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Review

The patent expiration for first-generation biological drugs has prompted the development of a new group of biopharmaceuticals – follow-on biologics. The extent of studies needed in the process of follow-on biologics approval is incomparably greater than in the case of generics but reduced in comparison to innovative biologics. The basis for the approval is to show the similarity sufficient to ensure the same quality, safety and efficacy as the reference medicine. In oncology, the most widely used among so far registered follow-on biologics are biosimilar granulocyte colony-stimulating factors, and in the hitherto clinical practice, there have been no concerns about their effectiveness and safety. It is expected that along with the patent expiry of next biologics, the number of follow-on biologics will increasingly grow, that implies the need to develop and implement specific regulations for this new class of medicine.

Key words: follow-on biologics, granulocyte colony-stimulating factors, oncology.

Follow-on biologics in oncology – the need for global and local regulations

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Biological and biosimilar drugs

Biological drugs play a very important role in the treatment of cancer. They are used both in anticancer treatment (monoclonal antibodies, interferons) and in adjuvant treatment (factors stimulating the growth of granulocyte colonies – G-CSF, erythropoietin), forming an integral part of many standard therapies. Aside from oncology, biological drugs are of significant benefit in the treatment of auto-immune diseases (e.g. rheumatoid arthritis), viral diseases (viral hepatitis) and genetic conditions (hemophilia). In addition to the monoclonal antibodies and cytokines mentioned above, biological therapeutic agents include recombinant clotting factors, enzymes and hormones. A fundamental property shared by all biopharmaceuticals is the fact that they are produced within the cells of living organisms using complex biotechnological methods or, less commonly, isolated from these cells. A considerable part of biological therapeutic agents are copies of proteins performing vital functions in the human body, produced by DNA recombination. The production process is extremely complex, encompassing multiple stages: isolation of gene encoding the desired protein, development of cell line and establishment of cell bank system. The synthesis of protein molecules also incorporates posttranslational modification (PTM), e.g. deamination, glycosylation or phosphorylation.

Since the production of biologicals is complicated and patients often require prolonged treatment, biological therapy is very expensive. High cost is a factor markedly reducing patient access to this treatment modality. The patent protection of many biological drugs has either expired recently or is expiring soon. Consequently, a new group of drugs has been launched on the pharmaceutical market, called follow-on biologics or biosimilars. The former name is more common in North American countries, while the latter is usually used in Europe. Poland has not, as yet, adopted a unified nomenclature system, and both names are used interchangeably. Follow-on biologics are a new group of biopharmaceutical agents which are similar, though not identical, to their reference products and therefore require a separate registration process following patent expiry [1–3]. Since biosimilars are not generic versions of innovator drug products, the term "biogenerics" is a misnomer and should not be used. Generic drugs are chemical and therapeutic equivalents of their reference products whose patent protection has expired. Since brand name drugs and their generics are identical in terms of active substances and pharmacokinetics, no formal pre-clinical and clinical trials evaluating their efficacy and safety are mandatory. The generic drug registration process only requires an assessment of bioequivalence performed in a small group of healthy volunteers, which markedly reduces the costs involved [4]. Cost reduction associated with generic drugs compared to innovator drugs is very significant, in the range of 70–80% [5, 6]. Since generic drugs are exact copies of innovator drug products, they are automatically substitutable. As opposed to generic drugs, follow-on biologics are not copies of innovator drugs. It is impossible to produce exact copies of biologic medical products because of the size and complex structure of the molecules, and complexity involved in the production process

[7]. Every change, even the slightest, of production conditions at any stage can bring about changes in quality, cleanliness and biological characteristics, and thus affect the clinical activity and safety of using the drug. Consequently, there are differences even between different batches of biological drugs from the same manufacturer. Furthermore, manufacturers of follow-on biologics do not have access to the methodology of manufacture of innovator drugs. All these factors combined, there is no possibility to reproduce a biological drug precisely. Moreover, despite the major progress that has been made in analytical techniques in recent years, there are, as yet, no methods that would make it possible to determine biological equivalence of biotechnological drugs. It is thus obvious that follow-on biologics cannot be launched on the market in the same way as conventional generic formulations.

Regulations laid down by the EMA are much more rigorous for biosimilars than for conventional generics or changes in the production process introduced by the manufacturers of original drugs. Their approval is conditional upon demonstrating similarity to the original drug, ensuring the same quality, safety and efficacy as the reference drug [8–10]. The most reliable tool for demonstrating equivalence is still controlled clinical testing [10]. In addition to results of comparability studies, manufacturers of biosimilars are required to present data confirming that their product satisfies strict quality control standards applicable to all biopharmaceuticals. Biosimilars, just like any other medical products, are subject to ongoing post-marketing surveillance to ensure their safety. Batches of biological drugs (both originator products and biosimilars) that fail to meet the requirements set by regulators must be destroyed.

Overview of legal regulations governing the registration and use of biosimilar drugs on the example of G-CSF

When biosimilars became available on the market, it became necessary to develop a legal framework regulating the process of registration, market launch and use of biosimilar drugs. The first legal regulations allowing the registration of biosimilar drugs were adopted in the EU in 2004. Two years later, in 2006, the European Medicines Agency (EMA) authorized the marketing and use of the first biosimilar product, Omnitrope (somatotropin) in EU countries. As of today, marketing authorization has been granted to a total of fourteen biosimilars produced on the basis of four products (somatotropin, erythropoietins: α and ς, filgrastim). Another four applications have been either rejected or suspended. Registration requirements applicable to biosimilar drugs are much more stringent than for generics, however less rigorous than for innovator biologics. The main prerequisite is that the reference drug is registered in the EU. The dosage form, dose and route of administration of the biosimilar drug and reference drug must be identical. Guidelines issued by EMA consist of two parts. The first part contains general guidance addressing comparative assessment of drug quality, pre-clinical and clinical trials [10] and evaluation of immunogenicity [11]. The second part comprises product-specific guidelines, developed separately for erythropoietin, interferon, G-CSF or monoclonal antibodies [12–14]. For the drug to be eligible for the simplified registration procedure, it is necessary to demonstrate the similarity of primary and secondary structures, and biological properties, between the biosimilar and reference product. An integral element of the registration application is a post-marketing pharmacovigilance plan which sets out post-authorization actions allowing the identification of potential rare adverse events including immunogenicity and lack of drug activity [10]. Regulations providing rules for the registration of biosimilar therapeutic agents are gradually being adopted in other parts of the world as well. In 2006, Australia adopted EMA's guidelines for the registration of similar biological medicinal products [15]. In 2010, Canada formally introduced provisions regulating the registration of subsequent entry biologics which are largely based on corresponding EMA guidelines [16]. Also in 2010, the WHO Expert Committee on Biological Standardization prepared guidelines regarding evaluation of similar biotherapeutic products (SBP) [17] to ensure their global quality and safety particularly in Asian and South American countries which have less rigorous drug approval regulations than the EU. According to the guidelines, the names "follow-on protein product" or "biosimilar product" refer exclusively to biotherapeutic products which are marketed on the basis of comparability studies demonstrating similarity between similar biotherapeutic products and their originator products with regard to biological and clinical properties and the immunogenicity potential (WHO guidelines). Biotherapeutic products that are not shown to be similar to the original product (reference biotherapeutic product) should neither be described as "similar" nor called "SBP" [17].

Out of all biosimilar products authorized for marketing so far, the most important group for oncological treatment consists of granulocyte colony-stimulating factors (G-CSF). Three biosimilar filgrastim molecules have so far been approved in EU countries: XM02 [18–21], EP2006 [22, 23] and PLD108 [24]. Seven pharmaceutical products containing these molecules are currently available on EU markets. Three are marketed in Poland: TevaGrastim from TEVA (XM02), Zarzio from Sandoz (EP2006) and Nivestim from Hospira (PLD108), launched several months ago. Biosimilar G-CSF products have been approved for use in the same indications as the reference filgrastim product (Neupogen from Amgen) on the basis of comparability studies showing similarity between the biosimilar product and the reference product in terms of quality, efficacy and safety in preventing severe neutropenia and febrile neutropenia in cancer patients receiving chemotherapy [24–29]. Table 1 lists clinical trials conducted in compliance with applicable EMA guidelines to demonstrate the equivalence of the XM02 molecule and the reference product Neupogen in terms of clinical pharmacology (two phase I trials), and safety and efficacy (three phase III trials) [18]. In phase III trials XM02 was demonstrated to be non-inferior to Neupogen in terms of safety and efficacy in reducing the duration of severe neutropenia and the number of episodes of febrile neutropenia [25–28]. The adverse event profile was similar between XM02 and Neupogen, too. Also, no significant changes were noted during the comparability study in any of the groups in results of laboratory tests, physical examination or vital functions [25–28].

Clinical trials focused on just one indication. The other indications, i.e. promotion of the recovery of the hematopoiet-

Table 1. Clinical trials that demonstrated (according to the EMA guidelines) equivalence of the molecule XM02 and the reference product Neupogen in terms of clinical pharmacology (two phase I studies), and safety and efficacy (three Phase III studies) [18]

Trial type	Trial code	Goal	Subjects	Trial design	Investigated product: dose, dose regimen, route of administration	Number of subjects in the study groups	Duration of treatment
PK (PK/PD)	XM02-01-LT	Comparison of PK and PD	Healthy volunteers	cross-over 2-arm 2-stage	T: XM02 vs. R: Neupogen single dose: A: 5 μg/kg sc B: 10 μg/kg sc	56 (2 × 28)	Single dose
BE (PK/PD) 4 groups 2-stage	XM02-05-DE	Demonstration of PK and PD equivalence	Healthy volunteers	cross-over	XM02 vs. Neupogen single dose 1: 5 μg/kg sc 2: 10 μg/kg sc 3: 5 μg/kg sc 4: 10 μg/kg sc	144 (4 × 36)	Single dose
efficacy	XM02-02-INT	Demonstration of equivalence: – efficacy (DSN) – safety – PK (subgroups)	Breast cancer patients receiving chemotherapy (CTX)	randomized, with placebo and active control	XM02 vs. Neupogen vs placebo (1 cycle of CTX followed by XM02 5 μg/kg Sc)	140 136 72	In the CTX cycle: 5–14 days (to ANC ≥ 10 × 10^9/l); to 4 cycles
safety	XM02-03-INT	Assessment of: – safety – efficacy (DSN) – PK (subgroups)	Lung cancer patients receiving chemotherapy (based on platin compounds)	randomized, with active control	XM02 vs. Neupogen 1 cycle of CTX followed by XM02: 5 μg/kg sc	158 79	In the CTX cycle: 5–14 days (to ANC ≥ 10 × 10^9/l); to 6 cycles
safety	XM02-04-INT	Assessment of: – safety – efficacy (DSN) – PK (subgroups)	NHL patients receiving chemotherapy (CHOP)	randomized, with ctive control	XM02 vs. Neupogen (1 cycle of CTX followed by XM02: 5 μg/kg sc	63 29	In the CTX cycle: 5–14 days (to ANC ≥ 10 × 10^9/l); to 6 cycles

PK – pharmacokinetics, PD – pharmacodynamics, BE – bioequivalence, DSN – duration of severe neutropenia (days), CTX – chemotherapy, NHL – non-Hodgkin lymphoma, CHOP – cyclophosphamide, doxorubicin, vincristine and prednisone

ic system in post-transplant patients, HSC mobilization (from bone marrow to peripheral blood) in cancer patients and healthy donors of PBSC and in patients with severe chronic neutropenia (congenital, cyclic, idiopathic) and chronic HIV-associated neutropenia, were extrapolated from the originally authorized drug. The extrapolation of indications makes it possible to approve a biosimilar drug in indications that were not assessed in clinical trials [30]. Extrapolation is only possible if the mechanisms of action of the original and biosimilar drugs in specific indications are the same. Major concerns with regard to biosimilar G-CSF products have included their use in paediatric oncology and in healthy donors of haematopoietic cells who do not benefit therapeutically from G-CSF treatment [31]. Recently, there have been publications and conference reports demonstrating the efficacy and safety of G-CSF biosimilars used to achieve mobilization of haematopoietic system cells, also in healthy donors [32–35]. No significant differences have been observed in terms of the CD34+ cell count, the number of leukaphereses and the number of biosimilar G-CSF injections between patients receiving a biosimilar version of G-CSF and a historical control group in which PBSC mobilization was performed using the original G-CSF product. Nevertheless, continued long-term follow-up is advisable focusing on adverse reactions including immunogenicity, the effect on leukocyte function and granulopoiesis, and the quality of haematopoietic cells [36]. Another frequently raised concern is the question of higher immunogenicity of biosimilar drugs relative to original products. Immunogenicity is not associated solely with biosimilars, but represents a fundamental problem concerning the safety of use of all biological drugs [37]. Induction of immune response is typical for biological therapeutic agents and usually has no clinically significant consequences. In some cases, however, it may have serious repercussions. Neutralizing antibodies directed against drug molecules may adversely affect the drug's efficacy and directed against endogenous molecules lead to their destruction [38]. The induction of antibodies against endogenous molecules is a very serious side effect. The most commonly cited example is the development of antibody-mediated pure red cell aplasia (PRCA) in kidney failure patients treated with recombinant human erythropoietin (rHuEPO) in 1998–2003, resulting in the formation of neutralizing antibodies against both recombinant and endogenous EPO. The most likely explanation of those incidents is the use of a different stabilizer in the epoetin β formulation [38–41]. There are a number of factors potentially increasing drug immunogenicity including contamination, structural modifications and storage conditions. This is why quality control procedures are key for ensuring proper quality and safety of therapy [42]. Immunogenicity assessment is necessary both in pre-marketing clinical trials and post-marketing pharmacovigilance programmes. Recombinant G-CSF formulations have relatively low immunogenicity. No antibodies against G-CSF have been detected either in pre-marketing clinical trials or in the study by Aapro *et al.* comparing cost-efficiency of originator and biosimilar G-CSF [43]. According to formal registration documents released by EMA, impurity levels in biosimilar formulations of erythropoietin and filgrastim are lower than in the original reference products [44].

Identification of potential rare adverse events is only possible during long-term follow-up in the clinical setting, over a markedly longer period than that required for drug registration during phase IV trials. Such studies are particularly important for drugs that are authorized for use under the simplified registration procedure. The year 2010 saw the launch of MONITOR-GCSF, an observational phase IV study with an international focus, including Poland [45]. It is an international, prospective, observational, pharmaco-epidemiological study to evaluate the efficacy and factors affecting treatment outcomes in cancer patients receiving a biosimilar G-CSF product in the prophylaxis of febrile neutropenia. The trial involves 75 European medical centres. Plans are in place to recruit at least 1.000 patients treated with chemotherapy due to breast cancer, bladder cancer, lung cancer, prostate cancer, ovarian cancer, large B-cell lymphoma and plasma cell myeloma [45]. Clinical practice has not, so far, given rise to any concerns regarding the efficacy and safety of biosimilar G-CSF formulations.

Follow-up aimed at determining adverse events is inextricably linked to the problems of exchangeability and substitutability. Automatic substitution, i.e. the exchange of one drug for another by a pharmacist without the physician's knowledge, makes it more difficult to establish what particular pharmaceutical product has been used if any adverse reactions arise. Automatic substitution is not a recommended practice in the EU, however legal regulations governing this issue are adopted at a local level. Appropriate regulatory provisions are in place in only several countries including France, Germany, Greece, Spain, Slovenia, Italy and Sweden. The issue, however, is unregulated in Poland.

The advent of G-CSF biosimilars was addressed in the most recent (2010) update of EORTC (*European Organisation for Research and Treatment of Cancer*) guidelines for the use of G-CSF to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours [46]. The authors recommend approved filgrastim biosimilars as an available option to prevent febrile neutropenia and its complications (recommendation grade A). However, on account of differences in the complex manufacturing process and the fact that biosimilars are not generics, exchanging an original G-CSF product for a biosimilar formulation should be regarded as a change of therapeutic management and hence should not be implemented without the physician's and patient's knowledge. It should also be noted that the identification of a G-CSF product is currently only possible based on the commercial name and batch number because INN (international non-propriety names) of biosimilar drugs are the same as those of their reference products (WHO 2006 recommendation) [47]. Development of a uniform nomenclature for biosimilar products and their corresponding innovator products remains a controversial issue. Supporters of unified nomenclature believe that it would help avoid unnecessary confusion and be a valuable help to medical practitioners. Opponents, on the other hand, claim that it would make it more challenging to ascertain the origin of a particular drug if any adverse events occur. Another debatable point concerns information included in the Summary of Product Characteristics and in the Patient Information Leaflets. At present, a considerable

part of such information is adopted from corresponding documents of the innovator drug (comparability studies of the biosimilar drug are listed without providing specific details and there is no information about the extrapolation of any indications apart from the prophylaxis of febrile neutropenia) [48–54]. Similarly to standardized nomenclature, the issue has been intensely debated recently.

Conclusions

The expiry of patent protection on the first marketed biological drugs has opened up the way for a new group of generic drugs, called follow-on biologics or biosimilar drugs, to enter the pharmaceutical market. Biosimilars are marketed with a view to lowering costs, however potential savings will not be as significant as for generic drugs. Biologics require a much more complex and expensive manufacturing process and appropriate registration procedures, which means that biosimilar drugs are on average 10–30% cheaper than innovator drugs [55, 56]. Nevertheless, considering high costs and increasing use of biological drugs, savings in the region of 10–30% are still important. In 2009, in Europe alone, the use of biosimilar drugs translated into savings worth 1.4 billion Euro [57]. According to estimates, a 20% reduction in costs of biosimilar drugs compared to originator drugs will generate annual financial savings of ca. 1.6 billion Euro [58]. The number of biosimilar drugs is expected to grow along with the expiry of patent protection of other biopharmaceuticals. Regulatory authorities worldwide will thus need to draw up regulations governing approval, marketing and use of biosimilar drugs, especially in view of the fact that some of the policies in place are controversial and many issues remain unresolved. In view of the growing number of biosimilar drugs on the market, it is equally important for physicians, pharmaceuticals and people in charge of reimbursement of treatment costs to possess an in-depth knowledge of this class of drugs.

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