BIOSIMILAR MEDICINAL PRODUCTS – LEGISLATIVE DECISIONS AND MARKET ENTRY

G. Petrova[1], V. Boyadzhieva[2,3], N. Stoilov[2,3], K. Tashkov[1]

[1]Faculty of Pharmacy, Medical University – Sofia
[2]Faculty of Medicine, Medical University – Sofia
[3]University Hospital „Sv. Ivan Rilski“ – Sofia

Abstract. *Biosimilar drugs, structurally identical and manufactured similarly to original biologic drugs, offer potential cost reductions in therapeutic practice, albeit with variations in adoption across European countries. This review synthesizes findings from literature examining legislative decisions and their effects on biosimilar market entry in Europe. Drawing from scientific articles and official documents, the review reveals that biologics constitute 36% of European drug expenditure, with the market valued at € 78.6 billion in 2021 and growing annually at 10.5% over the past five years. Approximately 15% of new active substances centrally approved by the EMA in 2020 were biologics. The European biosimilars market is projected to reach €8.8 billion in 2021. Various measures are being implemented to boost biosimilar uptake, including pricing strategies, reimbursement policies, and substitution practices. Access, measured in terms of availability and time to entry, is still difficult in a number of countries, but legislative measures are helping biosimilars enter European markets more quickly.*

Key words: *biosimilar medicinal products, european markets, legislative decisions*

Introduction

In recent decades, targeted biological therapies have revolutionized the treatment of significant diseases such as cancer, autoimmune disorders, and multiple sclerosis. The synthesis of biological drugs using living organisms and biotechnological methods, such as recombinant DNA technology, differs significantly from classical chemical synthesis. Therefore, specific legislation tailored to these medicinal products is necessary [1, 2]. Biological drugs, characterized by their larger molecular size, composition of amino acids, and categorization into three types (replacement therapy, monoclonal antibodies, and designer proteins), require distinct regulatory frameworks [3]. A comparison between small chemical molecules and biological drugs is outlined in Table 1. Unlike small molecules, biological drugs are highly sensitive to production methods and biotechnological processes, and they have the potential to trigger immune-mediated reactions [4].

The increased complexity of production, research, and clinical testing makes bringing biologic products to market significantly more resource-intensive. A 2017 analysis by the Boston Consulting Group revealed that the average production cost of a biological product (including biosimilars) in America is $60, whereas the average cost per package of a chemical drug product is $5 (including generic drugs) [6]. This disparity underscores one of the primary distinctions between the markets for biological and biosimilar medicinal products – the competitiveness of the environment. The ease of synthesis con-

Table 1. Main differences between biological molecules and chemical molecules (adapted from Declerck et al. [5])

Biological medications	Little chemical molecules
Production by means of live cell cultures	Production through chemical reactions
High molecular weight (> 1 KDa)	High molecular weight (0.1-1 KDa)
Complex, heterogeneous structure	Defined, rectilinear structure
Highly dependent on the production process	Largely independent of the production process
Difficult to characterize	Absolutely characterizable
Unstable	Stable
Immunogenic	Non-immunogenic

tributes to intense competition in the generic medicinal products sector, leading to cost optimization in the production process [7]. Conversely, the intricate scientific methods required for synthesizing biological drugs hinder high competition, primarily due to the lack of understanding of internal processes in host cells, thereby complicating the production of biosimilars [8, 9]. Additionally, biological products are frequently administered in hospital settings, further contributing to the high costs of therapy. These factors collectively drive up treatment costs, underscoring the importance of analyzing the introduction of biosimilars into the pharmaceutical market and the potential savings they could yield. A 2020 analysis by IQVIA indicates that access to biosimilars could result in savings of $100 billion over the next 5 years [11]. Similar prospects are observed in Europe, where biologics constituted 36% of the total drug market in 2021, with estimated savings from the use of biosimilar drugs reaching 30 billion euros [12]. Despite the advantages associated with biosimilar medicines, their availability remains limited, exacerbating the gap between Western and Eastern European countries (Figure 1).

In order to facilitate the process of taking biosimilar medicines, the European Commission holds annual conversations with stakeholders where all aspects of biosimilars are considered. The European Commission has an essential role in the training of medical professionals, since the synthesis of biological medicines is strictly specific and even a reference, original product can become „biosimilar“ by definition if the manufacturer changes something in the production process [13]. In its latest guidance from 2017, the European Medicines Agency (EMA) defined 3 terms related to biological therapy – substitutability, switching, and substitution [14]. Substitutability refers to the substitution of a biological product for another that has the same clinical effect, substitution of an originator for a biosimilar, or a biosimilar for a biosimilar. Switching describes switching from one biologic to another with the same therapeutic target. Substitution is seen as an aspect of pharmaceutical substitution of an original with a biosimilar due to financial considerations.

Obviously, the production, pricing, substitution of biological products and their biosimilars is a subject with strict specificity and many individual characteristics. This has given rise to interest in looking at legislative decisions and the availability of biosimilars on the market.

Materials and Methods

A literature review was conducted of studies published in the last 10 years on the legislation and availability of biosimilar medicinal products, published official legislative documents and their impact on the market of biological medicinal products in Europe. Three of the open studies that examine the market at EU level, Eastern Europe, and Bulgaria were systematized and discussed sequentially by year of publication. The databases covered are PubMed and Google Scholar. Keyword filter was “biosimilar”, “Policies” OR “Policy”, “Uptake”, “Access” OR “Accessibility”

Results and Discussion

One of the most extensive studies in this field was conducted by Moorkens et al. in 2017 15. In this study, the authors surveyed 24 countries, including

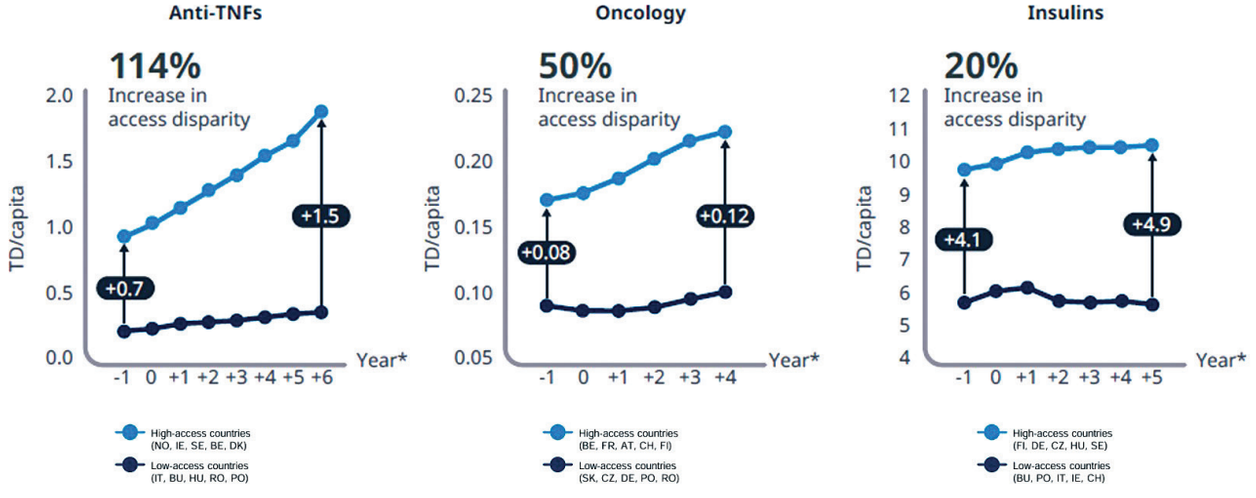


Fig. 1. Availability of biosimilars between Western European and Eastern European countries

20 EU members and 4 non-EU countries – Russia, Iceland, Norway, and Serbia – regarding their local legislation concerning biological originals and biosimilars. The survey questionnaire was structured into five sections: Market availability, Pricing, Reimbursement, Policies controlling demand, and Availability of policies influencing receptivity to biosimilars for selected biologics. Regarding market availability, a greater prevalence of biological products was observed, particularly in hospital environments (see Table 2).

For the most part, the selected products are available in both outpatient and inpatient settings, with the exception of infliximab outside the EU. According to the authors, the restrictions are mainly due to the local organization of the health care system.

Due to the high costs associated with their use, the authors also looked at the number of reimbursed biological molecules with the corresponding international non-proprietary name (Table 3). Of the countries examined, only Germany reimburses all biosimilar medicinal products available and registered on the European market.

Countries within the European Union exhibit relatively higher access, particularly in more developed markets. These larger markets boast a greater variety of reimbursed products, resulting in improved accessibility. However, regulations on medicinal products vary among all countries, with notable differences. The most prevalent pricing mechanisms include intra-reference pricing, where the percentage of price reduction may differ between countries and may be fixed or variable within a certain range. External reference pricing is also common, particularly in countries with lower economic development. The practice of free pricing is limited to very few countries (see Table 4). Overall, nearly all states have implemented various mechanisms for determining the marginal cost of outpatient care.

All countries aim for prices lower than the reference. 13 out of 24 countries implement internal reference pricing within a single INN. 14 countries provide incentives to prescribe biosimilars. Only 6 countries allow substitution.

The study reveals an intriguing correlation between affordability and policy implementation. While half of the states enforce a prescription-quota policy mandating physicians to prescribe biosimilars, very few permit substitution of biosimilars at the pharmacy level. Furthermore, quota principles are often not obligatory and lack additional biocompatibility training. This underscores the significance of the EMA and the European Commission, which conduct regular training sessions for interested parties [16, 17]. Norway emerges as a model country, having conducted a study on the safety and efficacy of switching between an originator and a biosimilar molecule18. Such an approach may enhance physicians‘ understanding and attitudes toward prescribing biosimilars, a necessity underscored by various European studies indicating potential gaps in comprehension [19].

Pricing and reimbursement policies emerged as significant economic factors influencing the cost of biosimilar therapy. Therefore, the second study focused on the Eastern European perspective, examining legislation and specifically, the presence of distinct legislative elements for this drug class [20]. The authors conducted a survey among Bulgaria, the Czech Republic, Hungary, Estonia, Croatia, Latvia, Lithuania, Poland, Slovakia, and Romania, querying local experts about available pricing and reimbursement policies for biologics. Additionally, they gathered information on reimbursed biologic products for 2014 and 2015.

The legislative analysis revealed that no country had specific legislative requirements for the pricing and reimbursement of biosimilars. Generally, biosimilars were available on the market at a lower cost

Table 2. Number of products available on the market in A. ambulatory and B. Hospital settings in the countries

Product	Filgrastrim		Epoetin		Somatropin		Insulin		Follitropin		Infliximab		Etanercept	
Availability	A	H	A	H	A	H	A	H	A	H	A	H	A	H
EU														
Number / Countries	14	21	16	20	14	17	20	16	17	15	7	19	13	19
Outside EU														
Number / Countries	2	4	2	4	4	3	4	4	2	4	0	4	3	4

Table 3. Number of reimbursed biological molecules across the countries

Product	Filgrastim	Epoetin	Somatropin	Insulin	Follitropin	Infliximab	Etanercept
EU							
Austria	4	3	1	-	-	2	1
Belgium	4	2	1	1	2	2	1
Bulgaria	2	2	1	1	2	2	1
Croatia	5	2	1	1	2	2	-
Czech Republic	4	2	1	1	2	3	1
UK	4	2	1	1	1	2	1
Estonia	3	-	1	1	2	2	-
Finland	4	2	1	1	1	2	1
France	5	2	1	1	2	3	1
Germany	8	7	1	1	2	3	1
Ireland	5	1	1	1	1	2	1
Italy	5	2	1	1	2	2	1
Latvia	4	1	1	-	1	2	-
Malta	1	-	-	-	-	1	-
Netherlands	4	3	1	1	2	3	1
Poland	5	1	1	1	2	2	1
Portugal	3	2	-	-	1	1	-
Slovenia	4	1	1	1	2	1	-
Spain	5	3	1	1	2	3	1
Sweden	4	2	1	1	1	2	1
Outside EU							
Iceland		-	1	-	1	2	1
Norway	3	1	1	1	2	2	1
Русия	2	-	1	-	-	-	-
Serbia	2	1	1	-	-	2	1

Table 4. Policies Regarding Biosimilars in Analyzed Countries

Country	Pricing Mechanism	Internal Reference Pricing	Prescribing Stimulus	Substitution
EC				
Austria	First Biosimilar 38% of original, Second- additional 15%; Reference observes 30% reduction in next 3 months	Yes	Yes	No
Belgium	Price is negotiated, obligatory price reduction for reference	No	Yes	No
Bulgaria	No differences between biosimilar and reference	No	Yes	No
Croatia	First Biosimilar 15% lower prices, Second a further 10%	Yes	No	No
Czech Republic	First Biosimilar – 30% without change in reference product	Yes	No	No
UK	Quantity negotiation of price, discounts	No	Yes	No
Estonia	At least 15% price reduction	Yes	Yes	Yes
Finland	At least 30% lower wholesale price	No	Yes	No
France	Between 10-20% lower prices, fixed price	Yes	Yes	Yes
Germany	Free pricing, discounts in tender procedures	Yes	Yes	Yes/No
Ireland	Negotiated prices, typically 10-20% lower	No	No	No
Italy	20% lower price	No	Yes	No
Latvia	First - under 30%, Second further 5%, Third additional 5%	Yes	No	Yes
Malta	Tenders under INN, based on listed price	No	No	No

than the original product, utilizing internal reference pricing. However, reimbursement levels varied significantly among countries. Interestingly, although all countries permitted substitution or switching to a biosimilar, they all experienced higher costs for originator molecules. This study underscores the necessity to implement measures to promote the prescription of biosimilars and educate healthcare professionals. Few professionals are aware that even originator companies modify and optimize the manufacturing process, potentially leading an originator molecule to be considered a biosimilar [21].

The absence of a clearly defined pricing policy for biological and biosimilar medicines at the European level results in significant price variability among original products within the EU. This issue is also the focus of research in the third study conducted by Manova et al. [22], which investigated price disparities in the field of rheumatoid arthritis across 17 European countries. The authors analyzed the price and availability of originator products in these countries, using Bulgaria as the reference basket. They found that at the manufacturer level, price differences for original products ranged from 22% to 69%, while at the pharmacy level, differences could be between 62% and 95%. Among the six medicinal products studied – adalimumab, etanercept, rituximab, golimumab, tocilizumab, infliximab – four had biosimilars available in all countries. Interestingly, biosimilars showed a price gap of 33% to 36% compared to the

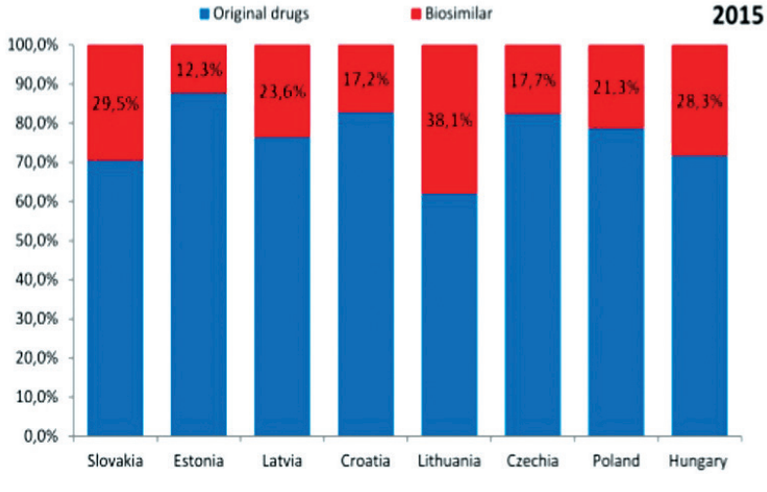


Fig. 2. Cost ratio of original (blue) and biosimilar LPs (red)

reference product, confirming the positive impact biosimilars have on healthcare costs.

In conclusion, it can be observed that European countries influence each other consistently, and there is a resemblance in policies regarding biological medicines. Specifically, approaches to pricing and reimbursement are similar. However, there is variability in the level of development of policies related to the training of medical professionals, interchangeability between originator and biosimilar products, and methods for price control in hospital and outpatient settings. Although most countries have public procurement for hospital products [23], allowing for discount mechanisms, these mechanisms are not available in pharmacy practice. In the future, improved education of specialists and patients about the differences between biological and biosimilar products is expected to be the main obstacle to the adoption of biosimilars.

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✉ *Адрес за кореспонденция:*
Константин Ташков
e-mail: ktashkov@pharmfac.mu-sofia.bg

✉ *Correspondence address:*
Konstantin Tashkov
e-mail: ktashkov@pharmfac.mu-sofia.bg