

# Regulatory aspects of biological medicines in Bosnia and Herzegovina

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## ABSTRACT

The use of the biological medicines, also called “biologics,” has contributed to the progress of the treatment of many chronic diseases, such as cancer, rheumatoid arthritis, Crohn’s disease, multiple sclerosis, and psoriasis. However, biologics are expensive for healthcare systems in several countries. Their availability has been a global issue, which has affected many patients that suffer from various diseases. A biosimilar medicine, also called “biosimilar,” is a medicine with similar characteristics in terms of quality, biological activity, safety, and efficacy as the approved original biological medicine, known as “originator biologic.” Biosimilars generate competition within the market because they lower the prices of biologics and thus allow for an increase in patient access. However, there are barriers when it comes to the acceptability rate of biosimilars and how interchangeable they are with the originator biologic. In this review, we present a national regulatory framework for biologics along with its limitations, a system of monitoring the safety profile of biologics, the guideline for interchangeability, and a list of approved and available biologics in Bosnia and Herzegovina. Additionally, recommendations were made here in order to provide opportunities for greater acceptance of biosimilars and better access to biologics. These recommendations include, but are not limited to, strengthening the national regulatory framework for biologics, capacity building, increasing awareness among healthcare providers for reporting adverse drug events and active pharmacovigilance, and better definitions of interchangeability. Finally, awareness among healthcare providers regarding biosimilars and biologics should be raised through continuous education and workshops, and by including this important topic in the graduate and postgraduate curriculum programs in the country.

**KEYWORDS:** Original biological medicines (originator biologics); biosimilars; regulatory approach; interchangeability; safety

## INTRODUCTION

A biological medicine, also known as a “biologic,” is a medicine that contains a biologically active substance (biological macromolecule) from a biological source, such as living cells or organisms (human, animal, or plant), and microorganisms such as bacteria or yeast [1]. According to the United States Food and Drug Administration (FDA), biologics include a wide range of products such as vaccines, blood and blood components, allergens, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed

of sugars, proteins, nucleic acids, or a complex combination of these substances. Biologics can even be living entities such as cells and tissues [2]. They offer treatment options for patients with chronic diseases such as diabetes, autoimmune diseases, cancers, rheumatoid arthritis, Crohn’s disease, multiple sclerosis, and psoriasis [1,3-5]. The use of biologics has contributed to the progress in the treatment of these diseases, and this area is of great importance for public healthcare at the global level.

Biologics are much more structurally complex than the small chemical molecules. Therefore, manufacturing process of biologics is more complex. They are often produced by biotechnological methods and other cutting-edge technologies using sophisticated cell systems and recombinant DNA technology, polymerase chain reaction (PCR), hybridoma technology, and lab-on-a-chip [1-3]. These technologies are one of the reasons biologics are more expensive compared to small chemical drugs. Biologics are frequently costly for healthcare systems globally and access to them may be a problem for many patients worldwide [6-13].

The basic principle of the pharmaceutical legal framework is to ensure a high level of health care by providing medicines of high quality, safety, and efficacy with adequate access through the competitiveness of the pharmaceutical industry on the market.

A period of eight years from the initial marketing authorization (MA) of an originator medicine, also known as an

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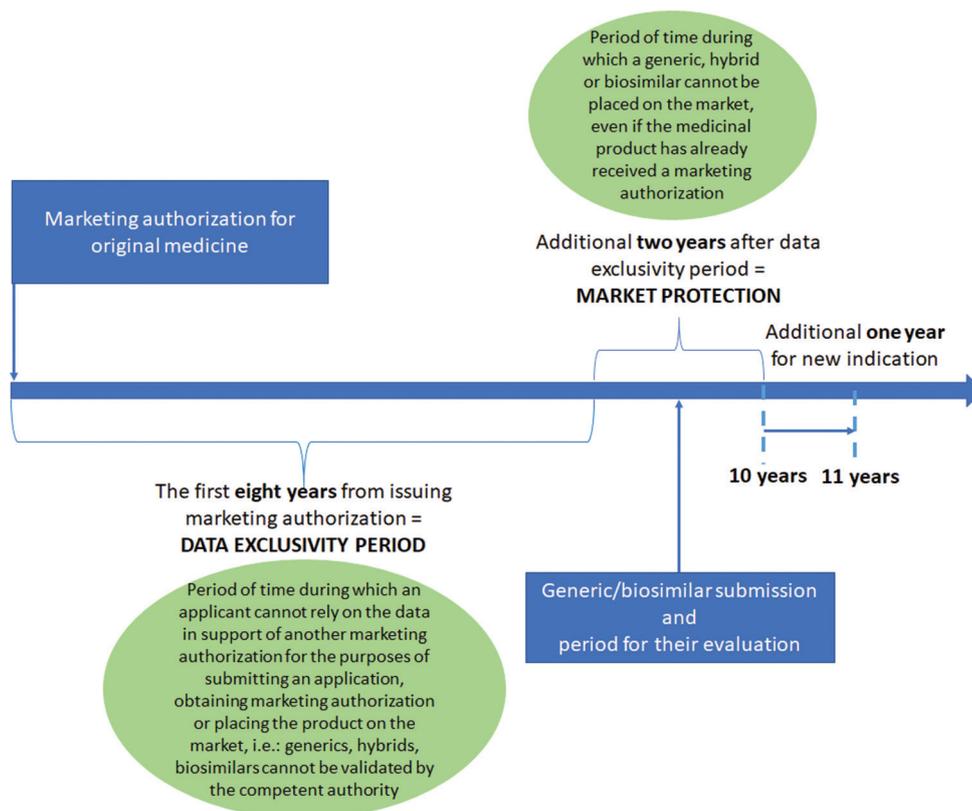
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“originator”, is known as the data exclusivity period. During this period, the marketing-authorization holder (MAH) benefits from the exclusive rights to the results of preclinical tests and clinical trials on the originator medicine. After this period, the MAH is obliged to share this information with companies wishing to develop copy versions of the originator [14]. The data exclusivity period is followed by two more years, also called “market protection”. At the end of a ten-year period of marketing protection, generic medicines, also known as “generics”, and biosimilar medicines, also known as “biosimilars”, are able to come to the market, as this period marks the end of the MAH benefits (Figure 1). A ten-year period can be extended to a maximum of eleven years if during the first eight years of those ten years, the MAH has obtained an authorization for one or more new therapeutic indications [15].

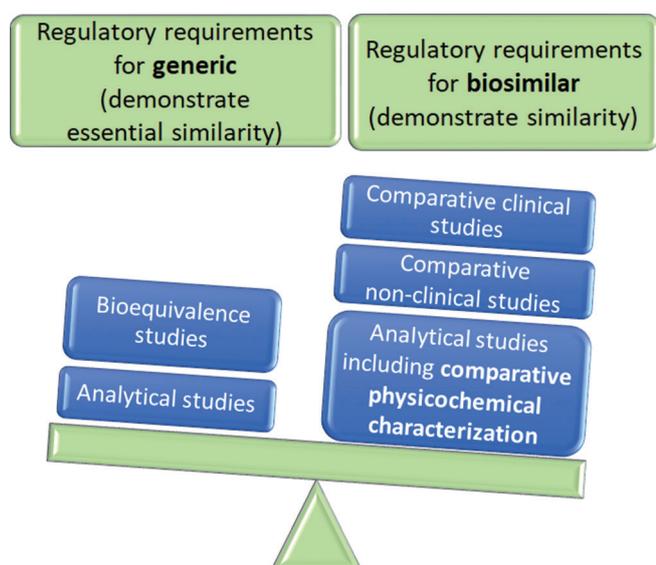
Generics and biosimilars are often offered at lower prices than the originator drug, potentially reducing costs for patients and the healthcare system [16]. The prices of originators decrease after the MAH loses market exclusivities [9]. Thus, reduction of costs could result in savings for the healthcare systems and increasing number of patients having the access to the necessary medicines [5,9,10,13,17-19]. Prices per treatment day (total market) have been reduced in almost all markets but to different degrees from -65% to 2%, due to

a combination of factors. These factors include the level of competition, the acceptance of non-accessible market products (primarily differentiated by fewer injections), as well as development costs of originators and biosimilars [5].

Biologics are extremely sensitive to manufacturing conditions and therefore more difficult to characterize and produce than small chemical medicines. They are made by living organisms, which are naturally variable and the active substance in the final biologics can have an inherent degree of minor variability (microheterogeneity). A minor change in manufacturing may lead to differences in the structure, stability, or other quality aspects of the final product. All of these factors have the potential to affect tolerability and/or efficacy and increase the risk of immune responses through the appearance of anti-drug antibodies and allergic reactions. Therefore, this minor variability must fall within the acceptable range to ensure consistent quality, safety, and efficacy. This is done by adjusting the manufacturing process to guarantee that the active substance fits into the desired specifications range. This degree of minor variability can be present within or between batches of the same biological medicine [1,20]. Due to the fact that “the process is the product”, the regulatory approach is different for biosimilars than for generics [21], i.e., biosimilars meet the more demanding regulatory requirements than generics (Figure 2).



**FIGURE 1.** Data exclusivity period and market protection. “Without prejudice to the law on the protection of industrial and commercial property, medicinal products for human use which have been authorized in accordance with the provisions of this regulation shall benefit from an eight-year period of data protection and a ten-year period of marketing protection, in which connection the latter period shall be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies” [15].



**FIGURE 2.** Comparison of regulatory requirements between generics and biosimilars.

Generics are defined as essential similar small molecule drugs with the same qualitative and quantitative composition of the active substance, and the same pharmaceutical form as an already approved originator [22-24]. The essential similarity between an originator and a generic has been demonstrated by the appropriate bioequivalence studies.

Biosimilars are defined as similar biological medicines with a proven similarity in terms of quality, biological activity, safety, and efficacy as the already approved originator biologics [1]. Similarity between originator biologic and biosimilars is evaluated based on a “head-to-head” and “step-by-step” approach. It must be based on the extensive product characterization and an abridged non-clinical and clinical data package [1]. Regulatory bodies for medicines, such as the European Medicines Agency (EMA), FDA, the World Health Organization (WHO), and The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) have prepared a regulatory framework with many guidelines, which include the regulatory requirements for similarity assessment between originator biologics and proposed biosimilars in an approval process. The expertise of the regulatory competent authorities responsible for the licensing of biologics is of crucial importance for the appropriate evaluation [6].

The robustness of this regulatory framework ensures the maintenance of high levels of quality, safety, and efficacy of approved medicines while supporting innovation.

The success in treating various chronic diseases is highly dependent on the access to biologics, whereby biosimilars, with their lower market prices, provide the chance for increased accessibility. However, this is globally still not the case, and there are few major reasons why the attempt to broaden increased access has not been fully successful. One

factor is the lack of competition in the market and a lack of sufficient uptake of biosimilars to generate price competition with their originator. There are several reasons for the variable uptake and utilization. These include the lack of incentives for healthcare professional to use biosimilars; lack of trust in biosimilars among healthcare providers and patients; similarity, but not essential similarity between originator biologics and biosimilars with the perception that biosimilars are not as good as the originator biologics; lack of clear guidance, government policies or clinical guidance with defined conditions for interchangeability of originator biologic with the biosimilars; possible appearance of unknown adverse effects; and the “innovator’s reach” by shifting towards patented alternatives and interfering with intellectual property rights [11,14,25-28]. A lack of incentive policy implementation with regard to biosimilar uptake and utilization or the variation in incentive policies in Europe or across the globe have also potentially influenced the market dynamics [29].

The main role of regulatory authorities is to ensure that only high-quality, safe, and effective biosimilars are available in the market. Experience with the introduction of generics has shown that gaining the trust of all stakeholders, including policy-makers, regulatory competent authorities, and healthcare professionals is essential for increasing access [30].

In this review, the results of the benchmarks investigation for biologics in Bosnia and Herzegovina (B&H) have been presented. The national legal framework and regulatory requirements, data exclusivity period, labeling and monitoring of safety profile, interchangeability, and a list of approved and available biologics for the B&H market were discussed.

## DATA SOURCES

The Agency for Medicinal Products and Medical Devices of Bosnia and Herzegovina (ALMBIH) is the regulatory competent authority at the state level. For the research of the national legal framework for biologics, we used the legal documents from the internet presentation of the Official Gazettes of B&H [31] and legal documents from the ALMBIH website [32]. Information regarding data exclusivity, labeling and monitoring of safety profile, and interchangeability of biologics was taken from the ALMBIH website [33] and compared with the European Union (EU) requirements published on the EMA website [34]. A list of the approved biologics for the B&H market was created by inquiring into the database at the ALMBIH [35]. Medicines are listed by their Anatomical-Therapeutic-Chemical classification [36].

Bosnia and Herzegovina has two entities and the Brčko District. The Federation of Bosnia and Herzegovina (Federation of B&H) and the Republic of Srpska (RS) are entities with their own constitutions. Each entity is responsible

for maintaining health care within its territory. The RS has one health insurance fund, the Health Insurance Fund of the Republic of Srpska (HIF RS) [37]. On the other hand, the Federation of B&H consists of ten cantons, with each canton having its own health insurance fund. At the entity level of the Federation of B&H, there is the Health Insurance and Reinsurance Institute of the Federation of B&H (HIRI F&B) [38]. A list of biologics that are reimbursed by above-mentioned health care insurance funds were downloaded from their websites.

Preventative vaccines and plasma-derived products, as well as their recombinant analogs, were excluded from the scope of this review article because the focus is on biologics, which contribute to the progression and treatment of many chronic diseases, such as cancer, rheumatoid arthritis, Crohn's disease, multiple sclerosis, and psoriasis.

## SECTIONS ON POLICY OPTIONS FOR BIOLOGICS IN B&H

### Legal framework and requirements for licensing

The ALMBIH was established in 2009 as the sole competent authority for medicine and medical devices for the B&H market. One of its main responsibilities is to authorize medicines based on a positive assessment of quality, efficacy, safety (Q/E/S), and risk/benefit ratio. The evaluation of Q/E/S is prepared by the internal experts and experts from the Committee for Medicines for Human Use which functions at the state level [39]. Sometimes, during the process of issuing MA for radiopharmaceuticals, a new originator biologic, or biosimilar which has not been previously approved for the EU market, the ALMBIH assigns an expert from the List of experts of B&H. This list includes experts from B&H and former Yugoslavian countries [40]. Based on Article 20 paragraph 6 of the Medicinal Products and Medical Devices Act of B&H (Official Gazette of B&H, number 58/08), the director of ALMBIH, with the prior consent provided by the Professional Board, will endorse the List of experts B&H.

The legal framework for licensing medication for the B&H market is available in the Medicinal Products and Medical Devices Act of B&H (Official Gazette of B&H, number 58/08) [39] and the Rulebook on procedure and manner for issuing MA approval (Official Gazette of B&H, number 75/11) [41]. A fast-track procedure of issuing MA is established by Article 32 and Article 33 of that Rulebook. This procedure refers to medicines that have previously been approved for the EU market by the centralized procedure, decentralized procedure, or mutual recognition procedure. In such case, ALMBIH accepts an assessment report by the Committee for Medicinal Products for Human Use or an assessment report from the referent member state within the decentralized procedure

or mutual recognition procedure. In a situation where the requirements stated in Articles 32 and 33 have not been met, ALMBIH itself makes an assessment based on Q/E/S.

A separate legal document with regulatory requirements for approval of biologics for the B&H market does not exist. The national regulatory framework for licensing is the same for both conventional pharmaceuticals and biologics, except for the regulatory requirements for biosimilars that are more extensive than regulatory requirements for generics. These are present in Article 27 of the Rulebook on procedures for issuing MA approval [41].

During the process of issuing MA for biologics, dossiers are reviewed and evaluated according to the specific EMA guidelines for active biological substances (e.g., monoclonal antibody, low-molecular-weight heparin, etc.), as well as the ICH, and WHO guidelines. Assessment of quality, comparable non-clinical and clinical studies, is performed in accordance with the EMA requirements. These requirements include demonstrating the similarity between originator biologic and proposed biosimilar in terms of quality, safety, and efficacy. Immunogenicity studies are also required prior to approval. Only an originator biologic approved on the basis of a complete registration dossier (complete Q/S/E data) can serve as a comparator for head-to-head studies with the proposed biosimilar to demonstrate similarity in terms of Q/E/S [6,41]. Dosage form, strength, and route of administration of the biosimilar should be the same as for the originator biologic. A comprehensive assessment of the quality characterization of the originator biologic and biosimilar is a prerequisite for the reduction of non-clinical and clinical data required for authorization.

The licensing procedure of an originator biologic or biosimilar for the B&H market does not require previous assessment performed by the EMA or approval issued by the European Commission (EC) through the centralized procedure [24,39]. This is in contrast with the regulatory requirement in the EU member states [24], as well as the countries of the East European region (Bulgaria, Romania, Slovenia, Croatia, Serbia, Montenegro, and the Republic of North Macedonia). Since the licensing procedure in BIH does not resemble licensing procedures of neighboring countries, it becomes a considerable challenge for ALMBIH.

The ALMBIH has an insufficient number of highly educated healthcare employees (Master Pharmacy degree and Medical Doctor degree) – this has remained to be true since its establishment. This is a consequence of employment discontinuation at the state level and lack of independence of the ALMBIH (it is financed from the budget of B&H and is part of the state administration) [39]. Therefore, the staff and the lack of independence remain to be the reason for undeveloped internal expertise. Due to the lack of internal experts for the

assessment of Q/E/S of biologics, the ALMBIH has to assign an expert from the list of experts B&H.

A comparison between the B&H and EU regulatory requirements for biologics is given in Figure 3.

### Data exclusivity period

The data exclusivity period of eight years and the market protection period of two years have been defined as ten years in the EU (Figure 1). In the United States, the data exclusivity period for small molecule drugs has been defined as 7 years [42] and 12 years for biological medicines [6,43].

Based on the Article 34, paragraph 1, point (c) of the Medicinal Products and Medical Devices Act of B&H (Official Gazette of B&H, number 58/08), the data exclusivity period in B&H is defined as 8 years with additional 2 years for the market protection period, which is the same as the EU. The data exclusivity period and the market protection period are mandatory for issuing MA and apply to the B&H market generics and biosimilars only from July 2021. Previously, it was not mandatory to follow the data exclusivity and market protection period based on the Article 141 of the Medicinal Products and Medical Devices Act of B&H [39], and decisions of the Professional Board (Official Gazette of B&H, number 57/13 and number 75/18) [44,45].

### Labeling and monitoring of safety profile

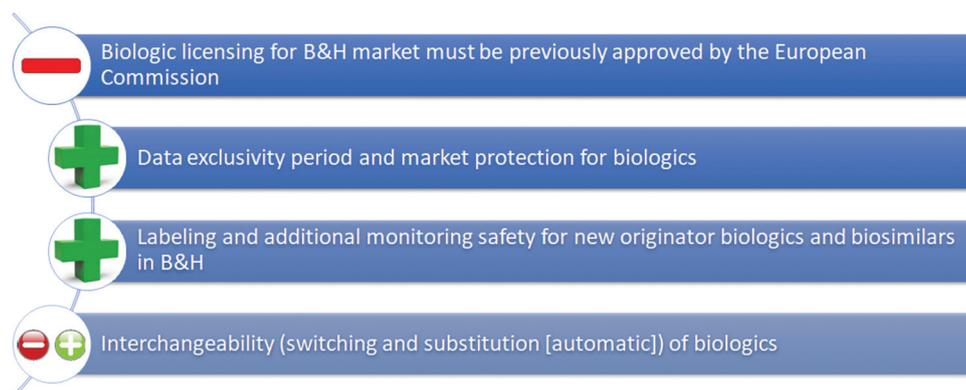
Since January 2018, all biological medicines (originals and biosimilars) approved by ALMBIH ten or less years ago, as well as all newly approved biologics, have been put under additional monitoring on the B&H market. These medications are labeled with a black upside-down triangle (▼) on the packaging. Additionally, the medication comes with a Patient Information Leaflet and a Summary of Product Characteristics (SmPC) in one of three official languages in B&H (Bosnian, Croatian or Serbian) [33]. This symbol is an alert to all healthcare professionals to closely monitor biologics, be more vigilant with these medicines, and to report any

suspected adverse drug reactions (ADR) [1]. For each biosimilar approved for the B&H market, there is information in the SmPC that the biologic the patient is using is similar to an appropriate originator biologic.

Regarding the information presented above, monitoring the safety profile of biologics during the post-marketing period (especially of biosimilars) is emphasized more than with the other available medications on the B&H market. In 2019, ALMBIH became a full member of the Uppsala Monitoring Centre – WHO. Although no online reporting solution for healthcare professionals and MAHs has yet been developed to date, ALMBIH has created a guide for detecting and reporting the ADRs with certain specific requirements for monitoring the ADRs of biologics. Each report form should provide a brand name, International Nonproprietary Name (INN), batch number, and all the other facts critical for traceability of the product [33,46]. Reporting forms and educational materials are available on the ALMBIH website [47]. However, during the period 2011-2018 year, the number of the reported ADRs in B&H was lower compared to the other nearby countries such as Croatia, Serbia, Montenegro, and Slovenia [48]. In the Department of Pharmacovigilance, which is an organizational unit of the ALMBIH, there are only three employees (one Master Pharmacy degree and two technical employees). The lack of highly educated healthcare employees in the department is the reason for lack of causality assessments and it holds responsibility for the insufficient development of the pharmacovigilance system in B&H. Additionally, insufficient education in the field of pharmacovigilance and lack of knowledge of healthcare professionals on how the pharmacovigilance system in B&H functions (whom to report and where to find an ADR reporting form) are also reasons for underreporting in B&H [48,49]. Due to these facts, all the safety information on biologics and other medicines are taken from EMA.

### Interchangeability (switching and substitution)

Interchangeability of biologics is a responsibility of each individual country. The EMA's definition of interchangeability



**FIGURE 3.** Compliance between the B&H and EU regulatory requirements for biologics –: Insufficient harmonization; +: Harmonization requirements; –+: No unique requirements at the level of EU; B&H: Bosnia and Herzegovina; EU: European Union.

is as follows: “Interchangeability of biologics refers to the possibility of exchanging one biologic for another one that is expected to have the same clinical effect. This could mean replacing an originator biologic with a biosimilar (or vice versa) or replacing one biosimilar with another. A replacement can be done by:

- Switching, which is when the prescriber decides to exchange one biologic for another biologic with the same therapeutic intent.
- Substitution (automatic), which means obtaining an interchangeable biologic at the pharmacy level without consulting the prescriber” [1].

The FDA has presented a different definition of interchangeability: “The biological product may be substituted for the reference product without the intervention of the health-care provider who prescribed the reference product, thus corresponding to the EMA’s definition of automatic substitution” [12].

The EMA does not make a distinction between biosimilars and interchangeable products. In fact, the EMA has abstained from taking an official position on the interchangeability of biosimilars. In the USA, a distinction is made between interchangeable products and biosimilars, which is defined in the Biologics Price Competition and Innovation Act of 2009 [29].

There is no government policy document for regulating switching and substitution of biologics in B&H to date. However, switching of biologics (between originator and biosimilar) is recommended by ALMBIH and requires appropriate monitoring [33]. The prescribing physician is responsible for this decision, while pharmacists dispense the prescribed biologics. Uncontrolled exchange between biologics without adequate clinical monitoring must be avoided. If this exchange takes place, detailed product and batch information must be recorded in the patient file to ensure the traceability of the product in the event of problems (appearance of ADR, e.g., an allergic reaction) [33,50]. Substitution of biologics in B&H has not been recommended yet.

Contrary to generics, in most European countries, automatic substitution of biosimilars is neither allowed nor recommended [13]. Based on the experience with the introduction of generics, it can be assumed that the clearly defined guideline for interchangeability (switching and substitution) would benefit the uptake of biosimilars, and in this way stimulate competition in the market.

### Approved biologics and availability of biologics

A list of the approved biologics (by INNs) for the B&H market [35] is presented in Table 1. Biologics approved by the ALMBIH without evaluation by the EMA and approval by the EC are marked with an asterisk in Table 1. This includes the

originator biologic CIMAvax-EGF® (conjugated rEGF-rP64K) which is produced by the Center of Molecular Immunology in Havana, Cuba (approval expired in 2021, and has not been renewed). In addition, there is a biosimilar Herticard® (rituximab) and a biosimilar Acellbia® (trastuzumab) which are both produced by the Russian biotechnology company BIOCAD. There is a biosimilar GENSULIN® (human insulin), which is produced by Bioton that is located in Poland. The approval for Herticard® was withdrawn in 2021 by the MAH.

Only biologics included in the list of medicines, which are reimbursed by health insurance funds, are accessible to patients. Lists of biologics which are reimbursed by the HIFRS and HIRIF&B are shown in Table 1. These medications are procured only centrally, at the level of the responsible health insurance fund, within tender procedures.

## ACTIONABLE RECOMMENDATIONS

Clearly define and adopt a legal framework and the requirements for licensing of biologics

Biosimilars elicit a greater chance for broader accessibility of expensive biologics, for example, monoclonal antibodies, to patients within the health insurance system in B&H and worldwide. Expertise in regulatory assessment of biologics is essential for ensuring quality, safety, and efficacy during the licensing of the product and what happens to the product post-licensure and when it is distributed into the market. The role of the regulatory authority is very important, however, the regulatory framework and regulatory requirements for biologics in B&H are insufficient and not clearly defined. The ALMBIH has not developed internal expertise for the biologics. Due to the infrastructure currently in place, this has caused a lack of trust in the biologics approved by ALMBIH [51,52]. With respect to this, it is necessary to strengthen the regulatory system for biologics in B&H by adopting national guidelines and policy documents that are in line with EU regulations. The EU guidelines provide and present requirements for individual classes of biologics. Also, best experts in this field are included in the process of assessing and issuing MAs for biologics.

Develop an internal expertise for biologics within the ALMBIH

ALMBIH should aim to employ highly educated professionals to become the internal expertise for biologics – increase capacity, experience, and competency in the assessment of Q/S/E and risk/benefit ratio for biologics. Gaining the trust in the assessment of biosimilars performed by ALMBIH is one of the main challenges that is in the way of accepting the biosimilars as an option for increasing biologics access in

**TABLE 1.** List of approved biologics comparing with biologics reimbursed by the most important B&H health-care funds (approved and available biologics)

ATC	INN	No. of approvals for biologics issued by ALMBIH	No. of approvals issued for biosimilars by ALMBIH	Biologics accessible through HIF RS	Biologics accessible through HIRI F&B
A10AB	Insulins and analogs for injection, fast-acting				
A10AB01	Insulin (human)	4	2*	√	NA
A10AB04	Insulin lispro	3	Not approved	√	NA
A10AB05	Insulin aspart	2	Not approved	√	NA
A10AB06	Insulin glulisine	2	Not approved	√	NA
A10AC	Insulins and analogs for injection, intermediate-acting				
A10AC01	Insulin (human)	4	2*	√	NA
A10AD	Insulins and analogs for injection, intermediate- or long-acting combined with fast-acting				
A10AD01	Insulin (human)	4	2*	√	NA
A10AD04	Insulin lispro	2	Not approved	√	NA
A10AD05	Insulin aspart	1	Not approved	√	NA
A10AD06	Insulin degludec and insulin aspart	2	Not approved	x	NA
A10AE	Insulins and analogs for injection, long-acting				
A10AE04	Insulin glargine	6	1	√	NA
A10AE05	Insulin detemir	1	Not approved	√	NA
A10AE06	Insulin degludec	3	Not approved	√	NA
A10AE54	Insulin glargine and lixisenatide	3	Not approved	√	NA
A10BJ	Glucagon-like peptide-1 (GLP-1) analogs				
A10BJ03	Lixisenatide	3	Not approved	x	x
A10BJ05	Dulaglutide	2	Not approved	x	x
A16A	Other alimentary tract and metabolism products				
A16AB02	Imiglucerase	1	Not approved	x	x
A16AB07	Alglucosidase alfa	1	Not approved	x	x
B01AB	Heparin group				
B01AB01	Heparin	3	3	√	√
B01AB04	Dalteparin	3	Not approved	√	√
B01AB05	Enoxaparin	17	11	√	√
B01AX05	Fondaparinux	1	1	x	x
B02BD	Blood factors				
B02BD01	Factor II, VII, VIII IX, X, human protein C, protein S, von Willebrand's factor	1	1	x	x
B02BD02	Coagulation factor VIII	26	14	√	√
B02BD04	Coagulation factor IX	7	2	√	√
B02BD06	von Willebrand factor and coagulation factor VIII in combination	4	4	√	√
B02BD08	Coagulation factor VIIa	2	Not approved	√	√
B02BX06	Emicizumab	4	Not approved	√	x
B03XA	Other antianemic preparations				
B03XA01	Erythropoietin	3	2	√	√
B03XA02	Darbepoetin alfa	3	Not approved	x	√
B03XA03	Methoxy polyethylene glycol-epoetin beta	4	Not approved	√	√
B05AA	Blood substitutes and plasma protein fractions				
B05AA01	Albumin	15	14	√	NA
C10AX	Other lipid-modifying agents				
C10AX14	Alirocumab	2	Not approved	x	x
G03GA	Gonadotropins				
G03GA02	Human menopausal gonadotropin	3	2	x	x
G03GA05	Follitropin alfa	4	Not approved	x	x
G03GA07	Lutropin alfa	1	Not approved	x	x
G03GA08	Choriogonadotropin alfa	1	Not approved	x	x
H01AC	Somatropin and somatropin agonists				
H01AC01	Somatropin	12	1	√	x
H01BA	Vasopressin and analogs				
H01BA04	Terlipressin	1	Not approved	x	x
H01BB	Oxytocin and analogs				
H01BB02	Oxytocin	3	3	√	x

(Contd...)

TABLE 1. (Continued)

ATC	INN	No. of approvals for biologics issued by ALMBIH	No. of approvals issued for biosimilars by ALMBIH	Biologics accessible through HIF RS	Biologics accessible through HIRI F&B
H01CB	Somatostatin and analogs				
H01CB02	Octreotide	5	2	√	√
H04AA	Glycogenolytic hormones				
H04AA01	Glucagon	1	Not approved	√	x
H05AA	Parathyroid hormones and analogs				
H05AA02	Teriparatide	2	2	x	x
J06BD	Antiviral monoclonal antibodies				
J06BD01	Palivizumab	1	Not approved	√	√
L01FA	Clusters of differentiation 20 (CD20) inhibitors				
L01FA01	Rituximab	11	7*	√	√
L01FA03	Obinutuzumab	1	Not approved	√	√
L01FC	Clusters of differentiation 38 (CD38) inhibitors				
L01FC01	Daratumumab	2	Not approved	x	x
L01FD	Human epidermal growth factor receptor 2 (HER2) inhibitors				
L01FD01	Trastuzumab	8	6*	√	√
L01FD02	Pertuzumab	1	Not approved	√	√
L01FD03	Trastuzumab emtansine	2	Not approved	√	√
L01FE	Epidermal growth factor receptor (EGFR) inhibitors				
L01FE01	Cetuximab	1	Not approved	√	√
L01FE02	Panitumumab	1	Not approved	x	√
L01FF	Programmed cell death protein 1/death ligand 1 (PD-1/PDL-1) inhibitors				
L01FF02	Pembrolizumab	2	Not approved	√	√
L01FF05	Atezolizumab	2	Not approved	√	√
L01FG	Vascular endothelial growth factor (VEGF/VEGFR) inhibitors				
L01FG01	Bevacizumab	2	Not approved	√	√
L01FX	Other monoclonal antibodies and antibody drug conjugates				
L01FX05	Brentuximab vedotin	1	Not approved	√	√
L01FX14	Polatuzumab vedotin	1	Not approved	x	x
L01XX	Other antineoplastic agents				
L01XX44	Aflibercept	2	Not approved	x	√
L02AE	Gonadotropin-releasing hormone (GnRH) analogs				
L02AE04	Triptorelin	2	Not approved	x	x
L03AA	Colony-stimulating factors				
L03AA01	Lenograstim	1	Not approved	x	√
L03AA02	Filgrastim	2	2	x	√
L03AB	Interferons				
L03AB07	Interferon beta-1a	4	Not approved	√	√
L03AB08	Interferon beta-1b recombinant	1	Not approved	√	√
L04AA	Selective immunosuppressants				
L04AA23	Natalizumab	1	Not approved	√	√
L04AA33	Vedolizumab	1	Not approved	√	√
L04AA34	Alemtuzumab	1	Not approved	x	x
L04AA36	Ocrelizumab	1	Not approved	√	√
L04AB	Tumor necrosis factor-alpha (TNF- $\alpha$ ) inhibitors				
L04AB01	Etanercept	4	Not approved	√	x
L04AB02	Infliximab	3	2	√	√
L04AB04	Adalimumab	11	7	√	√
L04AB06	Golimumab	2	Not approved	√	x
L04AC	Interleukin inhibitors				
L04AC07	Tocilizumab	3	Not approved	√	x
L04AC10	Secukinumab	2	Not approved	√	x
L04AC16	Guselkumab	1	Not approved	x	x
L04AC18	Risankizumab	1	Not approved	x	x
M05BX	Other drugs affecting bone structure and mineralization				
M05BX04	Denosumab	1	Not approved	x	x
R03DX	Other systemic drugs for obstructive airway diseases				
R03DX05	Omalizumab	2	Not approved	x	x

(Contd...)

**TABLE 1.** (Continued)

ATC	INN	No. of approvals for biologics issued by ALMBIH	No. of approvals issued for biosimilars by ALMBIH	Biologics accessible through HIF RS	Biologics accessible through HIRI F&B
R05CB13	Dornase alfa (deoxyribonuclease)	1	Not approved	√	x
S01LA	Anti-neovascularization agents				
S01LA04	Ranibizumab	1	Not approved	√	x
S01LA05	Aflibercept	3	Not approved	√	√
S01LA06	Brolucizumab	2	Not approved	x	x
V03AB	Antidotes				
V03AB37	Idarucizumab	1	Not approved	x	x

x: Not included in the lists of medicines which are reimbursed by health insurance funds;

√: Included in the lists of medicines which are reimbursed by health insurance funds; NA: Not applicable (reimbursement for medicine is regulated at the cantonal level). \*Biosimilars approved by ALMBIH without assessment by the European Medicines Agency and without approval issued by European Commission. ATC: Anatomical-therapeutic classification; INN: International Nonproprietary Name; ALMBIH: Agency for Medicines and Medical Devices of Bosnia and Herzegovina; HIF RS: Health Insurance Fund of Republic of Srpska, HIRI F&B: Health Insurance and Reinsurance Institute of the Federation of Bosnia and Herzegovina

the healthcare system. The decision to approve the biosimilars should go beyond mere cost-savings opportunity, as quality and patient safety must also be important. When biosimilars are approved, they need to be comparable to the appropriate originator biologics. They should meet the determined standards for quality, efficacy, and patient's safety. Therefore, assessment of biologics in the process of issuing MA by ALMBIH must be appropriate and in accordance with all EU, ICH, and WHO standards.

### Improve the pharmacovigilance monitoring system

Biologics on the B&H market are under additional monitoring and they are labeled with the ▼ sign. However, the pharmacovigilance program in B&H is insufficient to create an accurate database containing data on each biologic's clinical use, including patient registries and retrospective or prospective observational post-marketing studies. ALMBIH should improve their pharmacovigilance system in collaboration with other stakeholders. Online ADR reporting is one method that can increase the reporting rate. This method was primarily proposed by pharmacists. ALMBIH should popularize ADR reporting by providing additional education, training, and information to the healthcare professionals about this issue [48]. It should employ new highly educated professionals with the necessary experience and competency to perform assessments regarding the safety profile of biologics. The lack of highly educated employees (pharmacists and medical doctors) could be temporarily resolved by the engagement of a committee with experts from B&H who can introduce and establish a causality assessment.

### Establish national conditions for interchangeability (switching and substitution)

The interchangeability (switching and substitution) of biologics is not clearly defined in B&H. Health-care professionals

and other stakeholders in B&H need a government policy document that would precisely determine the conditions for switching and performing substitutions of originator biologics with the biosimilars and between biosimilars. By strengthening the Agency's internal expertise for biologics and improving pharmacovigilance system, the automatic substitution of originator biologic with biosimilars should be recommended.

### Improve the accessibility of biosimilars (promote biosimilar uptake)

Except for advanced stem cell and gene therapy which are not approved in the B&H market, the range of the licensed biologics for the B&H market is otherwise satisfactory (Table 1). However, the previous studies reported the limited accessibility of biologics and the limited use of biosimilars in B&H [9,10,52]. An important way to improve the accessibility of biologics in B&H is to put the important biologics on the list of reimbursed medicines. Education directed at healthcare professionals and key physicians would help fill the knowledge gaps, improve confidence in biosimilars, and increase biosimilar prescribing [53]. In order to raise awareness and knowledge regarding biologics among healthcare professionals, this topic should be included in medical and pharmacy graduate and post-graduate curricula by introducing subjects such as pharmaceutical biotechnology, clinical use of biologics, the role of the pharmacist, regulation of biologics, etc. Several large surveys have shown a lack of knowledge and trust in biosimilars among patients and other stakeholders (policy-makers and payers) [25,26]. It is important to set up a close collaboration among all stakeholders to communicate, develop, and disseminate factual information about biosimilars. The European Society for Medical Oncology has developed a nuanced approach emphasizing the role of Health Technology Assessment processes as well as the need to address the economic impact of high-cost medications on long-term sustainability [54]. According to Knežević and Griffiths [21], robust manufacturing processes

with many in-process quality controls and consistency of quality from a lot-to-lot are important features for the efficacy and safety of the biologics. As previously emphasized, consistency is crucial because minor changes can lead to major adverse effects of biologics, such as immunogenicity, with potentially serious clinical implications [27]. Consequently, one of the new specific regulatory requirements for approving biologics should be a high level of consistency in the manufacturing process with more frequent in-process controls.

## CONCLUSION

The lack of the policy document which would precisely determine the conditions for licensing and interchangeability of biologics, lack of internal expertise within ALMBIH, and underdeveloped pharmacovigilance system in B&H contribute to the lack of wider trust in biosimilars by healthcare professionals, patients, and stakeholders. This situation and consequently better accessibility of biologics in B&H could be improved by:

- Adopting the clearly defined regulatory framework and requirements, as well as related terminology for originator biologics and biosimilars,
- Increasing internal capacity, expertise, and competency in the assessment of Q/E/S and risk/benefit ratio of biologics,
- Encouraging a process of ADRs reporting through permanent education and training,
- Establishing the causality assessment for ADR reports,
- Adopting the government policy document with well-defined conditions for interchangeability of biologics,
- Raising the awareness of healthcare professionals about biosimilars, and biologics in general including this topic in the graduate and postgraduate curriculum programs.

Finally, a collaboration with other national regulatory authorities and the WHO should be ensured in order to promote and implement a global approach to the regulation of biologics.

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