

# The Polish Expert Group Position Statement on the Safety of Biological Treatments with Monoclonal Antibodies and Fusion Proteins: An Update

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## Abstract

**Objective:** The introduction of biological drugs, including monoclonal antibodies and fusion proteins, into therapeutics is among the greatest achievements of modern medicine. These agents have been successfully used in oncology, haematology, rheumatology, gastroenterology, ophthalmology, dermatology, and allergology. Herein, we present a consensus of expert opinion regarding biologics use as an update to the Expert Group Position Statement published in 2014. Considering the rapid development within this field and the evidence accumulated in the last few years with the use of innovative biologics and biosimilars, an update has become necessary. The importance of real-world evidence from observational studies and medical registries and the way it complements data from randomised studies will be highlighted. Therefore, the expert opinion regarding switching between bio-originator and biosimilar therapeutics, immunogenicity, pharmacovigilance, and the costs of biological treatments is constantly in flux.

**Methods:** An expert panel of national consultants, members of the coordination teams of Polish drug programs, and specialists with expertise in biological treatments participated in this study in order to establish a consensus on the most critical aspects of biological treatment in Poland. A modified Delphi method was performed to achieve a consensus on relevant statements, which was met if at least 80% of experts agreed or disagreed with the discussed statement.

**Results:** The current expert position on the use of biosimilars in everyday practice was thoroughly investigated. For nine of the presented statements, panellists agreed that the expected cost savings due to biosimilars introduction, safety of extrapolation of indications, single switching bio-originator and biosimilar. Moreover, the overall access to biological treatment in Poland was explored.

**Conclusion:** The present analysis will serve as a guide to physicians that prescribe biological treatments to aid them in the critical analysis on the use of biosimilars and will further support treatment decisions and patient education on the subject.

## Introduction

This work represents a needed update on the Expert Group Position Statement published in 2014, concerning the safety of monoclonal antibodies and fusion proteins treatment.<sup>[1]</sup> The need for an update is a result of the rapid developments in this field as well as new patient expe-

riences with treatments accumulated in recent years [2]. One of biggest hurdles associated with biological treatment, particularly with monoclonal antibodies and fusion proteins, is the high cost. In the case of bio-origimators, this high cost is due to the specificity of the manufacturing technology as well as the need to conduct appropriate clinical trials.<sup>[3,4]</sup> In Poland, biologic therapies are conducted through specific drug programs. As of now (1.04.2019) there are 101 drug programs (62 of them non-oncology related) with over 120,000 patients enrolled. Since the previous statement was published, numerous new biological therapies have been introduced, including natalizumab (multiple sclerosis), secukinumab (plaque psoriasis), vedolizumab (ulcerative colitis), aflibercept (age-related macular degeneration-AMD), anakinra (autoinflammatory syndromes), eculizumab (paroxysmal nocturnal hemoglobinuria), alirocumab (heterozygous familial hypercholesterolemia), rituximab (granulomatosis with polyangiitis, microscopic polyangiitis, pemphigus). The cost of these therapies affects the patient inclusion criteria in drug programs. Fewer patients meet inclusion criteria and those patients who qualify have diseases that are more advanced or severe.

The considerable cost of biological treatment is an issue in every country where such treatment is available. The proposed solution to reduce economic impact without affecting treatment efficacy and safety is introducing biosimilars - products highly similar to bio-originator drugs with expired patents.

Since the Expert Group Position Statement was published in 2014, biosimilars have been introduced in clinical settings with approval by the European Medicines Agency (EMA), which requires extensive analytical and clinical studies to confirm that there are no clinically significant differences between biosimilars and bio-origimators.<sup>[4-14]</sup> In addition, observational studies and Real World Evidence (RWE) results have been published as well as meta-analyses regarding switching between bio-origimators and biosimilars.<sup>[15-25]</sup> Recommendations regarding using biosimilars in some medical fields have been developed.<sup>[26]</sup>

Despite the positive evidence for switching to biosimilars, the safety of switching is still a major concern for physicians and patients, discussed even on social media platforms.<sup>[27-30]</sup>

## Objective

This study aims to provide a consensus from Polish experts in numerous medical fields on the topic of biological treatment, with Polish systemic health care solutions taken into account. The presented position is based on data from references and on experts' own experience.

## Methods

### Expert Group

The position statement was developed in collaboration with national consultants (or their delegates), experts in different fields of medicine (rheumatology, allergology, gastroenterology, oncology, dermatology, ophthalmology, clinical immunology, paediatrics, and haematology) who deal with the issues of biological therapy.

A modified Delphi process was implemented in order to develop the position statements.<sup>[31]</sup> This particular method is used in cases where clinical data is scarce or controversial.

The first two phases consisted of online voting, where experts anonymously rated discussed issues using the VAS (Visual Analogue Scale) from 1 (I completely disagree with the presented opinion) to 10 (I fully support the presented view). During these phases, it was also possible to make comments. The third phase was a face to face meeting, where controversial issues were discussed, and the conclusions presented in this paper were made.

Based on available data, the following issues were selected to discuss: the possible benefits of introducing biosimilars, their registry process, and the extrapolation of indications; switching from biologics to biosimilars, including non-medical indications to do so; safety monitoring of biological therapies; and the cost and legal aspects of biological therapies.

Preliminary statements can be found in the supplementary materials.

## Results

Ultimately, 9 statements achieved at least 80% consensus from the expert panel. The summary of results is presented in [Table 1](#).

During the discussion, no consensus was reached regarding patient consent, however 70% of experts thought that the patient should be informed before switching the bio-originator to a biosimilar (VAS 8.2). Similarly, 70% of experts were against automatic substitution at the pharmacy level (VAS 2.6).

Participants deemed safety data regarding multiple switching to be insufficient for this kind of practice to be encouraged as of now, although it may change in the future (70%, VAS 8.4).

During the discussion, the current state of pharmacovig-

ilance in Poland was a controversial topic. More specifically, two experts deemed it sufficient, three had no opinion, and five participants considered it insufficient.

The experts chose not to make any statements about drug-tendering procedures or legal issues regarding biological treatment since they considered those to be outside their areas of expertise.

## Discussion

The presented position statements encompass different issues associated with biological drug therapies. Biologics are one of the most rapidly developing branches of modern medicine, including both reference drugs and biosimilar drugs i.e. analogues of innovative drugs with expired patents.<sup>[1]</sup> This publication responds to the growing need of Polish physicians involved in biological therapies, most of them via drug programs, for resources to aid in decision-making related to biologics.

A significant part of the updated consensus is the experts' attitude towards biosimilars and drug switching. It is believed that the introduction of biosimilars is associated with benefits such as reduced costs and increased availability of the treatment, which was confirmed by budget impact analyses conducted in various European countries.<sup>[32-36]</sup>

There are, however, some concerns associated with the slow implementation of changes in drug programs despite cost reductions achieved by using biosimilars. For example, although there was a switch from infliximab to a biosimilar drug in a Crohn's disease/ulcerative colitis drug program in 2014, the change to the length of the therapy was delayed until 2016. Furthermore, the inclusion criteria for patients with Crohn's disease in drug programs have yet to be changed.

In comparison to 2014, studies have indicated biosimilars are safe by extrapolation from clinical indications as well as safe when single switching from a reference drug to a biosimilar drug.<sup>[26]</sup> The results of the NOR-SWITCH study, which has proven that switching from infliximab to a biosimilar (CT-P13) is not associated with a decrease in efficacy (prespecified non-inferiority margin of 15%), is a strong argument in favour of switching. The year-long study was carried out in patients in stable condition who suffered from Crohn's disease, ulcerative colitis, spondyloarthropathy, rheumatoid arthritis, psoriatic arthropathy, and psoriasis.<sup>[22]</sup> The study was not designed to assess switching for a single indication. Data from 2 observational studies regarding inflammatory bowel disease patients confirm the results from the NOR-SWITCH study.<sup>[37]</sup> In the experts' opinion, the data on the safety of multi-

ple switching is still insufficient, although there are two promising studies conducted among psoriasis patients, who were treated with either the biosimilar etanercept<sup>[38]</sup> or the biosimilar adalimumab.<sup>[39]</sup> Currently, it is strongly recommended to carefully consider each case of implementing such therapy. Experts agree that multiple switching should be defined more precisely and assessed not only in randomised studies, but also in observational studies, and by using data from medical registries that are soon expected to be implemented.<sup>[26]</sup>

The experts emphasised that any potential reduction in treatment costs must not overshadow the safety of the therapy.<sup>[1]</sup> Patient groups who should be observed especially carefully are the ones who had adverse reactions in the past and the ones with refractory disease failed two or more biological courses.<sup>[40]</sup> In those cases, issues that are particularly relevant are immunogenicity and the physician independence in choosing a particular drug.

Pharmacovigilance of biological therapies is still considered a significant issue in Poland. On the one hand, those therapies are mostly conducted through drug programs that require a very careful and thorough assessment of efficacy and safety during the treatment period. On the other hand, follow-up periods of patients who finish the program are too short to effectively monitor long-term adverse reactions such as cardiovascular complications or malignancy. In other countries this data is collected mostly through medical registries.<sup>[41,42]</sup>

In the process of creating this expert consensus, the importance of nocebo effect was emphasized. This effect, while being difficult to objectively assess, is a significant reason to terminate biological treatment in cases of

switching to a biosimilar drug for non-medical causes.<sup>[43,44]</sup> It is recommended that both patients and health care providers are educated on the current evidence on biosimilars, and that the patients should be educated in an understandable way.

In summary, the presented consensus should serve as a guide for physicians involved in biological therapies. Its significant advantage is the multi-disciplinary scope of the experts involved as well as their experience in creating and conducting drug programs in Poland. The consensus was reached through a multi-step discussion process that also involved a face to face meeting of experts. In order to achieve a statement validity, at least 80% of experts must have agreed on it. The findings in this study can serve as the basis for introducing biosimilar therapies in a safe and thoughtful manner as well as making those therapies more accessible in Poland.

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Marcin Czech (Ministry of Health - Undersecretary of State), Andrzej Czesławski (URLIPB), Jakub Gierczyński (Lazarski University), Krzysztof Kopeć (Polish Association of Pharmaceutical Industry Employers), Maciej Niewada (ISPOR Poland Chapter), Katarzyna Połujan (Infarma), Irena Rej (Chamber of Commerce Pharmaceutical Poland).

Table 1. The Polish Expert Group Position Statement on the safety of biological treatment with monoclonal antibodies and fusion proteins: results of the Delphi method

Consensus statement	VAS (mean+/-SD)
1. It is to be expected that availability of biosimilars will significantly decrease biological treatment costs in Poland, which will facilitate implementing international recommendations in those therapies- including drug programs existing in Poland	8.8 +/-1.1
2. The extensive process required by regulatory institutions such as the EMA or the Food and Drug Administration-FDA of comparing biologics and biosimilars, including the structure, function, pharmacokinetics, pharmacodynamics, immunogenicity, and efficacy, is sufficient to prove the similarity of a biosimilar to its reference medicine.	9.0 +/-0.9
3. Registered biosimilars can have the same indications and contraindications in regard to monotherapy or combination treatment as their reference biological drugs.	9.1+/-0.99
4. Considering that biologics and their reference drugs have no clinically meaningful differences in structure, function, pharmacokinetics, and immunogenicity, proving that a biosimilar drug is safe and efficient in regard to a single indication should be sufficient to extrapolate indications.	9.0+/-1.1
5. Current study results prove that a single switch between a reference drug and a biosimilar drug is safe and does not affect treatment efficacy.	8.8+/-1.4
6. Switching should be approved by a physician.	9.9 +/-0.3
7. Both patients and health care providers should be educated on the topic of biosimilars in order to avoid the nocebo effect that has been observed while switching to a biosimilar drug.	9.5+/-1.1
8. In particular clinical settings and patient groups, assessment and monitoring of immunogenicity should be available.	9.5+/-1.1
9. It is necessary to standardise pharmacovigilance tools, with trade names taken into account, and to implement them in everyday clinical practice.	9.3 +/-1.3

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9. Both patients and health care providers should be educated on the topic of biosimilars in order to avoid the nocebo effect that has been observed to occur while switching to a biosimilar drug.
10. Considering the similarity of a biosimilar and its reference drug, it is not necessary to assess immunogenicity in everyday clinical practice.
11. Pharmacovigilance regarding biological therapies in Poland is currently insufficient.
12. Biological drugs and biosimilars in Poland should be purchased through tendering procedures.
13. Legal regulations regarding informing patients about treatment types should be tailored to biological therapies and their unique issues.

## Supplementary materials

1. It is to be expected that the availability of biosimilars will significantly decrease biological treatment costs in Poland, which will facilitate implementing international recommendations for those therapies-including drug programmes existing in Poland.
2. The extensive process (required by regulatory institutions such as EMA or the Food and Drug Administration-FDA) of comparing biologics and biosimilars, including the structure, function, pharmacokinetics, pharmacodynamics, immunogenicity, and efficacy, is sufficient to prove the similarity of a biosimilar to its reference medicine.
3. Registered biosimilars can have the same indications and contraindications in regard to monotherapy or combination treatment as their reference biological drugs.
4. Considering that biologics and their reference drugs have the same structure, function, pharmacokinetics, and immunogenicity, proving that a biosimilar drug is safe and efficient in regard to a single indication should be sufficient to extrapolate indications.
5. Current study results prove that a single switch between a reference drug and a biosimilar drug is safe and does not affect treatment efficacy.
6. Current study results are insufficient to recommend multiple switching, although it may change in the future.
7. Switching to a biosimilar should be approved by both physician and patient.
8. In cases where some drugs are deemed interchangeable, automatic substitution without the physician's involvement is acceptable.

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