

Biological medicinal products and similar biological medicinal products - guidelines for understanding of similarities and differences

Biological medicinal product is a medicinal product which contains one or more active substances that are made of or that are derived from biological material. Some of the aforementioned active substances are otherwise found in human body, such as proteins: insulin, growth hormone and erythropoietin. Active substances of biological medicinal products are larger and more complex than active substances in conventional (non-biological) medicinal products. Only living organisms are capable of reproducing such complexity.

Complexity of active substances which are part of biological medicinal products, as well as the manner in which these active substances are manufactured, may lead to occurrence of differences (variability) in active substance molecules, especially in different production lots of medicinal products. Due to this complexity and specificity, biological medicinal products have immunogenic potential, and critical points in their manufacture are selection of expression system, isolation process, purification of formulation (which are related to good manufacturing practice) and critical points in terms of biological medicinal products are also manner and conditions of transport and storage (which are related to good distribution practice).

Biological medicinal products include:

- Blood and plasma derivatives;
- Vaccines;
- Allergens;
- Recombinant human proteins;
- Recombinant monoclonal antibodies;
- Products for cellular and gene therapy.

Beginning of development of biological medicinal product dates from the period 1982-1986, when use of recombinant DNA was initiated. The first biological medicinal products that have been granted a market authorization were growth factor (rHGh), insulin and erythropoietin. Era of recombinant monoclonal antibodies started in 1995.

What is a similar biological medicinal product?

Similar biological medicinal product (also, biosimilar medicine) is a medicinal product of biological origin, that is similar to reference biological medicinal product, but which does not meet the conditions in the definition of generic medicinal products, in terms of differences pertaining to raw materials and differences in manufacturing processes of that similar biological medicinal product and reference medicinal product of biological origin.

Similar biological medicinal products also enable significant cost savings to health care systems and treatment of larger number of patients, since their prices are, in average, 60-75% lower than prices of reference medicinal products of biological origin.

What is the approval process for similar biological medicinal products?

Marketing authorization for similar biological medicinal product is issued on "step by step, case by case" basis. It is necessary to submit complete documentation on quality, documentation with abridged comparative nonclinical studies data and risk management plan for similar biological medicinal product, i.e. to show and prove comparability with reference medicinal product (comparison with reference biological medicinal product for every indication and dosage). So far, all similar biological medicinal products arriving to the European Union market were subject to centralized procedure of marketing

authorization granting, which means that the Committee for Medicinal Products for Human Use (CHMP) and Pharmacovigilance Risk Assessment Committee (PRAC) issued a positive opinion on their quality/efficiency/safety, i.e. a positive opinion on benefit/risk balance. Within its scope of work, CHMP additionally consults with working groups of experts, specialized in the fields of biological medicinal products (Biologics Working Party, BWP) and similar biological medicinal products (Biosimilar Medicines Working Party, BMWP). Assessment of quality/efficiency/safety in European Medicines Agency is being carried out at the highest scientific, technical and regulatory level, which includes experts from all member states of the European Union. Furthermore, all similar biological medicinal products for which the marketing authorization is granted in Bosnia and Herzegovina, have been approved through centralized procedure of marketing authorization granting, which means that scientific and technical assessment of their quality/efficiency/safety was carried out by European Medicines Agency (EMA) and that their marketing authorization was granted by the European Commission.

The manufacturer has an obligation to, with aim to obtain marketing authorization for similar biological medicinal product, carry out comprehensive studies that will prove that similar biological medicinal product is similar to reference biological medicinal product in terms of quality/efficiency/safety.

Development of similar biological medicinal product starts with comprehensive characterization of physical, chemical and biological properties of active substance and with nonclinical *in vitro* studies, while data obtained through these studies serve to determine the extent and type of nonclinical *in vivo* studies and clinical trials involving humans, which will have to be carried out with aim to prove similarity. Bearing in mind that reference biological medicinal product has been granted a marketing authorization in the European Union for a number of years and that its clinical benefit has already been proven, some of the studies that have been carried out for reference medicinal product do not have to be repeated for the purpose of granting a marketing authorization for similar biological medicinal product. In accordance with the aforementioned reasons, development, extent of studies and data based on which the similar biological medicinal product has been granted a marketing authorization must be reviewed on case-by-case basis.

European Medicines Agency has issued numerous scientific guidelines which ensure observance of standards of quality, efficiency and safety of use of similar biological medicinal products, which are available through the following link: ***European Medicines Agency's scientific guidelines on biosimilar medicines.***

Similar biological medicinal products are manufactured on the basis of equally strict standards as all other medicinal products, which is confirmed by supervisory inspection of manufacturers carried out by regulatory authorities.

Scientific reliability of the approach to granting a marketing authorization for similar biological medicinal product is substantiated by extensive experience on European Union level, which enabled access to numerous good-quality, efficient and safe similar biological medicinal products to the patients, to this day. Information on all similar biological medicinal products, which were granted a marketing authorization through centralized procedure, including the summary of scientific assessment of documentation on medicinal product, may be found through the following link: ***Human Medicines – Biosimilars.***

Is similar biological medicinal product directly interchangeable with the reference biological medicinal product in the treatment of patients?

Unlike relationship between conventional medicinal product/generic medicinal product, in the relationship between biological medicinal product and similar biological medicinal product it is not possible to achieve that degree of “uniformity”.

Direct interchangeability (also known as *direct*, *automatic* or *generic substitution*) is a term that involves substitution of prescribed medical product with its parallel, which does not require consultations and specific monitoring by the treating physician. Direct interchangeability is possible for generic medicinal products only.

Even though the similar biological medicinal product basically exerts the same clinical effects as the reference biological medicinal product, these medicinal products are not directly interchangeable.

Due to their specificity, biological medicinal products may be substituted in the course of therapy of the same patient only in medically justified cases, on the basis of recommendation of prescribing physician, which will monitor this switch to another medicinal product.

Additionally, even if the patient is monitored by the treating physician, it is not recommendable to frequently substitute one medicinal product with another with the same biological active substance in the therapy of an individual patient, since the data on safety and/or efficiency of this manner of use of biological medicinal products, taking into consideration possible increased production of antibodies against medicinal product (immunogenicity of medicinal product with biological active substance) are insufficient. Also, when substituting one medicinal product with another, with both medicinal products containing the same biological active substance, it may be difficult to link delayed adverse effects to the medicinal product that caused them, and if possible differences in administration and preparation of different biological medicinal products are taken into consideration, probability of occurrence of medical errors, as well as decrease in patients' compliance, is higher.

The aforementioned statements pertain to the substitution of:

- one biological medicinal product with another biological medicinal product;
- reference biological medicinal product with similar biological medicinal product;
- similar biological medicinal product with reference biological medicinal product,
- one similar biological medicinal product with another similar biological medicinal product.

In conclusion, every biological medicinal product may be used to treat diseases and conditions for which its marketing authorization has been granted, regardless of whether the medicinal product is reference biological medicinal product or similar biological medicinal product, but the substitution has to be justified, recommended and monitored by the treating physician, while taking into consideration all of the aforementioned facts.

Active post-marketing monitoring of safety of medicinal products is mandatory for all medicinal products, but in case of biological medicinal products, it is necessary to additionally monitor, report and analyze adverse reactions on the level of medicinal product trade name and batch number, in order to enable accuracy in their traceability, due to specific characteristics of biological medicinal products.