International Federation
of Pharmaceutical
Manufacturers & Associations

Biotherapeutic Medicines

Grasping the New Generation of Treatments

IFPMA

Biotherapeutic medicines are an integral and valuable part of modern medicine for the treatment and prevention of serious illnesses and diseases

What are biotherapeutic medicines?

Biotherapeutic medicines are derived from proteins and other substances produced by living organisms, such as mammalian cells, viruses and bacteria. With a unique and diverse range of specific targets, biotherapeutic medicines open new avenues for delivering cutting-edge treatments for numerous diseases and wide patient populations.

Biotherapeutic medicines are unique

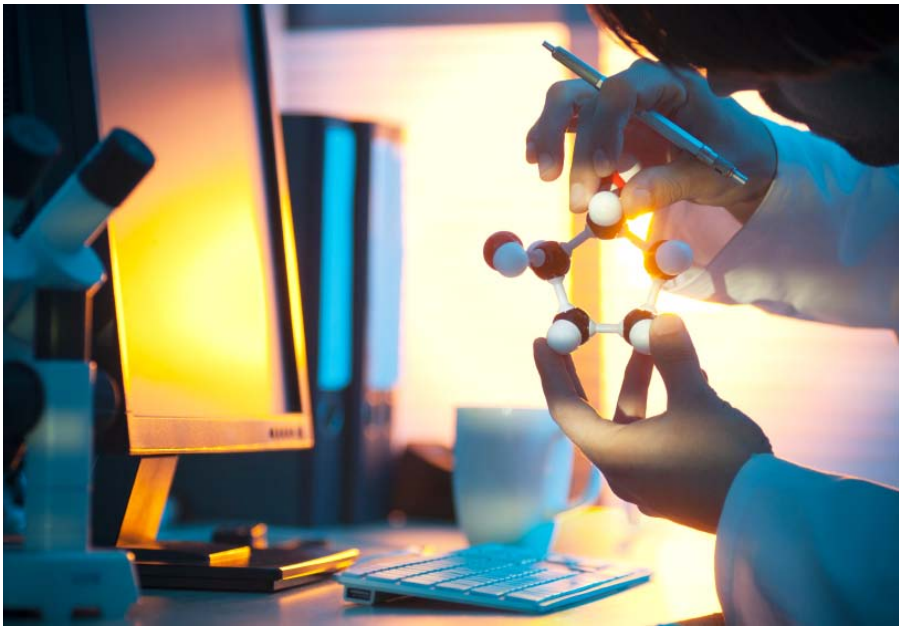
Biotherapeutic medicines[1] are made using living systems, which are more sensitive to change than the straightforward chemical synthesis process commonly used for small molecule medicines. The end product is therefore determined by a wide range of factors, which include the actual manufacturing process. Small changes in manufacturing can alter the final product, as biotherapeutic medicines are composed of larger and more complex molecules which are difficult to characterize. The high complexity of this process requires precision, conformance to good manufacturing practices and defined specifications in order to maintain the safety and efficacy of the product over time. Approximately 250 in-process tests are carried out for a biotherapeutic medicine, compared to around the 50 done for a chemically-synthesized small molecule medicine[2].

Understanding the differences

Biotherapeutic and chemically-synthesized small molecule medicines

Biotherapeutic Medicines: Medicines whose active ingredients are or are derived from proteins (such as growth hormone, insulin, antibodies) and other substances produced by living organisms (such as cells, viruses and bacteria). They are larger and more complex than chemically-synthesized medicines and their characteristics and properties are typically dependent on the manufacturing process itself.

Chemically-synthesized small molecule medicines: Medicines produced through a step-by-step chemical synthesis process. They are characterized by a small molecule composition and are relatively simple organic compounds containing few functional molecular groups.



[1] Biotherapeutic medicines can also be referred to as biologics, biological medicines and biopharmaceuticals.

[2] "Guide to Biological Medicines", EuropaBio. Available at: http://www.europabio.org/sites/default/files/report/guide_to_biological_medicines_a_focus_on_biosimilar_medicines.pdf

Why biotherapeutic medicines matter

More than 350 million patients worldwide are leading healthier lives thanks to biotherpeutic medicines

Lives touched: Biotherapeutic medicines benefit more than 350 million patients worldwide[3], treating widespread diseases such as cancer and diabetes, as well as rare illnesses. Being similar in structure to molecules naturally-produced in the human body, biotherapeutic medicines have great therapeutic impact in many disease areas and can additionally serve to diagnose other diseases. They have moreover proven to be effective in the treatment of conditions that had not been positively addressed by chemically-synthesized small molecule medicines. Over the past 30 years, medical advances in biotherapeutic medicines have focused on treating many chronic diseases – including cancer, diabetes, hepatitis C, and chronic renal failure – as well as less common ones such as hemophilia, Fabry's disease, growth deficiency, multiple sclerosis and Crohn's disease[4].

Tangible benefits: Many patients are leading healthier lives as a result of biotherapeutic medicines, often without realizing the source of these products. Until the 1980s, insulin extracted from animals was used to treat diabetes. In 1982, researchers produced human insulin of superior quality by recombinant DNA technology using a culture of *E. coli* bacteria. This became the first approved biotherapeutic product. Human insulin benefits today the vast majority of diabetic patients who require insulin treatment.

- ***Biotherapeutic medicines & cancer*** - Major strides in fighting cancer successfully go hand in hand with improved diagnostics, treatments and prevention methods. Biotherapeutic medicines play a role in the discovery and development of biomarkers[5]. Today, biomarkers help in predicting the risk of cancer, diagnosing it, and indicating a potential effective course of treatment.
- ***Biotherapeutic medicines & autoimmune diseases*** - If left untreated autoimmune diseases such as Crohn's disease and rheumatoid arthritis can lead to early mortality. Biotherapeutic medicines have proved successful and have had a highly positive impact in the treatment of these diseases.

[3] "Guide to Biological Medicines", EuropaBio. Available at: http://www.europabio.org/sites/default/files/report/guide_to_biological_medicines_a_focus_on_biosimilar_medicines.pdf

[4] "What are biopharmaceuticals?" http://www.ebe-biopharma.org/index.php?option=com_content&task=view&id=26&Itemid=102

[5] A biomarker is a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease

Examples of available biotherapeutic products

Biotherapeutic Class	Diseases and Conditions Treated
Anti-CD20	Cancer, rheumatoid arthritis
Anti-HER2	Cancer
Anti-TNFs	Rheumatoid arthritis, psoriasis, Crohn's disease, ulcerative colitis
Vascular endothelial growth factor (Anti-VEGF)	Cancer, macular degeneration
Bone Morphogenic Protein-7	Bone repair
Consensus Interferon	Hepatitis C
Erythropoietin (EPO)	Chronic anemia
Follicle-Stimulating Hormone (FSH)	Infertility
Glucagon	Hypoglycemia
Granulocyte Colony-Stimulating Factor	Cancer, neutropenia
Granulocyte-Macrophage Colony-Stimulating Factor	Cancer, bone marrow transplantation
Human Chorionic Gonadotropin	Infertility
Human Insulin	Diabetes mellitus
Interleukin-2	Cancer
Anti-Interleukin-6	Rheumatoid arthritis
Interferon α-2a and 2b	Cancer, hepatitis
Interferon- γ -1b	Chronic granulomatous disease, osteoporosis
Interferon β-1b and Interferon β-1a	Multiple sclerosis
Platelet-Derived Growth Factor (PDGF)	Diabetic ulcers

"Similar, but not identical": What are similar biotherapeutic products (SBPs)?

As their name implies, similar biotherapeutic products (SBPs) are "similar" but not identical versions of their innovative biotherapeutic medicine of reference. Whereas producing generic versions of off-patent chemically-synthesized medicines is relatively easy – it involves copying a stable chemically-synthesized molecule with a single identifiable structure – producing an SBP is far more complicated due to the complex molecular structure and the unique manufacturing process required for biotherapeutic medicines.

Indeed, unlike chemically-synthesized medicines, it is impossible for SBPs to be exact copies of the reference innovative biotherapeutic.

Regulating similar biotherapeutic products

Science-based regulatory standards for medicines are essential to ensure patient safety. Because of this – and given the complex nature of biotherapeutic medicines – SBPs require distinct regulatory standards than those applied to generic medicines. Regulatory authorities are increasingly aware of the need for specialized pathways and specific development and evaluation standards to address the unique nature of SBPs. These standards require thorough analytical characterization and quality studies as well as abbreviated pre-clinical and clinical development programs to show high similarity to the reference innovative biotherapeutic medicine in terms of quality, safety and efficacy.

The use of similarity exercises is part of the unique pathway needed to appropriately assess SBPs and to ensure they are comparable to the innovative reference product. In 2005 the European Medicines Agency (EMA)[6] implemented a regulatory framework exclusively for the authorization of SBPs. Furthermore, in 2009 the WHO developed guidelines to serve as a blueprint for countries for the development and evaluation of SBPs[7].

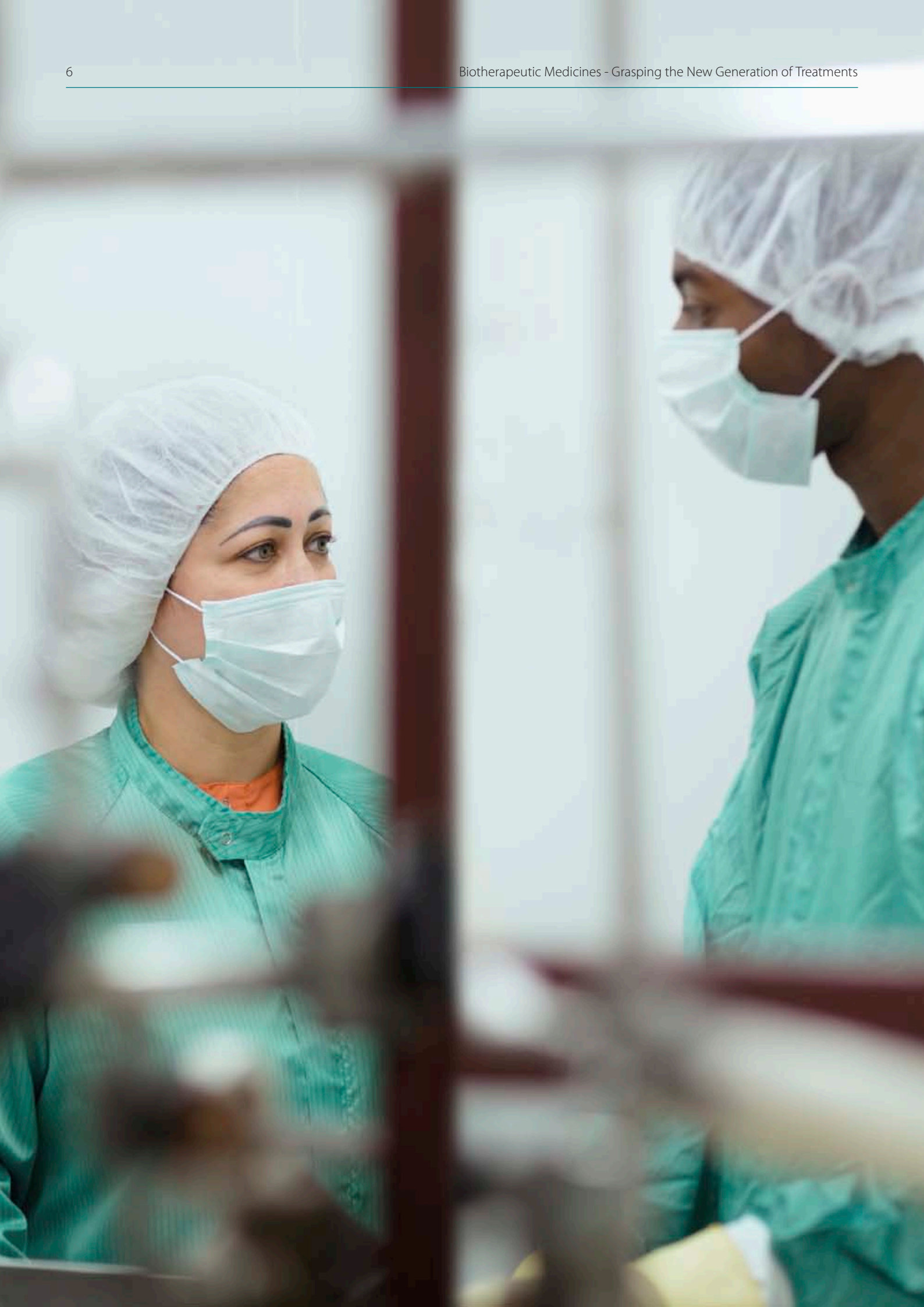
The incorporation of similarity exercises to regulate SBPs is vital to ensure that the quality, safety and efficacy are highly similar to those of the innovator reference product. This risk-assessment process should ensure that there are no clinically meaningful differences with the reference product before the SBP receives marketing authorization, thus minimizing risks to patients. Purported copies of biotherapeutic medicines that have not undergone head-to-head comparisons with an appropriate reference product put patient safety at risk and should not be licensed via biosimilar pathways[9].

Similar Biotherapeutic Products (SBPs) are also referred to as biosimilars, follow-on biologics and subsequent entry biologics.

[6] In 2006 the first SBPs were authorized. Since then additional authorizations have regarded treatments for kidney failure, rare diseases and over 76% of approvals for cancer. The EMA Guidelines are available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf

[7] "Guidelines on evaluation of Similar Biotherapeutic Products (SBPs)", WHO. Available at: http://www.who.int/entity/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf

[8] Source: http://www.ifpma.org/innovation/biotherapeutics.html



Grasping the new generation of treatments

Biotherapeutic medicines are an important and integral component of modern medicine that targets many chronic and acute disease areas with highly-specific treatments. These complex medicines allow both the individual patient, through improved quality of life, and ultimately, society to benefit from their use.

Further research and development into biotherapeutic medicines will continue to expand opportunities to treat an ever increasing number of diseases, and intellectual property rights will remain a crucial incentive for such innovation.

As more SBPs enter the market, national regulations will need to encompass multiple areas, reaching beyond regulatory approval. They will need to address issues such as pharmacovigilance systems[9] for monitoring the use of medicines and the prescription practices of healthcare providers. Effective oversight in all these areas will help to manage risk and maximize benefits for patients.

[9] "Position Paper on Pharmacovigilance Principles for Biotherapeutic Medicines", IFPMA. Available at: http://www.ifpma.org/fileadmin/content/Innovation/Biotherapeutics/Pharmacovigilance_Principles_vF.pdf

Glossary

Active ingredient: The component of a drug that provides medicinal value. Many drugs combine several active ingredients, and the interaction between these ingredients may be critical to the function of the drug.

Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease.

Biotechnology: The collection of processes that involves the use of biological systems. For some industries, these processes involve the use of genetically engineered organisms.

Biotherapeutic medicines: Medicines whose active ingredients are or are derived from proteins (such as growth hormone, insulin, antibodies) and other substances produced by living organisms (such as cells, viruses and bacteria). They are larger and more complex than chemically-synthesized drugs and their characteristics and properties are typically dependent on the manufacturing process itself.

Chemically-synthesized small molecule medicines: Medicines produced through a step-by-step chemical synthesis process. They are characterized by a small molecule composition and are relatively simple organic compounds containing few functional molecular groups.

Generic medicines: Generic medicines are identical to the original chemically-synthesized small molecule medicine in terms of active substance used, dosage, strength, route of administration, safety, efficacy and intended use. A generic can be marketed by anyone after the intellectual property (e.g. patent or data protection) for the original medicine expires.

Monoclonal antibodies (MABs): Discovered in 1972[10], these therapeutic antibodies bind specifically to certain molecules and can prevent them from causing illness. They also guide the body's immune system to help it target agents that can cause illness – including infectious diseases, breast cancer and rheumatoid arthritis.

Similar biotherapeutic products (SBPs): SBPs are similar versions of an already authorised innovative biotherapeutic product, with demonstrated similarity to the latter in quality, efficacy and safety assessed through a direct (or head-to-head) comparison.

[10] César Milstein and Georges Köhler won the Nobel Prize for this notable achievement. Read more at: http://www.nobelprize.org/nobel_prizes/medicine/laureates/1984/

About the IFPMA:

IFPMA represents the research-based pharmaceutical companies and associations across the globe. The research-based pharmaceutical industry's 1.3 million employees research, develop and provide 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.

IFPMA manages global initiatives including: IFPMA Developing World Health Partnerships , which studies and identifies trends for the research-based pharmaceutical industry's long-term partnership programs to improve health in developing countries; IFPMA Code of Practice, which sets standards for ethical promotion of medicines; IFPMA Clinical Trials Portal, which helps patients and health professionals find out about on-going clinical trials and trial results.

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ISBN 978-2-940498-10-9