# BIOLOGIC MEDICINES:

## DELIVERING ON THEIR POTENTIAL FOR PATIENTS

A joint research report from the International Association of Patients' Organisations (IAPO) and the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)

# PREFACE

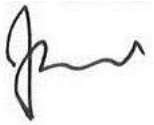
In the last 30 years, biologics have become an important part of modern medicine. Insulin, used by diabetics to regulate blood sugar, was the first modern medicine produced using biotechnological methods. Since then, biologic medicines have benefitted more than 350 million patients worldwide, treating widespread serious illnesses including cancer, heart disease, multiple sclerosis, anaemia, and rheumatoid arthritis.

The introduction of biologics in most practitioners' therapeutic arsenal is arguably one of the most striking medical wonders of recent times. Why? Simply because the impact of these new therapies can be felt in a wide number of disease areas, ranging from infectious diseases, mostly through preventive vaccines, to chronic diseases such as diabetes, cancer, and rheumatoid arthritis to name a few.

Innovation is at the core of finding new treatment for patient. In the case of biologics, it is often the result of painstaking work carried out over a number of years. One cannot completely discard an element of serendipity, but mostly it is the commitment, devotion, and perseverance of scientists that ultimately deliver such innovative solutions. However, we must not overlook the work that has to be done outside the lab in order to ensure patients' safety and well-being. The goal of today's innovation model is to create an ecosystem to provide patients with more lifesaving medicines, faster. To achieve this, the development and implementation of sound and robust science-based regulatory frameworks for such innovative products, including biosimilars, is paramount to achieve safe delivery of these medicines and provide patients and health care professionals with assured quality.

We share the same goal that patients everywhere should be treated with medicines that conform to high quality standards. In particular, we all need to do our part and feed into national pharmacovigilance systems to actively monitor the safety and efficacy of biologics in clinical practice. Furthermore, it is imperative to outline what makes biologics so unique when comparing them to small-molecule medicines.

In this report, we aim to inform patients, global health community and policy makers on this complex and rapidly-evolving field of research. We strive to provide an evidence-based synthesis of what needs to be done to ensure the optimal, safe, and appropriate delivery of biologics to patients around the globe – and help raise awareness among patient organizations, doctors, pharmacists, policymakers, and others of the critical role each of us can play in making this happen.



**Jolanta Bilinska**
Chair, International Alliance of Patients' Organisations

**Thomas Cueni**
Director General, International Federation of Pharmaceutical Manufacturers and Associations

IAPO: The International Alliance of Patients' Organizations (IAPO) is a unique alliance of patients' organizations representing patients from around the world across all disease areas. Our vision is that the needs of patients are at the centre of all healthcare decision-making and, as importantly, that patients have a direct role as partners in all matters from health policy to individual health choices. But to be effective partners, patients must be knowledgeable. To that end, IAPO has been committed not only to producing quality educational materials but also to developing tools and providing training to ensure all patients can effectively engage in policy, advocacy, and informed decision-making.

This document is intended as a basic guide to biological medicines, including biosimilars, for patients, patient advocates and policy makers. It is a successor to IAPO's 2013 Biosimilar Toolkit, designed specifically to introduce patients to what was a relatively new but rapidly growing "category" of medicines known as biosimilars. These are essentially "copies" of biological medicines whose patents had expired. Although there were only a few biosimilars approved at that time, and primarily in Europe for a limited number of conditions, the toolkit was timely because the number and diversity of biosimilars were expected to increase significantly over the coming years. As importantly, biosimilars would be available in non-European countries, including low-and-middle income countries (LMICs) in Latin America, Asia, and Africa. Many of these countries were looking to biosimilars, because of their lower cost, as a means to making biologics available to their patients.

Our IAPO membership has grown to nearly 300 patients' organizations in 70 countries, many of which are classified as LMICs. We are encouraged by the health policy in many of these countries that are striving to address the goals of universal health coverage and essential medicines. Given their effectiveness, biological medicines should be a part of these programmes and biosimilars may help to make them accessible. However, many LMICs also had limited experience with the regulation of the originator biologics and limited healthcare infrastructure for monitoring and follow-up. Knowledgeable patients' organizations can play a key role in ensuring that their country develops appropriate infrastructure and adheres to international standards for approving and monitoring all biologics, which are inherently more complex than traditional medicines. They also need internationally benchmarked regulations for biosimilars.

Given this new environment for biological medicines, including biosimilars, IAPO and IFPMA have developed this guide and the accompanying Fact Sheets to provide patients with the information they need to

(1) understand biologics and biosimilars;

(2) know how biologics and biosimilars should be evaluated and monitored by their regulatory authority;

(3) know the requirements for their safe use (including follow up on adverse effects); and

(4) participate in an informed decision on use of biologics, including biosimilars.

International Alliance of Patients' Organizations
A global voice for patients

IFPMA: IFPMA represents the research-based biopharmaceutical companies and associations across the globe. Our industry's 2 million employees discover, develop, and deliver medicines and vaccines that improve the life of patients worldwide. Based in Geneva, IFPMA has official relations with the United Nations and contributes industry expertise to help the global health community find solutions that improve global health. At IFPMA we advocate policies and practices that encourage the discovery of and access to life-saving and life-enhancing medicines and vaccines for people everywhere. In the biotherapeutic field, biologic medicines are particularly difficult to manufacture because they are made using living organisms, which are more sensitive to change than the straightforward chemical synthesis process commonly used for small molecule medicines. The high complexity of this process requires precision, conformity with good manufacturing practices, and defined specifications in order to maintain the safety and efficacy of the product over time. Science-based guidelines provide clear direction for the development, manufacture, and supply of biologic medicines. They help to assure that treatments are safe, effective, and of quality. What's more, they provide a common platform to help regulators and industry alike to build shared understanding of what quality means and how to achieve it. This is why we advocate for strong regulatory systems so that people around the world have timely access to treatments that are of quality, effective, and safe. To make regulatory systems work more efficiently, we are committed to work through broad stakeholder engagement, including patient groups, policy makers, and science-based regulatory frameworks.

IFPMA
International Federation of Pharmaceutical Manufacturers & Associations

# INTRODUCTION

## WHO ARE THE AUTHORS OF THIS REPORT?

This report has been authored by the Institute for Optimizing Health Outcomes, Canada's multidisciplinary collaboration for patient-centered programs, education, research and advocacy for all persons living with health conditions and commissioned by the International Alliance of Patients' Organizations (IAPO), the global alliance representing patients of all nations across all disease areas, in collaboration with the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), representing research-based biopharmaceutical companies, and regional and national associations across the world.

## WHAT ARE THE SOURCES OF INFORMATION DISCUSSED IN THIS REPORT?

The report is based on a review of the existing literature and previous publications from IFPMA[1 2 3] and IAPO,[4] including the IAPO Biosimilars Toolkit.[4] It also draws from interviews with representatives from patient organisations, biopharmaceutical industry and regulatory authorities in nine LMICs. **The Health Policy Partnership** undertook this review of the literature and conducted the interviews.

## WHY IS THIS REPORT ON BIOLOGIC MEDICINES IMPORTANT?

A biologic medicine (also known as a biologic) is any medicine made using a living organism. While biologics such as insulin and vaccines have been in use for decades, most modern biologics are made using recombinant DNA technology, a series of processes used to combine or rejoin DNA sequences. They are increasingly important in the treatment of serious, debilitating, and life-threatening diseases including cancers, rheumatoid arthritis, and rare diseases. Biologics are different from traditional chemically-synthesized drugs. They are larger and more complex molecules and because they are made from living organisms, they are inherently more variable. They require a different regulatory process to ensure they are safe and effective.

# INTRODUCTION TO BIOLOGICS

## HOW DO BIOLOGIC MEDICINES WORK?

Biologic medicines work differently from traditional chemically synthesized medicines. The latter tend to treat the symptoms of a disease while biologic medicines change the way in which your body works to prevent, slow down, or stop the disease. Rheumatoid arthritis provides a good example. The first generation of chemically synthesized drugs includes painkillers, non-steroidal anti- inflammatory drugs (NSAID) and steroids that reduce pain and swelling of inflammation. The next advancements were the conventional disease-modifying anti-rheumatic drugs (DMARDs) that prevent joint damage by suppressing the immune system. The biologic DMARDs are bio-engineered to target specific proteins in the body that increase inflammation and work more quickly and more effectively.[5]

Traditionally in cancer treatment, chemotherapy drugs are used to kill cancer cells and sometimes other rapidly dividing cells. One type of biologic therapy for cancer is immunotherapy, which uses biologic medicines to stimulate the body's immune system to act against cancer cells. There is also a growing number of targeted cancer immunotherapies that block spread of cancer by interfering with specific molecules that are involved in the growth and progression of the disease.

Examples of biologic medicines include:

- Blood-derived products such as clotting factors and animal-derived products such as the anticoagulant heparin and vaccines.
- Different types of recombinant proteins such as: Insulin, epoetin (erythropoeitin) and follicle stimulating hormone (FSH); Imiglucerase, agalsidase, and other enzymes that 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.

For the purpose of this review, we will refer to biologics as the latter, using the term "Biologic" or Biologic Medicine" to refer to all biologically active protein products prepared by recombinant DNA technology which are used in the treatment of human diseases.

# HOW ARE BIOLOGICS DIFFERENT FROM CHEMICALLY SYNTHESIZED MEDICINES?

The following are the key areas of differences between biologics and chemically synthesized drugs or alternatively known as small molecule medicines.

## Synthesis

Biologics are made using living organisms whereas small-molecule medicines are made by chemical synthesis

## Size and structure

Biologics are large and complex protein molecular structures, whereas chemically synthesized medicines are typically small molecules. **For scale, a monoclonal antibody is approximately 25,000 times the size of ibuprofen.**

## Manufacturing

Biologics are made from living organisms, and the final product depends on the genetic sequence that was cloned but also the manufacturing process, in which slight variations may be introduced. In contrast, all copies of a small molecule drug are identical.

## Characterisation

Due in part to their large size and complexity, it may be difficult to anticipate the effect of a biologic in any specific individual. In contrast, it is relatively easy to use analytical methods to define the active pharmaceutical ingredient and thereby predict the clinical effect of a chemically synthesized drug.

## Stability

Compared to small molecule medicines, biologics are much more sensitive to handling and storage conditions during manufacturing and distribution because they are made from living organisms and are larger in size.

## Immunogenicity

**Compared to small molecule medicines, biologics are more likely to cause an immune response because of their complex structure and unique product characteristics due to their biological nature.**

# HOW ARE BIOLOGICS APPROVED AND MONITORED FOR SAFETY AND EFFICACY?

Biologics are a relatively new and evolving category of medicines, and many regulatory authorities are gaining experience on the approval process. Drawing upon the accumulated collective experience with biologics, the World Health Organization {WHO} has established, in consultation with experts, global regulatory guidelines that define minimum requirements for the approval of all biologic medicines.[5 6 7 8 9]

Key components are:

Manufacturing Process: ensuring consistent quality by controlling the manufacturing process. This requires systematically controlling the genetic consistency[7] and minimising the level of genetic impurities[6] of the cells reprogrammed to produce biologics; and systematically preventing or minimising the occurrence of biotoxins or viral contamination.[7] Proper monitoring, quality control and removal procedures are therefore needed throughout the manufacturing and development process.[5]

Clinical Studies: rigorous clinical studies in patients to demonstrate safety and efficacy. Beyond pre-clinical trials in cell cultures (*in vitro* studies), animals (*in vivo* studies) and clinical trials with healthy volunteers, all biologics must undergo clinical trials with patients who have the targeted disease or condition.[5]

Pharmacovigilance: post-approval monitoring of safety and efficacy of all biologics prescribed to patients in “real-world” clinical practice, also known as pharmacovigilance. Processes and systems for routinely collecting and analysing the use of biologics, beneficial outcomes, and adverse effects (defined as a response which is noxious and unintended, including lack of efficacy) are essential to ensuring the safe and effective use of biologics.

# INTRODUCTION TO BIOSIMILARS

## WHY ARE BIOSIMILAR MEDICINES IMPORTANT?

As a class, biologic medicines are generally more expensive than chemically synthesized drugs , due in part to the greater complexity in the development and manufacturing processes. As patents expire on the older biologics, manufacturers are permitted to produce "copies", which are not exact duplicates, but are "highly similar" to the "originator" biologics. These biosimilar medicines may offer a less-costly alternative to the originator or reference biologic due to reduced development costs. The availability of biosimilar medicines may increase patient access to biologics and allow resources to be directed toward the research and introduction of new innovative medicines.

## WHY ARE BIOSIMILARS NOT CONSIDERED IDENTICAL TO THE ORIGINATOR BIOLOGICS?

Traditional chemically synthesized drugs are small molecules. Generic copies are considered to be identical to the originators and have the same active pharmaceutical ingredients and work exactly the same way. Biologics are made from living organisms are much more sensitive to manufacturing conditions, thereby potentially leading to inherent variations.

There are several reasons why biosimilars are considered similar but not identical to the originator or reference biologic.[10]

1. Biologics are large, complex molecules and highly sensitive to changes in the manufacturing process. The structural blocks (amino acids) that makeup the originator biologic and the biosimilar are the same, but the way these blocks fold themselves into specific spatial conformations, might differ, so the final product is not an exact copy of the originator.

2. Upon patent expiry, biosimilar manufacturers have access to the final molecule for the active ingredient in the originator biologic product but they do not have access to the manufacturing process, which includes the original DNA-genetic molecule clone and original cell bank, the exact fermentation and purification process, and the active drug starting material.

## WHAT ARE ESSENTIAL SIMILARITIES BETWEEN A BIOSIMILAR AND ITS REFERENCE BIOLOGIC?

A biosimilar must have essentially the same biologic activity (effect on cells, tissues or organs), therapeutic efficacy, and safety profile (adverse events) **as the original biologic**. Biosimilars generally have the same strength and are used at the same dose, to treat the same medical conditions (although not all of the originator's medical conditions may be extended to the biosimilar) and usually have the same route of administration as the reference biologic.

Chemically synthesized drugs are small molecule medicines made by combining chemicals in a very discreet and stepwise manner. When the patent on a chemically synthesized drug expires, manufacturers are allowed to make generic copies, which are considered to be identical to the originator.[10]

This means the national drug regulatory authority (DRA) has found them to be the same in terms of:

- Active pharmaceutical ingredient
- Strength
- Use and effect
- Route of administration: how they are taken (for example as a pill, inhaler, or liquid)
- Bioavailability or bioequivalence: ability to reach the required level in the bloodstream at the right time and to the same extent with the same effect
- Testing standards.

# REGULATORY GUIDELINES FOR BIOSIMILARS

For all medicines, it is critical to adhere to high regulatory standards for manufacturing and clinical development. This is particularly true for biologicals and biosimilars. As they are derived from living organisms, rather than chemical synthesis, specific steps and precautions are needed in their manufacturing, development and delivery. These are clearly outlined in regulatory standards – most notably in the WHO guidelines – and adherence to these standards is a necessary step to allow more patients to benefit from the promise of biologicals and biosimilars across the globe. What's more, patients, doctors, pharmacists, regulatory agencies, and industries need to be more aware and engaged in the development and implementation of regulatory standards, to ensure best practices across the health care system.

## WHY IS REGULATORY APPROVAL OF BIOSIMILARS DIFFERENT FROM APPROVAL OF GENERICS?

Biologics are sensitive to variations in the manufacturing process and the starting materials. A biosimilar will never be an exact copy of the reference biologic as explained earlier. To be approved as a biosimilar, products must demonstrate high similarity to the reference biologic in manufacturing quality, biologic activity, clinical safety and efficacy, and in the rate of immune reactions. Specific clinical studies are required to demonstrate this equivalence.

The European Medicines Agency (EMA) developed the first biosimilar guidelines in 2005. In 2009, WHO developed a set of global (non-country specific) guidelines for similar biotherapeutic products (SBPs) (more commonly known as biosimilars) to assist and ensure local regulatory authorities adhere to international standards. WHO guidelines set out basic principles considered mandatory to assure safety, efficacy, and quality of biosimilars.

A synopsis of these principles follows:

Reference product: The reference product (RBP) is the originator product, which should be licensed based on full quality, safety, and efficacy data and should be authorized in the country or region in question. Wherever it may not be feasible, such as countries lacking nationally licensed RBPs, additional criteria (such as the product should be licensed and widely marketed in another jurisdiction with robust regulatory review processes) may be applied.

Quality: All aspects of quality and heterogeneity should be assessed, including head-to-head comparisons with the reference product (most often the commercial product).

Nonclinical data: Data should include pharmacodynamics (PD), pharmacokinetics (PK), and comparative repeat-dose toxicity studies in a relevant species. The pharmacokinetics of the biosimilar and RBP are compared in terms of absorption, bioavailability, and elimination characteristics. Clinically relevant pharmacodynamics (PD) markers should be selected and may be investigated in the context of combined PK/PD studies.

Clinical studies: Similarity of the efficacy of the biosimilar and the RBP will usually have to be demonstrated in adequately powered, randomized, and controlled clinical trial(s). Immunogenicity should always be investigated in humans before authorization. Efficacy trials with biosimilars are not designed to determine whether the medicine works but whether there are any clinically meaningful differences between the biosimilar and the RBP.

Pharmacovigilance: Drug safety monitoring, or a pharmacovigilance plan, at the post-marketing phase is included in the guideline to supplement the limited clinical data that is present during marketing authorization. In some cases an associated risk management plan is also advised.

While the definition of biosimilar and specific regulatory pathway varies across jurisdictions, most well established regulatory authorities (EMA, Health Canada, US FDA, Japan, Korea) incorporate these principles. In these settings, the approval process is tailored for biologic medicines, and the final conclusion on biosimilarity is based on the totality of evidence provided.

Regardless of the regulator, the comparability exercise involves three steps implemented hierarchically:

1. Analytical comparability, based on physical chemical structure and biologic activity.
2. Pre-clinical comparability, based on studies in cell cultures (*in vitro*) and in animals (*in vivo*).
3. Clinical comparability, based on how the biosimilar performs in clinical trial settings in patients with the appropriate condition, including how the biosimilar is absorbed and broken down in the body, how it works and the beneficial outcomes and potentially harmful effects.

## WHY ARE INTERNATIONAL GUIDELINES FOR REGULATION OF **BIOLOGIC MEDICINES** IMPORTANT?

Biologic medicines are increasingly important for diagnosing, managing, treating, and preventing many types of diseases. They will also be increasingly available in many countries, especially as older biologics come off patent and biosimilars are introduced. The WHO, in acknowledging that "growing numbers of countries are building the necessary scientific expertise to facilitate development of solid, scientifically-based regulatory frameworks that promote access to biologic products that are affordable, safe, efficacious, and of quality," also recommends "taking note of the relevant WHO quality standards that may be adapted to the national context and capacity."[11]

> **It is very important that regulatory authorities, also in low-and-middle-income countries, follow internationally benchmarked regulatory guidelines and gain expertise in the evaluation of originator biologics, for the development of standardized guidelines for evaluating biosimilars.**

Countries may also choose to participate in cross-border collaborations that allow them to pool resources and expertise. Examples of such cross-border initiatives include the International Pharmaceutical Regulators Forum, the ASEAN Common Technical Dossier (ACTD) and the African Medicines Regulatory Harmonization Programme.

## WHY ARE INTERNATIONAL GUIDELINES FOR REGULATION OF **BIOSIMILARS** IMPORTANT?

Biosimilars require less investment to develop and can be expected to be available at lower cost than the originator biologics. They may be more accessible to patients in emerging markets and especially attractive to lower income countries. **However, several examples of the risks of introducing biosimilars without rigorous regulatory guidelines have reinforced the need for adherence to international guidelines in evaluation.**

See **FACT SHEET: Biosimilars and the Importance of Adherence to International Regulatory Standards**

As importantly, the WHO regulatory guidelines for biosimilars identify requirements beyond the evaluation process to assure their safe and effective use. **The main principles and difference with generics are as follow.**

Clinical evaluation: Approval of biosimilars is based on clinical evidence, ideally from head-to-head trials with target patients, demonstrating a highly similar level of clinical benefit and safety compared to their RBP. Generics do not require clinical trial evidence, as the active ingredients are identical to their reference medicine.

Immunogenicity testing: Specific testing is needed in patients during the development of biosimilars to ensure that they do not cause any severe immune reactions. This level of testing is not required from generics as they are not produced from living organisms, and unlikely to elicit immune reactions.

Pharmacovigilance: The specific characteristics of such complex products' immunogenic potential requires more emphasis on PV monitoring in comparison to generics. Individual patients must be closely monitored to identify desired beneficial outcomes as well as adverse effects. Additionally, there should be systems to record and analyze collected information to capture how biosimilars are working in all types of patients in real-world settings.

Traceability of biosimilars: Ideally, each biosimilar should be clearly identified with a unique brand name, international non-proprietary name (INN), and batch number. This allows patients and health professionals to clearly know exactly which medicine they are receiving and will be increasingly important as more than one biosimilar is developed to the same reference biologic. In contrast, generics generally do not have unique brand names and share the same INN as their reference product, but should be traceable via batch number and name of manufacturer.

Recently the International Pharmaceutical Regulators Forum published the Template for Public Assessment Summary Information for Biosimilar (PASIB) following the good practice established with leading agencies like the EMA, the US Food and Drug Administration, Health Canada and many others, recommending its implementation to regulatory agencies. The proposed PASIB is intended to increase transparency on regulatory decision making for the approval of biosimilar products and to facilitate the transition from a local assessment report to one prepared in the English language that can be shared with other agencies.

The initiative proposed by IPRF promotes a common template enhancing alignment in communication and a harmonized approach on how to present the information and should encourage NRAs who do not currently publish their reviews to engage in this initiative.

# CHALLENGES IN THE USE OF BIOSIMILARS

## WHY IS PHARMACOVIGILANCE VITAL TO THE SAFE AND EFFECTIVE USE OF BIOLOGICS?

In evaluating a drug or medicine, regulators must balance the benefits against any potential harm. Not all of the potential positive or negative effects of a drug, especially a biologic, can be known prior to the time of market authorization. That is the primary reason why systems and procedures to monitor drug safety are essential to assure safe and appropriate use of biologic medicines. Traditionally, pharmacovigilance was mostly concerned with collecting data on adverse drug reactions (ADRs) but in an era where many highly innovative products that address serious unmet needs are coming to market with minimum clinical trial data, pharmacovigilance (post-market monitoring program) is essential to collect both beneficial and adverse outcomes when given to diverse populations in "real world" clinical settings.[12]

## WHY MIGHT PHARMACOVIGILANCE BE CHALLENGING WITH BIOSIMILARS?

In order to trace reported ADRs back to a specific biologic, it is important that each prescribed drug has a product-specific identifier. For biologics, the WHO guidelines recommend that each biologic be prescribed not only with the International Non-proprietary Name (INN) but also with the brand name and batch number to improve traceability to a specific biologic.[13] In practice, medicines are often prescribed and dispensed only by their non-proprietary names. A further challenge for biosimilars is that there is no agreement on an internationally consistent naming system for biosimilars.

## CAN BIOSIMILARS BE APPROVED FOR THE SAME CONDITIONS AS THE ORIGINATOR BIOLOGICS, WITHOUT CLINICAL TRIALS ON ALL INDICATIONS?

An originator biologic may be approved for multiple diseases or conditions. Manufacturers usually conduct clinical trials with the target patients for each condition. In contrast, a biosimilar manufacturer may request approval for conditions already approved for the originator biologic without necessarily demonstrating equivalence through clinical trials in each condition. This process of indication extrapolation is determined on a "case-by-case" basis and is based on a number of criteria, including the sensitivity of the patient population tested, the clinical outcomes used in the trials, the similarity in underlying cause across conditions, and similarity in how the drug works in each condition. In some cases a biosimilar might not be granted approval for all the conditions attached to the originator.

## HOW SHOULD SWITCHING FROM AN ORIGINATOR BIOLOGIC TO A BIOSIMILAR BE MANAGED?

The decision to switch from an originator to a biosimilar or between biosimilars should be a medical decision, and as such, the role of the physician in the decision to prescribe a biosimilar is essential. The benefits and risks of switching between an originator to a biosimilar or between biosimilars may vary by disease, severity and stage, therapeutic intent, potential impact of immunogenicity, the availability of alternatives, and other considerations unique to a specific clinical setting or patient. For instance, the benefits and risks of switching may vary between a patient taking a biologic for rheumatoid arthritis (RA) and a patient taking a biologic for metastatic breast cancer, or between an RA patient who may have other conditions, and/or be on other therapies, or whose disease is well managed with a current biologic versus an RA patient experiencing a relapse of disease. The benefits and risks to the patient should be carefully assessed by the prescribing physician, and decisions to switch patients should be informed by clinical practice on a case-by-case basis unique to each patient.

For these reasons, it is important that physicians maintain the freedom to prescribe the medicine they deem appropriate in consultation with the patient. Therefore, procurement practices should allow the physician to choose what medicine to prescribe in consultation with a patient (whether an originator or a biosimilar), based on what is in the best interest of the patient. Practices such as "winner take all" tenders do not maintain this flexibility, and can result in "forced switching", which effectively removes the prescribing choice from the physician. This practice is not in the best interests of the patient because, as noted above, switching should take into account patient history, e.g. the number of previous switches, the patient's other medications and/or other conditions, and the therapeutic options available, and only the prescriber can do this.

For this reason, physician organizations that represent specialties that use biologics should consider development of recommendations for the use of biosimilars in common clinical scenarios.

## WHAT IS "AUTOMATIC SUBSTITUTION" AND HOW DOES IT RELATE TO INTERCHANGEABILITY?

Automatic substitution is the substitution of a product by the pharmacy without the prescribing physician's consent. Most European countries deem such substitution to be inappropriate for biosimilars due to their complex nature, (i.e they are not generics). In the US, the term interchangeability is defined by law to mean a biosimilar can be substituted, by a pharmacist, without the intervention of the prescribing physician because it has been specifically assessed to be safe for that purpose by the regulatory authority.[a] A legal designation of interchangeability requires that the product meets an additional standard beyond biosimilarity.[b]

As of 2017, only the US has this unique regulatory framework, which requires rigorous scientific evidence beyond the demonstration of biosimilarity, to safeguard patients and enable automatic substitution. In countries outside of the US where no formal scientific framework exists, automatic substitution is not appropriate and only a physician, in consultation with the patient, should make the decision as to which medical product should be prescribed and dispensed.

## WHAT IS THE ROLE OF HEALTHCARE PROFESSIONALS IN HELPING PATIENTS MAKE AN INFORMED DECISION ABOUT THE USE OF BIOLOGICS AND BIOSIMILARS?

Patients seek information about treatment options from a variety sources; however, most say they rely on their physician (healthcare provider) when making a treatment decision. This is also true with respect to biosimilars, whereby a majority of patients report learning about biosimilars from the Internet, but they would accept a biosimilar if it were recommended by their doctor. Nevertheless, when asked about switching from their current biologic to a biosimilar, most respond that they would not want to switch.

This may be especially problematic in LMICs where there has been limited up-to-date information and training on the use of biologics, including biosimilars. In settings where biologics are newly introduced, it would be important to introduce these medicines with appropriate education and support for healthcare professionals (both physicians and pharmacists) as well as the appropriate monitoring systems.

a) When permitted by State Law.

b) This requires that the biosimilar (1) is expected to have the same clinical result in any given patient, and (2) for products administered more than once, the risk to the patient in terms of safety or diminished efficacy of alternating or switching between use of the originator product and the biosimilar is no greater than the risk of using the originator product without such alternation or switch. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/ucm216146.pdf

# CONCLUSION

Biologics have the potential to benefit millions of patients worldwide – across a large number of conditions. However, because of their unique characteristics, complexity and biological nature, **it is essential that all countries develop appropriate regulatory guidelines and the necessary expertise to assure their safety, efficacy, and quality.** As patents expire on older biologics, manufacturers are allowed to develop biosimilars, which are not identical to the originator biologics but are demonstrated through comparison clinical trials to achieve comparable effects in target patients. Biosimilars are expected to be available at lower cost and therefore more accessible especially in lower income countries. However, **it is paramount that all regulatory authorities adhere to international guidelines for their evaluation.** In addition, appropriate use of biosimilars requires post-approval monitoring with pharmacovigilance systems that systematically collect and analyse data. Biosimilars are not considered interchangeable with the originator biologic and there is limited, yet growing data on the effect of switching patients from their originator biologic to a biosimilar.

# GLOSSARY

## Bioequivalence

Two medicines are considered to be bioequivalent when equivalent bioavailability has been demonstrated (the rate and extent of the active substance which is absorbed from the medicine and becomes available in the systemic circulation).

## Biological Medicine

All biologically active protein products prepared by recombinant DNA technology which are used in the treatment of human diseases.

## Biosimilar

A biological medicine that is highly similar to another biological medicine which already has a marketing authorisation and has been approved for use in patients (reference medicinal product). Biosimilars contain a version of the active substance of an already approved medicine.

## Biosimilar Comparability Exercise

A comprehensive series of comparability tests and studies submitted to the regulatory authority which establishes that a medicine can be approved as a biosimilar. These tests must demonstrate that a biosimilar exhibits comparable quality, safety, and efficacy to the reference medicine. For quality comparability testing, a series of physiochemical and biological tests are carried out on the biosimilar and reference medicine to demonstrate similarity on a structural and biological level. Clinical comparability studies normally include clinical trial(s) demonstrating equivalent efficacy between the two medicines.

## Centralised Procedure

The European Union-wide procedure for the authorisation of medicines, where there is a single application and a single evaluation resulting in a single authorisation throughout the European Union including the European Economic Area (EEA).

## EMA

The European Medicines Agency, the agency responsible for the scientific evaluation of applications for European Union (EU) marketing authorisations for medicines in the centralised procedure.

## Generic Medicine

A medicinal product (usually a chemically synthesised small molecule) which has the same qualitative and quantitative composition as a reference medicine. Generic medicines must demonstrate bioequivalence with the reference product.

## Indication Extrapolation

Required to demonstrate efficacy in all indications. When a biosimilar has been shown to have comparable performance in a sensitive patient population, it may then be approved in some or all of the indications approved for the reference product, without the need for further clinical comparability trials. For extrapolation to be acceptable, the medicine must have the same mechanism of action in each indication and extrapolation is only approved by regulatory authorities on a case by case basis, taking into account the justification provided.

## International Non-Propriety Name (INN)

The INN is a unique name given to an active substance which is globally recognised 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 Organisation (WHO).

## Marketing Authorisation

A licence granted by a regulatory authority (for example, the EMA) which allows a company to market a medicine.

## Market Exclusivity

Companies which produce a reference biological medicine are granted a period of market exclusivity (typically 10 years from the first date of authorisation). It is only once this period has expired that other manufacturers may market their authorised biosimilar medicinal product.

## Reference Medicine

A medicine which has already been authorised within the EU and is used as the basis for a generic or biosimilar medicine. The reference medicine must be at the end of its data exclusivity period before a generic or biosimilar version can be marketed.

## Substitution

Practice of dispensing one medicine instead of another equivalent and interchangeable medicine at pharmacy level without consulting the prescriber.

## Switching

Decision by the treating physician to exchange one medicine for another medicine with the same therapeutic intent in patients who are undergoing treatment.

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IFPMA International Federation of Pharmaceutical Manufacturers & Associations

International Federation of Pharmaceutical Manufacturers & Associations

Chemin des Mines 9
P.O. BOX 195
1211 Geneva 20
Switzerland

International Alliance of Patients' Organizations
A global voice for patients

International Alliance of Patients' Organizations

CAN Mezzanine
49-51 East Road London
N1 6AH
United Kingdom