Biosimilars Trying to Enter the Ukrainian Market

by Evgenia V. PALIY

The past few decades have seen a real breakthrough in the field of biotechnology, which is being increasingly used in various fields, but especially in medicine. Patents for exclusive marketing of a number of original biotech drugs are expected to expire within the next few years. This provides an opportunity for manufacturing and development of biosimilars — official copies, reproduced of biotech medicinal products.

Today, science and medicine is becoming more focused on a personalized approach, when a drug is used to treat an individual patient and directly his specific disease, in contrast to commonly used chemical drugs for mass treatments. Biotechnological methods make it possible to obtain treatments with a desired outcome against specific diseases and pathologies, such as diabetes, cancer, etc.

Recently, certain pharmaceutical companies started creating copies of biological drugs which are known as biosimilars. But the nature of biosimilars, the unique targeted treatment, their complex and time-consuming production process present a row of challenges.

Awareness of the divergence between biosimilars and innovative drugs in terms of efficacy and safety is essential for proper prescription and safety of the patients.

In fact, the inconsistency of safety, quality and efficacy of biosimilars and the original bio drug is the most important issue which should be, and is, strictly controlled by government authorities when allowing the marketing of biosimilars. The reason is that such inconsistencies in quality and safety may have different results and can lead to extremely low therapeutic effect and sometimes even death of the patient. Due to the fact that biosimilars might perform differently from the branded original, regulatory authorities apply special procedure for their registration, different from the approval process for generic drugs.

It is commonly known that copies of chemical drugs (classic generics) are registered everywhere in the world through a simplified procedure and clinical studies. It is due to the chemical formula which is used in the course of creation of a classic generic. If the same formula and chemicals are used, the same effect and result is expected.

This is not the case with biosimilars. As was mentioned, the results of biotechnology production cannot be predicted. Biosimilars are not considered identical to the original drugs and that is why the degree of identity is the subject of investigation and regulation by registration authorities. For this reason regulatory authorities (both in the US and in Europe) require a number of studies, such as, *inter alia,* preclinical and clinical research to be provided and analyzed before allowing biosimilar on the market.

In Ukraine, unlike other CIS countries, including Russia, the issue of allowing biosimilars on the market is regulated at the legislative level. The legislation in this field is extremely young and does not cover all aspects of biosimilars life yet.

The Ukrainian legislator has taken into account new biotechnologies, its complexity, feasible efficacy and safety risks and introduced special standards and approaches for biosimilars expertise. In view of adaptation of Ukrainian legislation to international standards, in particular, the EU law, the Ministry of Health of Ukraine (MOH) in 2013 developed special norms and requirements with respect to biosimilars.

The procedure for registering biosimilars was introduced in the Order of MOH No.426 of 26 August 2005 as amended in January 2013.

The legislator introduced a more complicated registration procedure of biosimilars compared to classical generics with special requirements of the documents to be provided in the registration dossier of biosimilars. Thus, the requirement to provide proof of a good safety and effectiveness level of the biosimilar was introduced. In some cases it might be even necessary to provide identification studies, considering the peculiarities of each drug. And in case when the original registered bio drug has several indications, the law requires safety and efficacy proof for each indication of the drug separately.

Considering the possible difference in effect and composition between biosimilar and the original bio drug, the legislator required official confirmation by the applicant of the therapeutic effect, safety and quality of biosimilars in relation to the original drug by means of providing respective comparative preclinical and clinical trials.

It should be mentioned that in July 2013, the Ministry

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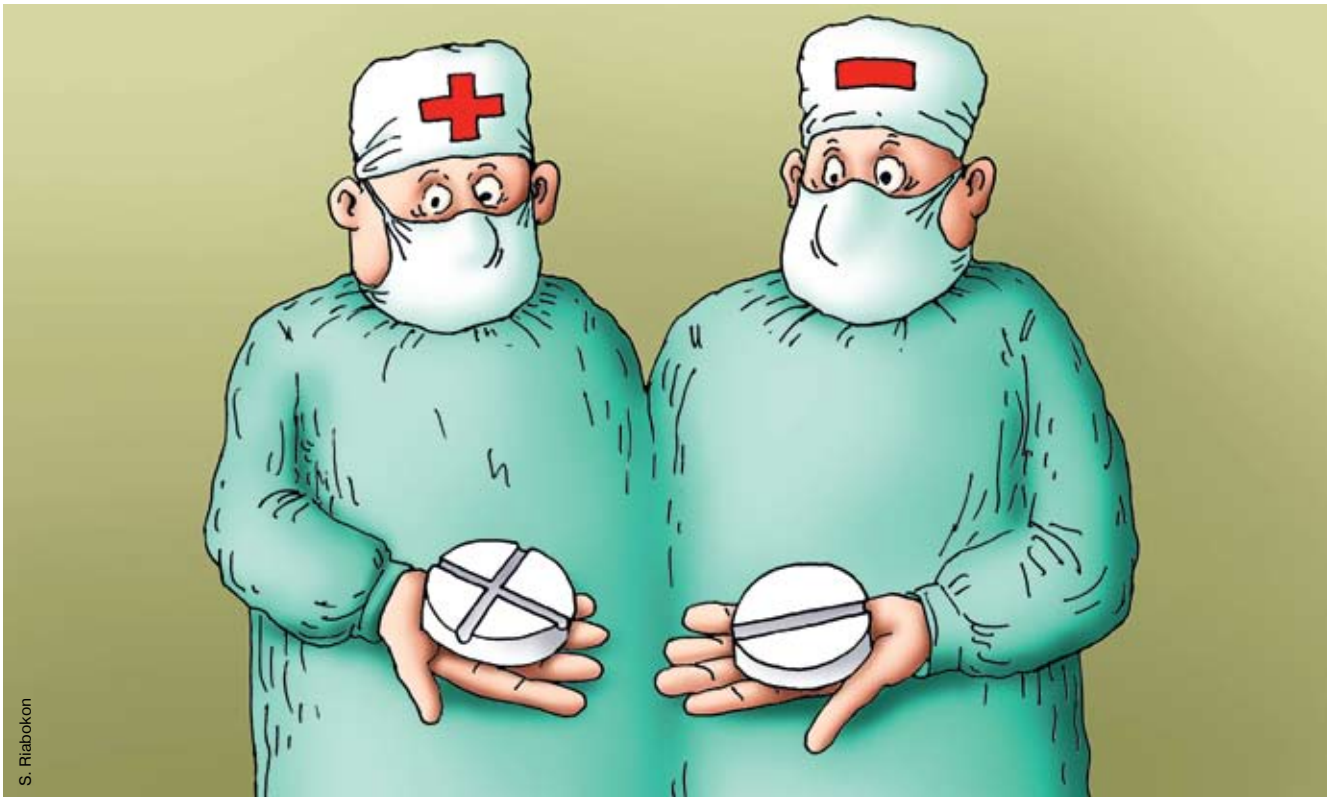

of Health toughened the biosimilars registration rules, approving by its Order No.582 of 8 July 2013 a number of guidelines on the safety of biotech products. These included the Guidelines on Medicinal Drugs, similar biotech drugs which contain proteins as active substances. Also, last year the State Expert Center of the Ministry of Health of Ukraine introduced special guidelines with respect to biosimilars — Peculiarities of biological / biotechnological products and biosimilars.

The Guidelines introduced requirements with respect to manufacturing, investigation of similarities of biosimilars and original drugs, application of analytical methods and bio activity of biosimilars.

The legislator sets the following general principles for biosimilars registration in Ukraine:

— the general approach for registration of generic medicines (based on bioequivalence with the original drug) cannot be applied;

— the prove of similarity relates to highly cleaned products which can be accurately described;

— the proof of similarity is applied by means of analytical procedures, clinical and regulatory experience;

— biosimilars have to meet the established requirements regarding efficiency, safety and quality and special requirements of EMA;

— certain differences are acceptable between biosimilars and original bio drugs.

According to the legal requirements and guidelines, in the process of registration a biosimilar has to show its similarity to the referent bio drug which was registered with a full dossier.

The comparison can be conducted based on the published information (for example, pharmacopoeia manuscript). So as to prove quality, safety and efficacy similarities extensive preclinical and clinical studies, the scope of which will depend on the composition and nature of the active substance based on the molecular structure should be conducted.

To obtain reliable results in similarity investigations the use is recommended of several different series of a medicinal drug.

In order to demonstrate similarity the legislator requires a comparison not only with a commonly available information (for instance European pharmacopoeia), the applicant is required to provide to the authorities all materials that were used during the comparison — namely the trade name, dosage form, the composition of the referent medicinal product, batch numbers, series of the referent drug.

If the similarity of the biosimilar and the original bio drug is proved on the basis of special studies, including analysis of the quality parameters with the use of special analytical methods, a shortened procedure of registration of a biosimilar may be

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considered. In such a case the applicant can go through limited preclinical and clinical studies for producing a biosimilar. The scope of studies depends on the result of the quality similarities.

In fact, the use of a similar manufacturing process, which was applied during creation of the original bio drug, does not guarantee that the biosimilar will be interchangeable with the referent drug. Moreover, the manufacturer does not usually have the full scope of information needed to compare it with a referent drug. And the legislator admits that the composition of biosimilar may differ from the referent drug, but any such difference as well as its possible result on effect and safety should be explained. Any statements on stability and compatibility of the biosimilar must be confirmed by one's own data and cannot be extrapolated from the referent medicinal product.

It should be noted that there is no regulatory requirement to re-demonstrate comparability of biosimilars with a referent medicinal product after registration of biosimilar, except for cases when the manufacturing process was changed.

The importance of the following pharmacological supervision cannot be underestimated due to the impossibility to obtain all information about safety and efficacy of the biosimilar during clinical trials. For this reason the pharmacological supervision — identification of risks, review of complains, statistics of the safety and efficacy — is extremely important during the life of the biosimilar, which was also introduced by Ukrainian legislators.

Therefore, the issues of biosimilars research, legitimacy for their development and circulation concern not only pharmaceutical companies, but the authorities supervising circulation of drugs maintenance on the market.

Due to the nature of the biotechnological process, when the precise manufacturing technology cannot be identically replicated even by the same manufacturer, a biosimilar cannot be an identical copy of the original biological drug and thus, have the identical treatment effect or safety characteristics. And that is why regulatory authorities strictly evaluate the safety and effect of biosimilars not only during their entry to the market, but also during their life and establish special rules and norms which should be strictly observed by pharmaceutical companies.

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