products, evaluating their efficacy, safety, and immunogenicity. A biosimilar study is not intended to re-establish clinical efficacy or safety; instead, the goal is to confirm that no clinically meaningful differences exist.
- The nature and scope of clinical trials depend on the uncertainty about biosimilarity after the structural, functional, and animal studies are completed. The study population, size, and duration should allow for the detection of clinically meaningful differences between products.
- Comparative clinical studies are conducted to demonstrate the similarity between the biosimilar and the reference product in a stepwise manner beginning with PK, PD (if relevant markers exist), and immunogenicity studies followed by comparative clinical efficacy and safety (including immunogenicity) study/studies.

- Pharmacokinetic (PK) studies designed to demonstrate similar PK profiles of the Biosimilar and the reference medicinal product concerning key PK parameters are an essential part of the biosimilar development program.
- The design of a PK study depends on various factors, including clinical context, safety, and PK characteristics of the reference product (target-mediated disposition, linear or non-linear PK, time dependency, half-life, etc.)
- PK measures include AUC $_{(0\text{-inf})}$, C_{max}, T_{max}, Vd: Volume of distribution, and $T_{1/2}$: Half-life.
- A human PD study to demonstrate a similar effect on a relevant PD measure(s) related to effectiveness or specific safety concerns (except for immunogenicity, which is evaluated separately) represents even stronger support for a biosimilarity determination.
- If residual uncertainty about biosimilarity remains, an additional comparative clinical study (ies) would be needed to further evaluate whether there are clinically meaningful differences between the two products.

5.4. Efficacy trials

- In the absence of surrogate endpoints for efficacy, it is usually necessary to demonstrate comparable clinical efficacy of the biosimilar and the reference medicinal product in adequately powered, randomized, parallel-group comparative clinical trial(s), preferably double-blind, by using efficacy endpoints.
- The study population should generally be representative of approved therapeutic indication(s) of the reference product and be sensitive to detect potential differences between the biosimilar and the reference.
- In general, an **equivalence design** should be used, the use of a non-inferiority design may be acceptable if justified based on a strong scientific rationale and taking into consideration the characteristics of the reference product, e.g. (safety profile/tolerability, dose range, dose-response relationship).

5.5.Efficacy endpoints

- The primary endpoints of a biosimilar clinical trial will usually be chosen to detect clinically relevant differences between the proposed biosimilar and the reference

product, and it is important to note that the endpoints may be different from those used for the approval of the reference product.

- Recognizing that the preferred endpoint to prove efficacy in cancer, e.g. progression-free survival (PFS) or overall survival, may not be feasible or sensitive enough to demonstrate biosimilarity between a proposed biosimilar and the reference product, the EMA recommends using a clinical endpoint that measures activity as a primary endpoint, such as objective response rate (ORR) or pathological complete response (pCR).

5.6. Clinical safety

- Clinical safety is important throughout the clinical development program and is captured during initial PK and/or PD evaluations and also as part of the pivotal clinical efficacy study.
- Care should be given to comparing the type, severity, and frequency of the adverse reactions between the biosimilar and the reference product, particularly those described in the reference product. The applicant should provide in the application dossier an evaluation of the specific risks anticipated for the biosimilar.
- This includes in particular a description of possible safety concerns that may result from a manufacturing process different from that of the reference product, especially those related to infusion-related reactions and immunogenicity.

5.7. Immunogenicity data needed for approval of a biosimilar:

- At least one clinical study should compare the immunogenicity profile of the proposed biosimilar and reference products about the nature, incidence, clinical relevance, and severity of the immune response.
- Immunogenicity testing of the biosimilar and the reference product should be conducted within the biosimilar comparability exercise by using the same assay format and sampling schedule which must meet all current standards.
- Clinical immunogenicity studies are generally required for biological medicines. In the case of monoclonal antibodies, they are always required, as it is more difficult to predict

the incidence of unwanted immunogenicity, the characteristics of the immune response, or the clinical consequences.

- Such studies look both at short-term immune responses (e.g. infusion-related reactions), as well as long-term (e.g. delayed responses due to an evolving immune reaction).
- Immunogenicity data required for approval include incidence, titer, and persistence of antibodies against the biological medicine (ADAs), neutralization assays (because neutralizing antibodies may reduce the effect of the medicine), assessment of the clinical impact and measures to manage the potential risk of immunogenicity (e.g. special monitoring of immune-mediated adverse reactions or use of concomitant medication to mitigate infusion reactions).
- Duration of the immunogenicity study should be justified on a case-by-case basis depending on the duration of the treatment course, the disappearance of the product from the circulation (to avoid antigen interference in the assays), and the time for the emergence of humoral immune response (at least four weeks when an immunosuppressive agent is used).
- Duration of follow-up should be justified based on the time course and characteristics of unwanted immune responses described for the reference medicinal product, e.g. a low risk of clinically significant immunogenicity or no significant trend for increased immunogenicity over time.
- In the case of chronic administration, one-year follow-up data will normally be required for pre-authorization. Shorter follow-up data pre-authorization (e.g. six months) might be justified based on the immunogenicity profile of the reference product. If needed, immunogenicity data for an additional period, up to one-year, could then be submitted post-authorization.
- Increased immunogenicity as compared to the reference product may become an issue for the benefit/risk analysis and would question biosimilarity. However, also lower immunogenicity for the biosimilar is a possible scenario, which would not preclude approval as a biosimilar.
- In case of reduced development of neutralizing antibodies with the biosimilar, the efficacy analysis of the entire study population could inaccurately suggest that the biosimilar is more efficacious than the reference product. It is therefore recommended

to pre-specify an additional exploratory subgroup analysis of efficacy and safety in those patients that did not mount an anti-drug antibody response during the clinical trial. This subgroup analysis could be helpful to establish that the efficacies of the biosimilar and the reference product are in principle similar if not impacted by an immune response.

5.8. Extrapolation

- If a biosimilar is highly similar to a reference medicine and has comparable safety and efficacy in one therapeutic indication, safety and efficacy data may be extrapolated to other indications approved for the reference medicine. This means that fewer clinical trials or no trials at all need to be carried out with the biosimilar in certain indications. Extrapolation of data to other indications is always supported by scientific evidence generated in robust comparability studies (quality, non-clinical and clinical).
- Extrapolation is a well-established scientific principle that has been used for many years, for example whenever a biological medicine with several approved indications undergoes major changes to its manufacturing process (e.g. new manufacturing site or development of new formulations). The potential effect of these changes on biological medicine's clinical performance is carefully evaluated with comparability studies (mainly quality and in vitro studies). If clinical studies are needed, these are conducted in one relevant indication and, based on all these data, extrapolation to the other indications is usually possible.
- **Criteria for extrapolation**

  Important considerations need to be borne in mind before an indication for a biosimilar can be approved based on extrapolated safety and efficacy data. These include:

  Mechanism of action

  - The mechanism of action of the active substance should be mediated by the same receptor(s) in both the initial and the extrapolated indication.
  - If the mode of action of the active substance is complex and involves multiple receptors or binding sites (as is often the case with monoclonal antibodies), it may be difficult to establish the contribution of each receptor or binding site to each indication. In this case, additional studies (non-clinical or clinical) will be

needed to prove that the biosimilar and reference medicine will behave similarly in the extrapolated indication.

Relevant study population

- Comprehensive comparability studies must show that the biosimilar is highly similar to the reference medicine (employing safety, efficacy, and immunogenicity data) in a key indication in a population in which potential differences in clinical performance can be detected.

Extrapolation across different clinical settings

- Data from a given indication (e.g. rheumatoid arthritis) may not be directly applicable in terms of safety or efficacy to an indication falling within another therapeutic area where the mode of action, posology, or pharmacokinetics may be different (e.g. oncology). In this case, additional studies may be needed.

Extrapolation of safety data

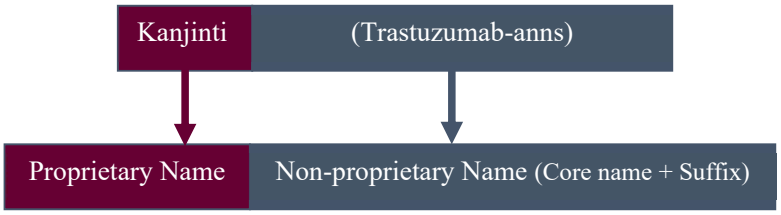
- Safety data can only be extrapolated after a comparable safety profile has been established for the biosimilar in one therapeutic indication. If comparability is shown at structural, functional, pharmacokinetic, and pharmacodynamic levels, and efficacy is comparable, then adverse reactions due to the biosimilar's pharmacological action can be expected to be the same and to occur at similar frequencies.

Extrapolation of immunogenicity data

- Extrapolation of immunogenicity data is not automatic, as it always requires justification. This is because immunogenicity is determined by more than product-related characteristics.
- Factors relating to patients (age, immune status), disease (comorbidities, concomitant treatments), or treatment-related factors (route of administration, length of exposure) also have to be considered.

6. Biosimilars naming:

- The naming convention has been adopted for all approved biologics to clearly differentiate products, increase safety, and facilitate pharmacovigilance.
- The naming and labeling of biosimilars have been controversial issues and there is a long-standing debate regarding the naming of biosimilars.
- The FDA's 2017 guidance stipulated that licensed biologic products should be assigned distinguishable, nonproprietary names.



- For each originator biologic product, related biologic product, or biosimilar, the nonproprietary name will consist of the core name and an FDA-designated, distinguishable suffix of four letters, which is devoid of meaning.

Table 3: Biosimilars naming examples

Reference Name	Non-proprietary Name	Proprietary Name (Trade Name)
Bevacizumab	Bevacizumab-awwb	MVASI™
Trastuzumab	Trastuzumab-dkst	Ogivri™
Filgrastim	Filgrastim-aafi	NIVESTYM™

7. Interchangeability, switching, and automatic substitution

- **Interchangeability** refers to the possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect.
- Interchangeability status is a second level of the approval pathway beyond biosimilarity and is only granted if:

  (1) additional clinical trials demonstrate that the biosimilar can produce the same clinical result as the reference product in any given patient.

  (2) additional clinical trials demonstrate the risk to efficacy or safety with alternating or switching between the biosimilar and reference product is not greater versus consistent use of the reference product.
- The purple book is an online database with information on all FDA-approved biologics. **Appendix (6)** contains additional information about the purple book.

Figure (5): Interchangeable Biosimilar (FDA approval requirements)

- **Switching** is when the prescriber decides to exchange one medicine for another medicine with the same therapeutic intent.
- **Substitution (automatic)** is the practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber.
- Biosimilars can be used in patients who have previously been treated with the reference product (treatment-experienced), as well as in patients who have not previously received the reference product (treatment-naïve).

- A switching study intended to support a demonstration of interchangeability is recommended to evaluate changes in treatment that result in two or more alternating exposures (switch/alternation intervals) to the proposed interchangeable product and the reference product **(Figure (6)).**
- Interchangeability, switching and automatic substitution are addressed differently in different countries, as well as the scope of their applicability **Appendix (5)** contains further information.
- EDA has a rigorous standard for biosimilar approval, patients and healthcare providers can feel confident in the safety and efficacy of a biosimilar product.

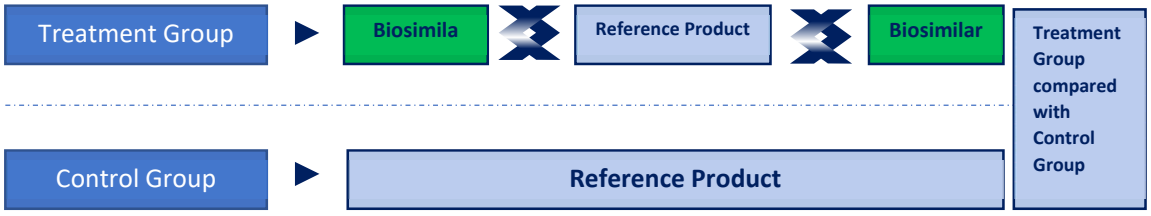


Figure (6): Switching study design

8. The biosimilars opportunities & challenges

Opportunities: Biosimilars improve access to much-needed cancer treatments by:

1. Enable cost savings to the patient, payor, and the health system through greater access to life-saving medicines.
2. Provide more treatment options for patients and access to innovative therapies.
3. Support competition, which may drive innovation and technological advancement among originator biologics.

Challenges:

1. In some cases, multiple biosimilars are available.
2. The differences in product presentation (e.g., routes of administration) between a biosimilar and the reference product or among biosimilars could create confusion. For

example, in addition to I.V. versions of rituximab and trastuzumab, subcutaneous versions have been developed.

3. There are also challenges associated with reimbursement, patient preference, incorporation into electronic medical records (i.e., order sets), and greater acceptance of biosimilars for supportive care versus more complex therapeutic oncology indications.
4. Health Care Professionals (HCP) reluctance to accept biosimilars as therapeutic equivalents to originator bio-therapeutics is cited as a common barrier to biosimilar implementation within healthcare institutions across the globe.
5. The lack of clear guidelines on substitutability and interchangeability with reference biologics will likely cause prescribers to exercise more caution in prescribing biosimilars until they gain comfort with the quality and efficacy of biosimilars.
6. Regulatory uncertainty: The regulatory policies governing biosimilars are still in flux.
7. Biosimilars face competition from at least two sources: **bio-betters** from branded companies and brand consciousness from healthcare providers **(See figure (7)).**

   Examples of bio-betters include ado-trastuzumab emtansine (Kadcyla) an antibody-drug conjugate, which is a bio-better of trastuzumab, that has been demonstrated to slow disease progression in patients with HER2-positive advanced cancer.

Figure (7): Comparison between biological reference drug, biosimilar and bio-better in terms of development time, overall cost of production, and patent protection.

IV. THE ROLE OF ONCOLOGY PHARMACIST IN BIOLOGICS AND BIOSIMILARS PRACTICE

Oncology pharmacists with an understanding of these complexities and the ability to assess available comparability data between products play a crucial role in the multidisciplinary effort to evaluate and implement biosimilar use within healthcare institutions. The oncology pharmacist's role is centred on three axes: Pharmacy and therapeutic committee (P&T), Education, and pharmacovigilance.

1. **Pharmacy and Therapeutics committee (P&T)**

- Pharmacy and therapeutics (P&T) committees develop formularies based on systematic evaluations of clinical evidence and objective assessments of relative economic, clinical, and humanistic outcomes. It is important to consider potential safety concerns when evaluating drugs for formulary inclusion.
- It is important to assess differences in safety profiles and immunogenicity between the products and to consider the sensitivity of the patient population in the biosimilar clinical trials relative to all populations and indications for which the biosimilar is being evaluated.
- Post-approval surveillance information should be included, if available, because safety events (e.g., delayed immune reactions) may occur after a study has ended and the biosimilar has entered clinical practice.
- Differences in product characteristics (e.g., differences in formulation, excipients, and containers that may lead to changes in agglutination and hence immunogenicity) and delivery (e.g., differences in dose and route of administration) should be considered for potential safety concerns, as should differences in infusion pain and compatibility with laboratory assays.
- Oncology pharmacists play an important role in the (P&T) committees, and they must be involved in the following activities:

Policy Development

- Oncology pharmacist plays an integral role in policy development, establishing and assisting in programs and procedures that ensure safe and effective medication therapy (e.g., clinical care plans, treatment guidelines, critical pathways, disease management protocols)
- Oncology pharmacists should participate in performance improvement activities related to procurement, prescribing, dispensing, administering, monitoring, and overall use of biologics and biosimilars.

***Economic considerations*:**

- In addition to drug acquisition cost, several economic factors should be considered during the formulary review.
- The P&T committee should also consider whether the difference in total cost between a biosimilar and its reference product supports full formulary conversion to the biosimilar.
- In addition to pressure from payers to use lower-cost drugs, there may be differences in payer requirements and prior authorizations between the biosimilar and reference products to consider.
- Institutional cost savings made through the use of biosimilars should be used to keep patient costs manageable and to stabilize budgets to maximize the number of patients served.

***Supply chain*:**

- Supply disruptions, which can be common with injectable oncology treatments, may cause delays and interruptions to treatment regimens, as well as increased healthcare costs and care management burdens.
- It is important to ensure that there are redundancies in manufacturing (e.g., having licenses for multiple facilities) to prevent shortages.
- Therefore, oncology pharmacists should review the biosimilar manufacturer's history for shortages and recalls due to product quality to ensure patient and physician confidence in the reliability of supply.

- Oncology pharmacists should also consider the manufacturer's product handling practices (e.g., the controlled temperature during distribution), supply chain security, and anti-counterfeit protection

2. Education:

- Oncology pharmacists are well positioned to act as resources for staff and patient education regarding the safety and efficacy of biosimilars as compared to originator products.
- Healthcare providers and patients need to be educated on how biosimilars differ from the reference product, how they are tested and approved economic considerations and the availability of clinical trials.
- Patients should be educated about biosimilars with resources that are evidence-based and tailored to patient demographics and health literacy. Such resources should be publicly available and adaptable to reflect the target population's needs
- **Oncology pharmacists** should formulate educational programs designed to meet the needs of professional staff, patients, families, and caregivers on matters related to biologics and biosimilars use.
- Staff education on biosimilars should reference published, evidence-based and peer-reviewed literature whenever possible.
- Educational materials should be updated and reviewed on an ongoing basis.
- Furthermore, education on product drift that results in differences between batches of originator bio-therapeutic, similar to those found between biosimilars and originator bio-therapeutics, may strengthen support for biosimilar use amongst clinicians.
- The **oncology pharmacist** should determine if the biosimilar manufacturer has patient education materials. Materials should be developed if they are not already available.
- FDA recognizes the importance of educating oncologists and other healthcare professionals who provide care for patients with cancer by offering educational programs and materials on biosimilars in general and particularly biosimilars used in oncology.

3. National medication error reporting (NO HARMe)

- Medication errors are global issues reported in several studies from all over the world at varying rates. All organizations concerned with patient safety and quality of healthcare, emphasize the need to report medication errors to prevent their recurrence. Medication error reporting should be done by all healthcare practitioners as being a crucial and preliminary step in the solidity measures taken for the safety of the patient and the quality of pharmaceutical care services provided.
- Reporting medication errors is a key step needed to address errors' root causes thus setting the corrective actions to prevent their recurrence and accordingly reduce them. Reporting also serves to set comparisons among different healthcare facilities and to identify the patterns, trends, the most common errors, and the most significant or serious events.
- Since information about biological and biosimilar medications has to be accessible from a trustworthy healthcare provider, like a physician, pharmacist, or nurse. All involved parties—including healthcare professionals, patients, and patient organizations require accurate information and some may suffer lapses of false information and incorrect attitudes about biosimilar medications. It has been noted that a lack of knowledge and instruction could result in major medication errors and delays in the patient's therapeutic progress.
- In this context, the US Food and Drug Administration (FDA) warns healthcare professionals that some electronic systems that deal with medications face the risk of confusing biosimilars, for example, the breast cancer drug Kadcyla (ado-trastuzumab emtansine) may be confused with Herceptin (trastuzumab), which could lead to medication errors. Because Kadcyla and Herceptin, being separate breast cancer medications, have very distinct dosage requirements and treatment plans, patients could be harmed by mixing up these medications.
- Therefore, drug products should be identified by the proprietary (brand) and non-proprietary names that are used on medication labels approved by regulatory bodies, according to publishers of drug information content. This will guarantee that adverse events are reported for the appropriate product and assist reduce medication errors.

4. **Pharmacovigilance:**

- Pharmacovigilance is critical in oncology, especially when it comes to biologics. As with any drug, the goal of a post-approval pharmacovigilance plan is to identify and understand, as fully as possible, the frequency and nature of AEs associated with a specific product, including potential risk factors for such AEs.
- As is the case with most biologics, including biosimilars, clinical testing preapproval may not identify all possible AEs; an evaluation of clinical safety, therefore, is continued in the post-marketing setting.
- Pharmacovigilance and patient-outcome monitoring are integral to the safe and effective use of biosimilars in different populations and indications.
- Monitoring and documenting our **Egyptian** experience with biologics (Reference products and Biosimilars) is a critical issue.
- Qualified Oncology Pharmacists are a real guarantee for good pharmacovigilance practices (GVP), they have great responsibilities to promote safety, and carefully follow cancer patients in the era of biologics and biosimilars.
- Oncology pharmacists should report the side effects of biosimilars even if they are the same as the effects seen with reference medicine.
- Pharmacists should ensure that a robust infrastructure is in place to support accurate product tracking and tracing of AEs of the administered biosimilars.
- The data should then be collated and analyzed regularly to identify potential signals. Healthcare professionals at all levels should record trade names and batch numbers including dispensing and patient administration.
- In cases where the product is dispensed at a community pharmacy, the tradename and batch number of the biological medicine should be provided to the patient.
- If a patient is switched from one biological medicine to another with the same active substance, it is important to record the tradename and batch number for each of them.
- Patient characteristics and automatic substitution vary throughout the world, making data comparisons challenging, and thus careful evaluation and comparison of published real-world data are necessary to determine applicability. So, Pharmacovigilance is necessary for the development of real-world evidence that provides clinician reassurance and contributes to the relevant body of literature.

- To this end, information on pharmacovigilance should be disseminated via medical schools, national societies, medical charities, and governments

A Call for Reporting

The Egyptian Pharmaceutical Vigilance Center (EPVC):
Address: 21 Abd El Aziz AlSoud Street. El-Manial, Cairo, Egypt, PO Box: 11451
Hotline: 15301 Fax: +202 – 23610497
Email: pv@edaegypt.gov.eg , pv.followup@edaegypt.gov.eg
Reporting link: www.edaegypt.gov.eg https://sites.google.com/view/epvc-reporting/healthcareprofessional-public-adverse-drug-event-reporting/reporting-other-adverse-drugevent-case

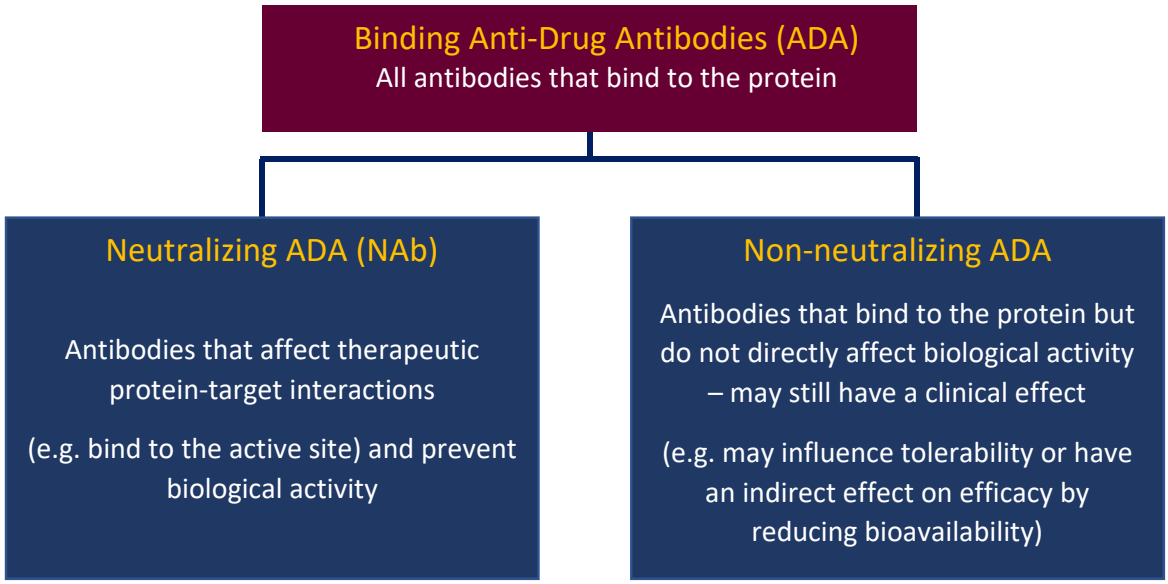
The Egyptian Drug Authority (EDA) Pharmaceutical Care Administration
General Administration for Drug Utilization and Pharmacy Practice:
NO-HARMe "National Office for Handling And Reduction Of Medication Error" is a national voluntary medication error and "near miss" reporting program founded for the purpose of sharing the lesson learned from medication errors. In case of any medication error, we invite all healthcare professionals including oncology pharmacists to share their experiences and report the detected medication errors to the Egyptian Drug Authority reporting system (NO HARMe) through the following link: https://edaegypt.gov.eg/10176?culture=ar-EG

APPENDICES

Appendix (1) Patent expiry dates for biologics used in Oncology

Reference product	Approval year EU/US	Patent expiration in EU/US
Trastuzumab (Herceptin)	2000/1998	2014/2019
Rituximab (Rituxan)	1998/1996	2013/2016
Bevacizumab (Avastin)	2005/2004	2022/2019
Brentuximab vedotin(Adcetris)	2012/2011	2023/ 2015-2031
darbepoetin alfa(Aranesp)	2001	2016/2024
Cetuximab (Erbitux)	2004	2014/2016
Ramucirumab(Cyramza)	2014	2023/2025
Pembrolizumab(Keytruda)	2015/2014	2028/2036
Nivolumab (Opdivo)	2015/2014	2026/2027
Pertuzumab(Perjeta)	2013/2012	2024/2026
Densomab (Xgeva)	2010	---/2016
Panitumumab (Vectibex)	2007/2006	2018/2020

Appendix (2) Anti-drug antibodies and their possible consequences



Appendix (3) MYL-1401O (Ogivri)
A case study exploring the data used to support Biosimilarity

1. Introduction

Ogivri (also referred to as MYL-1401O) has been developed as a similar biological medicinal product to the innovator product Herceptin (Trastuzumab)

Trastuzumab is a humanized recombinant IgG monoclonal antibody specifically directed against the HER2 receptor. Trastuzumab binds with high affinity and specificity to sub-domain IV, a juxta-membrane region of HER2's extracellular domain. The binding of trastuzumab to HER2 inhibits ligand-independent HER2 signalling and prevents the proteolytic cleavage of its extracellular domain, an activation mechanism of HER2. As a result, trastuzumab has been shown, in both in vitro assays and in animals, to inhibit the proliferation of human tumor cells that overexpress HER2.

Additionally, trastuzumab is a potent mediator of antibody-dependent cell-mediated cytotoxicity (ADCC). In vitro, trastuzumab-mediated ADCC is preferentially exerted on

HER2-overexpressing cancer cells compared with cancer cells that do not overexpress HER2. Trastuzumab (Herceptin) is currently authorized for the treatment of breast cancer and gastric cancer.

2. MYL-1401O (Ogivri) Biosimilarity assessment

2.1. Non-clinical in vitro assays

Comprehensive analyses of the proposed biosimilar and reference medicinal product were carried out using sensitive and orthogonal methods covering biological activity, primary structure, higher order structure, product-related substances, and purity/impurities.

Quality attribute	Analytical similarity summary
Protein content	Highly similar
Amino acid sequence	Identical peptide mapping
	Highly Similar intact mass
Conformation (Secondary and higher order structure)	Highly similar
HER2 binding	Highly Similar

Inhibition of proliferation	Highly Similar
ADCC	Highly Similar

Data were evaluated against pre-defined similarity assessment criteria. The biological activity was evaluated by a comprehensive set of functional assays and binding studies addressing both the Fab and Fc functions of the molecule.

2.2. Clinical studies

Study Number		
MYL-Her-1001	MYL-Her-1002	MYL-Her-3001
Type of Study		
PK bioequivalence, PD, safety, immunogenicity	PK, safety, immunogenicity	Confirmatory efficacy and safety, immunogenicity
Study Objective(s)		
1. To confirm PK bioequivalence between MYL-1401O and EU-Herceptin. **2. To assess comparative safety and tolerability** **3. To investigate PD parameters**	1. To demonstrate the PK similarity of MYL-1401O vs EU-Herceptin and US-Herceptin along with EU-Herceptin vs US-Herceptin 2. To further assess the similarity of PK among MYL-1401O, EU-Herceptin, and US-Herceptin. 3. To assess the comparative safety	1. To compare the independently assessed best ORR at Week 24 2. To compare independently assessed clinical activity at Week 24 (TTP, PFS, OS) 3. To descriptively compare safety, tolerability, and immunogenicity 4. To compare population PK 5. To assess the impact of shed ECD fragments on HER2 receptor on PK and efficacy parameters
Study Design		
Single-center, single-dose, 2-period, double-blind, crossover study.	Single-center, single-dose, randomized, double-blind, 3-arm, parallel-group study	Multicenter, double-blind, randomized, parallel-group study

Test Product(s), Dosage, Regimen, Route of Administration		
MYL-1401O, EU-Herceptin **IV (8 mg/kg single dose)**	MYL-1401O, EU-Herceptin, US-Herceptin IV (8 mg/kg single dose)	MYL-1401O, EU-Herceptin IV (8 mg/kg loading dose) followed by IV (6 mg/kg maintenance) every 3 weeks for 8 cycles
Number of Subjects/ Diagnosis		
22 randomized, 19 completed/ Healthy male subjects	132 randomized, 121 completed/ Healthy male subjects	500 randomized, 356 completed Part 1/ Patients with HER2+ metastatic breast cancer.
Duration of Treatment		
Single IV dose administered over 90 min		48 weeks
Results		
The submitted primary PK analysis showed PK comparability of the test and reference products at the dose of 8 mg/kg body weight given that the 90% confidence intervals for the ratios of both primary parameters (Cmax and AUC0-t/AUC0-∞) were well contained within the standard bioequivalence interval of 0.80–1.25 in studies Myl-Her-1001 and Myl-Her-1002. In addition, the terminal half-life, Vz and CL parameters were also similar across the groups. **Pharmacodynamics' findings support the available data for the overall comparability exercise.**		Therapeutic efficacy Out of 500 randomized patients, 458 were evaluable for efficacy. ORR at week 24 was 69.6% for MYL-1401O compared to 64% for Herceptin. The ratio of ORR was 1.09 with 90% CI (0.974 - 1.211) and 95% CI (0.954 - 1.237) within the pre-defined equivalence margins.
MYL-Her-3001 Results continued: **Secondary endpoints TTP, PFS, OS, and Duration of response (DR) were assessed in Part 1 and Part 2. Analyses of these endpoints in Part 2 (after 48 weeks of treatment in total) confirmed the similarity outcomes observed at the Week 24 endpoint. Tumor progression occurred in 41.3% and 43.0% of patients treated with Ogivri and Herceptin, respectively (p=0.684), 55.7% and 55.3% did not experience tumor progression or death (PFS, p=0.842) whereas 89.1% and 85.1% survived until 48 weeks**		

(OS, p=0.439), respectively. Additionally, 42.4% of MYL-1401O subjects compared to 44.5% of Herceptin subjects (p = 0.790) with objective response had tumor progression or died before the 48-week cut-off (DR). These findings were also confirmed through sensitivity analyses.

<u>Safety and immunogenicity data:</u>

- **Overall, treatment with MYL-1401O was well tolerated during 48 weeks and no new or unexpected safety signals were observed (mostly in line with Herceptin safety profile + taxanes).**
- **In MYL-Her-3001, at 48 weeks, the safety profiles were comparable between the 2 arms (MYL-1401O and Herceptin).**
- **The incidence of SAEs was similar in the treatment groups.**
- **The immunogenicity of MYL-1401O and Herceptin was assessed during 48 weeks by measuring the ADA levels in blood samples.**
- **The incidence of antidrug antibodies against MYL-1401O and Herceptin was very low and consistent with the literature.**
- **These antibodies were transient and the titers were low. Also, the incidence of neutralizing antibodies was very low and similar in both arms. Overall, the treatment-emergent immune response was similar between the 2 treatment arms. No association was observed between the presence of ADAs and efficacy (as measured by ORR), nor to ARRs.**
- **These results indicate that there was no clinically meaningful difference between MYL-1401O and Herceptin in terms of immunogenicity.**

Biosimilarity is supported by quality, non-clinical, pharmacokinetics, and pharmacodynamics, as well as from a clinical efficacy and safety point of view.

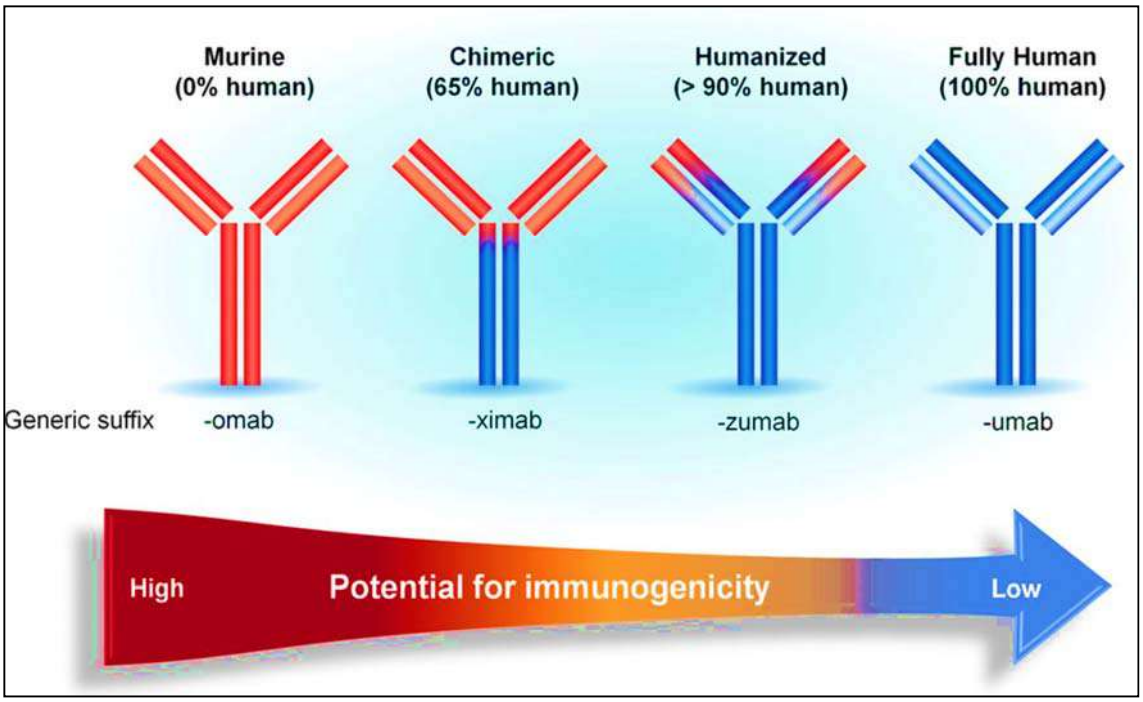
2.3. Extrapolation of safety and efficacy

1. Herceptin is authorized in the treatment of HER2-positive MBC, early breast cancer (EBC), and metastatic gastric cancer (MGC). The mechanism of action of trastuzumab is the same in all three indications (i.e., to inhibit the proliferation of human tumor cells that overexpress HER2). The target receptor involved in the mechanism of action in EBC and MGC is the same as in MBC (i.e., HER2). Trastuzumab is indicated in EBC and MGC only if HER2 positivity is demonstrated. The dosage is also similar for all the indications. Trastuzumab is administered by the same route in all indications.
2. The available safety data of the reference product does not indicate that there are any significant differences in expected toxicities for each condition of use and patient population. There are no toxicities that are related to off-target activities in MBC compared with EBC or MGC.
3. Research performed on the active substance of the reference product shows that it does not interact with several receptors that may have a different impact in the tested and non-tested therapeutic indications, and molecular typing has indicated that it does not have more than one active site other than the HER2 targeting area.

Overall, the results of the physicochemical, structural, and biological characterization studies together with the evidence from non-clinical and clinical studies support extrapolation to the other oncology indications

Appendix (4)

Types and nomenclature of the therapeutic monoclonal antibodies and their immunogenicity.



Example (Anti CD-20)	……..	Rituximab	Obinutuzumab	Ofatumumab

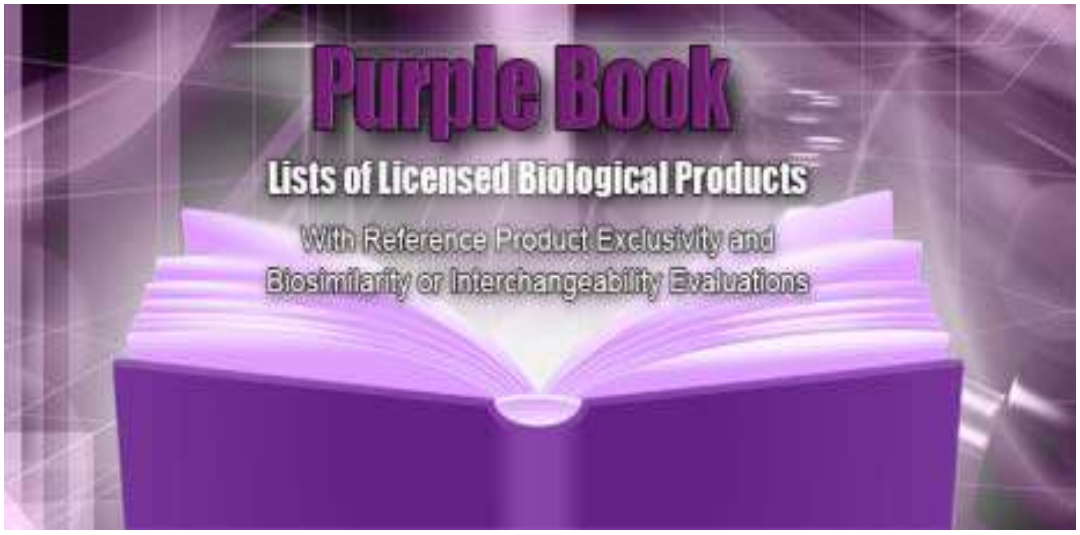
Appendix (5): Interchangeability, Switching, and Automatic Substitution in Different Countries /Authorities

	The EU	The UK	The US
Interchangeability			
Definition	"exchanging one medicine for another medicine that is expected to have the same clinical effect"	"Once a biosimilar is authorized, it is considered interchangeable with the RP, which means that a prescriber can choose the biosimilar over the RP (or vice versa) and expect to achieve the same therapeutic effect."	"the term interchangeable or interchangeability, in reference to a biological product/.../means that "the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product."
Requirements	No central EU requirements	No regulatory requirements	Interchangeable designation obtained via regulatory requirements
Switching			
Definition	"When the prescriber decides to exchange one medicine for another medicine with the same therapeutic intent"		
Requirements	No central EU requirements Regulatory level: EU member states	No regulatory requirements Regulatory level: National guidance	No regulatory requirements Regulatory level: State level
Substitution			
Definition	"dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber"		
Requirements	No central EU requirements Regulatory level: EU member states	"Substitution at the pharmacy level without consulting the prescriber is not permitted for biological medicines, including biosimilars"	Product-level interchangeability designation by the US Food and Drug Administration Regulatory level: US Food and Drug Administration State level laws

Source: Druedahl LC, Kälvemark Sporrong S, Minssen T, Hoogland H, De Bruin ML, et al. (2022) Interchangeability of biosimilars: A study of expert views and visions regarding the science and substitution. PLOS ONE 17(1): e0262537. https://doi.org/10.1371/journal.pone.0262537

Appendix (6): The Purple Book

The Purple Book: Database of Licensed Biological Products is a user-friendly online database with information on all FDA-approved biologics. It provides patients, payors, clinicians, and others with an accessible, easy-to-use online search engine with information about FDA-approved biologics, including whether a specific biologic is a reference product, biosimilar, or interchangeable biosimilar.



Features of the Purple Book

- Simple and advanced search options
- Auto-suggest search function
- Additional search filters
- Data download options
- Links to product labels (Drugs@FDA)
- Ability to show/hide sortable columns of information
- Ability to print or export search results
- A searchable glossary of terms

Appendix (7): Reporting Medication Errors to NO HARMe

- Egyptian Drug Authority established the National Office for Handling and Reduction of Medication errors (NO HARMe) to represent the national pool of medication error data in 2014, and its second version was launched in 2017. This reporting system was developed to facilitate the collection of medication error data at the national level, and hence to exchange experiences among healthcare providers.
- In 2022, EDA launched the third version of (NO HARMe) to allow healthcare providers to report medication errors that may happen during the use of pharmaceutical products, biological preparations, vaccines, cosmetics, or medical supplies through simplified steps.
- A specialized team from the Egyptian Drug Authority represented by the General Administration of Drug Utilization and Pharmacy Practice – Central Administration of Pharmaceutical Care investigates the event, rates its severity, and follows up on the consequences that may occur. The team may issue a report summarizing the accident and providing the corrective action to avoid the recurrence of the event.

REFERENCES

1. Lim LS, Mitchell P, Seddon JM, Holz FG, Wong TY. Age-related macular degeneration. Lancet 379(9827), 1728–1738 (2012).Crossref, Medline, Google Scholar.
2. The IQVIA Institute. Global Oncology Trends 2019. www.iqvia.com/insights/the-iqvia-institute/reports/global-oncology-trends-2019Google Scholar.
3. Pharmaceutical Technology. The world's most-sold cancer drugs in 2015 (30 March 2016). www.pharmaceutical-technology.com/features/featurethe-worlds-most-sold-cancer-drugs-in-2015-4852126Google Scholar.
4. Yip S. Top 10 best-selling drugs of 2019 (2020). https://www.pharmaintelligence.informa.com/~/media/informa-shop-window/pharma/2020 /files/reports/top-10-best-selling-drugs-of-2019.pdf
5. EMA. (2017). *Guideline on Immunogenicity assessment of therapeutic proteins* [Ebook]. Retrieved from https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-immunogenicity-assessment-therapeutic-proteins-revision-1_en.pdf
6. Kurki, P., van Aerts, L., Wolff-Holz, E., Giezen, T., Skibeli, V., & Weise, M. (2017). Interchangeability of Biosimilars: A European Perspective. *Biodrugs*, *31*(2), 83-91. doi: 10.1007/s40259-017-0210-0
7. Camacho, L., Frost, C., Abella, E., Morrow, P., & Whittaker, S. (2014). Biosimilars 101: considerations for U.S. oncologists in clinical practice. *Cancer Medicine*, *3*(4), 889-899. doi: 10.1002/cam4.258
8. *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues.* (2014). [Ebook]. Retrieved from http://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active_en-2.pdf
9. Immunogenicity Overview of Therapeutic Biologics – Creative Biolabs Blog. Retrieved 13 October 2021, from https://www.creative-biolabs.com/blog/index.php/immunogenicity-of-therapeutic-biologics/
10. Lammers, P., Criscitiello, C., Curigliano, G., & Jacobs, I. (2014). Barriers to the Use of Trastuzumab for HER2+ Breast Cancer and the Potential Impact of Biosimilars: A Physician Survey in the United States and Emerging Markets. *Pharmaceuticals*, *7*(9), 943-953. doi: 10.3390/ph7090943
11. Li, E., Subramanian, J., Jacobs, I., McKinley, J., Thomas, D., & Anderson, S. (2015). Development of biosimilars in an era of oncologic drug shortages. *Drug Design, Development And Therapy*, 3247. doi: 10.2147/dddt.s75219
12. Patent expiry dates for biologicals: 2016 update - GaBI Journal. (2021). Retrieved 13 October 2021, from http://gabi-journal.net/patent-expiry-dates-for-biologicals-2016-update.html
13. Protein structure: Primary, secondary, tertiary & quaternary (article) | Khan Academy. Retrieved 13 October 2021, from https://www.khanacademy.org/science/biology/macromolecules/proteins-and-amino-acids/a/orders-of-protein-structure
14. Rugo, H., Linton, K., Cervi, P., Rosenberg, J., & Jacobs, I. (2016). A clinician's guide to biosimilars in oncology. *Cancer Treatment Reviews*, *46*, 73-79. doi: 10.1016/j.ctrv.2016.04.003
15. Weise, M., Bielsky, M., De Smet, K., Ehmann, F., Ekman, N., & Narayanan, G. et al. (2011). Biosimilars—why terminology matters. *Nature Biotechnology*, *29*(8), 690-693. doi: 10.1038/nbt.1936
16. Wendy, M. (2021). *Biosimilar vs Biobetter – a two-horse race? White Paper* [Ebook].
17. Biosimilars. (2021). Retrieved 18 October 2021, from https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/biosimilars
18. Brumano, L., da Silva, F., Costa-Silva, T., Apolinário, A., Santos, J., & Kleingesinds, E. et al. (2019). Development of L-Asparaginase Biobetters: Current Research Status and Review of the Desirable Quality Profiles. Frontiers In Bioengineering And Biotechnology, 6. doi: 10.3389/fbioe.2018.00212
19. Dranitsaris, G., Jacobs, I., Kirchhoff, C., Popovian, R., & Shane, L. (2017). Drug tendering: drug supply and shortage implications for the uptake of biosimilars. Clinicoeconomics And Outcomes Research, Volume 9, 573-584. doi: 10.2147/ceor.s140063
20. FDA Purplebook. Retrieved 18 October 2021, from https://purplebooksearch.fda.gov/
21. Giuliani, R., Tabernero, J., Cardoso, F., McGregor, K., Vyas, M., & de Vries, E. (2019). Knowledge and use of biosimilars in oncology: a survey by the European Society for Medical Oncology. ESMO Open, 4(2), e000460. doi: 10.1136/esmoopen-2018-000460
22. Griffith, N., McBride, A., Stevenson, J., & Green, L. (2014). Formulary Selection Criteria for Biosimilars: Considerations for US Health-System Pharmacists. Hospital Pharmacy, 49(9), 813-825. doi: 10.1310/hpj4909-813

23. NCCN. (2021). NCCN Chemotherapy Order Templates (NCCN Templates) Appendix H [Ebook]. Retrieved from https://www.nccn.org/docs/default-source/clinical/order-templates/appendix-h-biosimilars.pdf?sfvrsn=cd742243_2
24. Purple Book: Lists of Licensed Biological Products. (2021). Retrieved 18 October 2021, from https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/purple-book-lists-licensed-biological-products-reference-product-exclusivity-and-biosimilarity-or
25. Stevenson, J., Popovian, R., Jacobs, I., Hurst, S., & Shane, L. (2017). Biosimilars: Practical Considerations for Pharmacists. Annals Of Pharmacotherapy, 51(7), 590-602. doi: 10.1177/1060028017690743
26. Tyler, L., Cole, S., May, J., Millares, M., Valentino, M., Vermeulen, L., & Wilson, A. (2008). ASHP Guidelines on the Pharmacy and Therapeutics Committee and the Formulary System. American Journal Of Health-System Pharmacy, 65(13), 1272-1283. doi: 10.2146/ajhp080086
27. Biosimilars in the EU Information guide for healthcare professionals. (2019). [Ebook]. Retrieved from https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf
28. Chaplin, S. (2017). Biosimilars in the EU: a new guide for health professionals. Prescriber, 28(10), 27-31. doi: 10.1002/psb.1617
29. European Medicines Agency. (2014). Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues [Ebook]. Retrieved from https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active_en-2.pdf
30. FDA Releases Program for Approval of BiosimilarsDOCUMENT: Draft Guidance for Industry from FDA: Scientific Considerations in Demonstrating Biosimilarity to a Reference ProductDOCUMENT: Draft Guidance for Industry from FDA: Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product. (2012). Biotechnology Law Report, 31(2), 142-143. doi: 10.1089/blr.2012.9905
31. Markus, R., Liu, J., Ramchandani, M., Landa, D., Born, T., & Kaur, P. (2017). Developing the Totality of Evidence for Biosimilars: Regulatory Considerations and Building Confidence for the Healthcare Community. Biodrugs, 31(3), 175-187. doi: 10.1007/s40259-017-0218-5
32. Weise, M., Kurki, P., Wolff-Holz, E., Bielsky, M., & Schneider, C. (2014). Biosimilars: the science of extrapolation. Blood, 124(22), 3191-3196. doi: 10.1182/blood-2014-06-583617
33. World Health Organization. (2009). GUIDELINES ON EVALUATION OF SIMILAR BIOTHERAPEUTIC PRODUCTS (SBPs) [Ebook]. Retrieved from https://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf
34. Azevedo, V., Dörner, T., Strohal, R., Isaacs, J., Castañeda-Hernández, G., Gonçalves, J., & McInnes, I. (2017). Biosimilars: considerations for clinical practice. Considerations In Medicine, 1(1), 13-18. doi: 10.1136/conmed-2017-100005
35. Bell, G. (2018). Biobetters vs. Biosimilars: Opportunities, threats & strategic implications. Journal Of Bioequivalence & Bioavailability, 10. doi: 10.4172/0975-0851-c2-035
36. Bittner, B., Richter, W., & Schmidt, J. (2018). Subcutaneous Administration of Biotherapeutics: An Overview of Current Challenges and Opportunities. Biodrugs, 32(5), 425-440. doi: 10.1007/s40259-018-0295-0
37. Cuellar, S., McBride, A., & Medina, P. (2019). Pharmacist perspectives and considerations for implementation of therapeutic oncology biosimilars in practice. American Journal Of Health-System Pharmacy, 76(21), 1725-1738. doi: 10.1093/ajhp/zxz190
38. Dylst, P., Vulto, A., & Simoens, S. (2014). Barriers to the Uptake of Biosimilars and Possible Solutions: A Belgian Case Study. Pharmacoeconomics, 32(7), 681-691. doi: 10.1007/s40273-014-0163-9
39. Final Guidance: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. (2005). Biotechnology Law Report, 24(3), 344-356. doi: 10.1089/blr.2005.24.344
40. Halimi, V., Daci, A., Ancevska Netkovska, K., Suturkova, L., Babar, Z., & Grozdanova, A. (2020). Clinical and Regulatory Concerns of Biosimilars: A Review of Literature. International Journal Of Environmental Research And Public Health, 17(16), 5800. doi: 10.3390/ijerph17165800
41. Khan, M., Aseeri, M., Alshamrani, M., Alnatsheh, A., & Alhamdan, H. (2019). Emerging Role of Biosimilars in Oncology-Hematology in Saudi Arabia: A Practical Perspective. Global Journal On Quality And Safety In Healthcare, 3(1), 22-29. doi: 10.4103/jqsh.jqsh_15_19
42. Nabhan, C., Valley, A., & Feinberg, B. (2018). Barriers to Oncology Biosimilars Uptake in the United States. The Oncologist, 23(11), 1261-1265. doi: 10.1634/theoncologist.2018-0066

43. Tabernero, J., Vyas, M., Giuliani, R., Arnold, D., Cardoso, F., & Casali, P. et al. (2016). Biosimilars: a position paper of the European Society for Medical Oncology, with particular reference to oncology prescribers. ESMO Open, 1(6), e000142. doi: 10.1136/esmoopen-2016-000142
44. Source: Druedahl LC, Kälvemark Sporrong S, Minssen T, Hoogland H, De Bruin ML, et al. (2022) Interchangeability of biosimilars: A study of expert views and visions regarding the science and substitution. PLOS ONE 17(1): e0262537. https://doi.org/10.1371/journal.pone.0262537
45. Biosimilars in the MENA Region: Regulatory Landscape
46. https://www.iapo.org.uk/sites/default/files/files/IAPO%20Quick%20Guide.pdf
47. https://www.fda.gov/drugs/drug-safety-and-availability/drug-safety-communication-fda-warns-about-potential-medication-errors-resulting-confusion-regarding#:~:text=%5B5%2D6%2D2013%5D,Herceptin%20(trastuzumab)%20and%20may%20result