**Professor Piotr Wysocki MD, PhD**

Department of Oncology, *Collegium Medicum*, Jagiellonian University, Krakow

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*Biosimilars: a position paper of the European Society for Medical Oncology, with particular reference to oncology prescribers*

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The era of biosimilars in oncology has just arrived. In February 2017, the European Medicines Agency (EMA) registered the first biosimilar for rituximab (Truxima®). In April, two additional biosimilars for rituximab (Rixathon® and Riximyo®) received a positive recommendation from the European Committee for Medicinal Products for Human Use (CHMP). This recommendation is a prerequisite for the registration of these drugs by the EMA, which is expected in June this year.

Monoclonal antibodies introduced into the oncology armamentarium at the end of the 1990s represent a breakthrough in the treatment of many cancers. However, the cost of therapies based on these drugs has significantly limited their widespread use, especially in countries with low expenditure on oncological treatment. For most anticancer drugs, being simplex chemical compounds (chemotherapeutics, hormonal drugs, small molecule kinase inhibitors), the expiry of patent protection was associated with the immediate emergence of generic drugs. This naturally led in a short time to a significant price reduction of original drugs and improved availability of new methods of systemic treatment. The production of generic drugs that are identical copies of the original ones is relatively easy because it is based on the synthesis of simple molecules with low molecular weight. The condition for marketing authorisation of a generic drug is only to show the same composition, form, bioavailability, and pharmacological properties as the original drug.

Compared to generic drugs, the production of biosimilars is a big challenge. The process of producing a biological drug based on living organisms (genetically modified cells) is extremely complex. The final product is a protein that owes its biological functions to a particular spatial structure. Spatial conformation is determined not only by the corresponding aminoacids sequence in the polypeptide chains, but above all by the processes that take place during post-translational protein modification (e.g. proteolytic processing, hydroxylation, glycosylation, phosphorylation, ubiquitination, or poly-rybosylation). It is then that a variety of sugar residues are attached to polypeptide chains, being responsible for the formation of bonds between polypeptide chains that give the protein an appropriate spatial structure that determines its normal – expected – function. In the case of antibodies, the appropriate spatial structure determines the critical pharmacological properties of these proteins, such as antigenic specificity, immune system affinity, half-life, or immunogenicity.

A potentially large number of variables (physical, chemical, and biological factors) can significantly alter the characteristics of the produced biological drug, even as a result of the subtle modifications of the functions of cells cultured in bio-reactors. Accordingly, manufacturing of a biological drug requires the use of highly sophisticated control and validation methods to ensure the expected pharmacologic activity of the end-product. The ideal situation is therefore the production of a biological drug under certain and unaltered conditions that allow exactly the same end-product to be obtained in a long-term perspective. However, taking into consideration the fact that biological drugs are produced in living cells whose functions depend on a large number of variables (e.g. age of cells, composition of the medium, ambient temperature, atmospheric pressure, electromagnetic radiation), it is known that the characteristics of biological drugs from one manufacturer can change over time, and the same biological drugs from different manufacturers may have minor differences. For example, due to the possibility of minor differences between the preparations of Herceptin® produced in Europe and the United States, some clinical trials compared at the same time biosimilars with trastuzumab-US and trastuzumab-EU.

Contrary to generic drugs, in case of biosimilars it is not enough to show that the drug is identical to the

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original according to chemical structure (e.g. the amino acid sequence in the polypeptide chains). As mentioned above, in case of biological drugs, the same chemical structure does not mean the same spatial structure, the same biological effect, and thus the same antitumor potential and safety profile. For biosimilars, it is necessary not only to prove invariable and optimal conditions of production, but first and foremost a comparable efficacy and safety should be demonstrated in clinical trials. For this reason, the marketing authorisation of biosimilars is a far more complicated, time-consuming, and costly process compared to generic drugs.

Regulatory agencies authorising the commercialisation of biosimilars pay special attention to numerous aspects related to the introduction of these drugs into clinical practice. First of all, they recommend long-term observation of patients with respect to possible delayed, atypical side effects, which could potentially be revealed. Every biologic drug, both original and biosimilar, is subject of special post-marketing surveillance (black triangle labelling). Due to the unavoidable differences in spatial conformation of the proteins and, consequently, slight differences in biological characteristics between particular biosimilars and original drugs, automatic substitution of biological drugs during therapy (from the original to biosimilar or vice versa) is not allowed. The lack of possibility for automatic substitution of corresponding biological drugs is primarily due to safety aspects and the need for accurate monitoring and reporting of adverse reactions, which is one of the basic principles of systemic treatment in the biosimilar era. The decision to change the drug should be made by the physician, based on current medical knowledge and in each case obtaining the patient's informed consent for such a procedure.

The introduction of biosimilar drugs is undoubtedly a big challenge for oncologists and pharmacists. They have to be aware not only of what biological drugs are and how much their functions depend on storage conditions, preparation and administration to patients, but they also have to always remember that biosimilars are not generic drugs.

Biosimilars in oncology represent great opportunity to reduce the significant limitations in access to modern systemic therapies without a significant burden on the payer's budget, provided that specific policies are followed. The expected increase in the availability of modern pharmacotherapy should not only improve the efficacy of systemic treatment in a large number of patient populations but, above all, by significantly reducing the costs of currently used drugs should finally allow reimbursement of long awaited new innovative biological therapies.