# *Access to Biosimilars in Central and Eastern Europe*

Writing Assignment

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# Abstract

The aim of this study was to evaluate access to biosimilar medicines in the region of Central and Eastern Europe (CEE). Biosimilars, medicines highly similar to a reference biologic medicine represent a significant breakthrough in therapy, as they can significantly reduce the costs of therapy. Central and Eastern Europe is composed of both members of the EU, which are under the regulatory purview of the EMA, and those that are not. Regardless of that, after the regulatory approval, specific policies on the use of biosimilars are imposed at the national level. As a region with an aging population, and lower GDP on average, there is both a higher unmet medical need and an economic rationale for the uptake of biosimilars.

This literature review has revealed that almost all nations in CEE have specific policies for pricing of biosimilars aimed at promoting their uptake. Pricing decisions are usually made using external reference pricing. Additionally, prices of biosimilars are often linked to the price of the reference prices, and there is a required difference in price between the originator and the biosimilar. Demand-side policies, such as those targeting or educating prescribers, however, are scarcely set in Eastern Europe. Furthermore, less biosimilars are reimbursed and used in CEE. Some countries have mandatory substitution in place, or a policy that treatment-naïve patients need to be started on a biosimilar, or that doctors have to prescribe by INN. The countries in CEE that are not EU members have even more impediments to access, including regulatory approval of biosimilars and even lower budgets. The use of biosimilars may not be as cost-effective in CEE in the short run, given that their prices are primarily set in the Western markets.

Despite the existing policies and a number of biosimilars available on the market, significantly less are available for patients in CEE. Furthermore, while able to characterise the policy aspect, it is difficult to measure the real-world use of biosimilars. Even though there is much to be done to improve access to biosimilars in CEE in the future, most of CEE countries have a solid, existing set of rules that enable biosimilar entry to the markets.

# Layman's Summary

This writing assignment studied the access to biosimilars in Central and Eastern Europe (CEE). Biosimilar medicines are a category of biologic medicines. Unlike most traditional medicines, which are small chemical molecules, biologic medicines originate from living systems, often take form of proteins or antibodies, with much more complex structures. Biologic medicines have made a breakthrough in the treatment of a number of diseases. Biosimilar medicines are made to be highly similar to an original biologic product, but due to the complex nature of their production, they can not be made identical. This also means that a highly rigorous process of determining the similarity between the original and the biosimilar is needed before they are put on the market. The European Medicines Agency was the first drug regulatory body to approve a biosimilar product.

The countries in Central and Eastern Europe are less rich than those in the West. Biosimilar medicines, with their lower prices, have the potential to lower the prices of treatment for many patients in CEE. In order to ensure access to biosimilar medicines, governments set in place a number of policies aimed at reducing their price. However, high prices, usually set in the Western markets remain an obstacle to access to these medicines for patients in need. Other policies that stimulate biosimilar uptake, such as those aimed at educating doctors about their safety and efficacy and alleviate their concerns about this relatively new subtype of medicines have been found to be effective. However, these policies are not commonly instituted in CEE. While a number of CEE countries are EU members, and thus have the European Medicines Agency that has capacities to evaluate and approve biosimilars, those that are not are tasked with doing that themselves. The regulatory bodies of these countries often lack capacity to independently review biosimilars.

In conclusion, there has been great progress in how biosimilars are priced and how they enter markets in Central and Eastern Europe. However, there is fewer biosimilars available in those countries and there is still much to be done to improve patient access to these important, cost-saving medicines.

# List of Abbreviations

| | |
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| **ADA** | Anti-Drug Antibody |
| **AEs** | Adverse Effects |
| **ALIMBiH** | Agencija za lijekove i medicinska sredstva Bosne i Hercegovine – Bosnian National Regulatory Authority |
| **ALIMS** | Agencija za lekove i medicinska sredstva – Serbian National Regulatory Authority |
| **ATM** | Access to Medicines |
| **bMARD** | Biologic disease-modifying anti-rheumatic drugs |
| **CEE** | Central and Eastern Europe |
| **CHMP** | Committee for Medicinal Products for Humans |
| **CInMED** | Crnogorski Institut za ljekove I medicinska sredstva – Montenegrin National Regulatory Authority |
| **EEA** | European Economic Area |
| **EMA** | European Medicines Agency |
| **EPR** | External Pricing Reference |
| **EU** | The European Union |
| **EU MS** | European Union Member State(s) |
| **EUR** | Euros (currency) |
| **GDP** | Gross Domestic Product |
| **HTA** | Health Technology Assessment |
| **INN** | International non-proprietary name |
| **LIMCs** | Low and Middle Income Countries |
| **MAA** | Marketing Authorisation Application |
| **mAb** | Monoclonal antibody |
| **MEAs** | Managed Entry Agreements |
| **NRAs** | National Regulatory Authorities |
| **PRAC** | Pharmacovigilance Risk Assessment Committee |
| **QTTP** | Quality Target Product Profile |
| **RFZO** | Republički fond za zdravstveno osiguranje – Serbian national fund for health insurance |
| **RMP** | Risk Management Plan |
| **SmPC** | Summary of Product Characteristics |
| **SUKL** | State Institute for Drug Control (Slovakia) |
| **USFDA** | United States Food And Drug Administration |
| **V4** | The Visegrad Group (Poland, Hungary, Czech Republic, Slovakia) |
| **WHO** | World Health Organisation |

*Access to Biosimilars in Central and Eastern Europe*

# I. Introduction

The rise of biological medicines (biologics) has been a key breakthrough in therapy since the beginning of the 21st century and has provided treatment options for a number of diseases, especially in areas of gastroenterology, rheumatology, dermatology and oncology. This has been associated with a global rise of treatment costs (1). Because of the nature of biologics, usually proteins by chemical structure, their manufacturing is more complex than for small molecule drugs (2). Their large molecular structure and the fact that they are made by living organisms gives rise to the fact that biologics have an inherent degree of variability within themselves, and their production is very tightly regulated in many regulatory jurisdictions. Due to this complexity, when speaking of biologics, it is practically impossible to make generic versions of such medicines. Therefore, in the biologics space, we are speaking of biosimilars. A biosimilar, according to the definition of the European Medicines Agency (EMA) is "a medicine highly similar to another biological medicine, already marketed in the EU (the so-called 'reference medicine')"(2). Biosimilars are biologic medicines made after the period of market protection (usually 10 years long) expires. They share all the features of biologic medicines in general. Furthermore, biologics are highly similar to the reference medicine, with no clinically meaningful differences when compared to the reference medicine. Minor variability between the biosimilar and the reference medicine are allowed, and they must comply with the same strict standards of quality, safety and efficacy to be approved(2). A vast majority of biosimilars are proteins, such as growth factors, hormones, fusion proteins or monoclonal antibodies (mAbs). One polysaccharide biosimilar is approved in the European Union (EU), a low-molecular weight heparin. Since the approval of the first biosimilar in the EU (and the world), the somatropin Omnitrope ®, the EU and the EMA have been global leaders in biosimilar regulation and policy (1). As of June 2021, 79 biosimilars have been approved by the EMA .

Access to Medicines (ATM) is an essential theoretical concept when discussing health-care delivery in any setting, and can holistically be observed as an interaction between a number of systems at several levels in one given country or at the international level. Bigdeli et al (3) have categorized 5 levels determinant to ATM starting from the level 1 (demand side) being the individuals, households and community, going over to the supply side at level 2 with health service delivery, the governance functions of the pharmaceutical sector at the third level, the health sector, and the two final levels overarching health sector governance, the national and international contexts (levels 4 and 5). This, most recent paradigm of understanding ATM, often used in the context of low and middle income countries (LIMCs), can prove itself useful in the understanding of the many complex factors that

influence access to biosimilar medicines in the areas of interest of this paper. The intricate web of factors from community to governance from manufacturers to healthcare practitioners, influence key elements of access to biosimilars, including regulatory capacity of any given country, pricing and reimbursement policies and finally the way this specific form healthcare is delivered (i.e. prescription practices).

From the perspective of health economics, there is a well-documented global struggle to keep novel biologic therapies cost-effective and available, as their price is often a barrier to patient access (4). This represents a significant barrier to access to these therapies, especially keeping in mind the fact that biologics prices are trending upwards (4). Biosimilars could provide for a competitive and sustainable market that makes biologic therapy more widely accessible at the lowest cost (4). Biosimilars are especially valuable for reducing prices of "blockbuster" biologics, i.e. well-used medicines treating wide-spread conditions. Upon the launch of a biosimilar, which is in general lower priced than the reference medicine, there are observed declines in the sale of the reference product, with the cheaper biosimilar taking some of its space, which is one mechanism by which biosimilars decrease prices of biologic treatment (5). Besides pricing policies, another important aspect of biosimilars policy is policy framework regarding prescription practices. The practice of interchangeability, which has multiple definitions, is defined by the EMA as ''the possibility of exchanging one medicine for another that is expected to have the same clinical effect" (6). Switching or substituting medicines is usually a matter of physician decision and national policy in the European context. While the EMA governs regulatory approval of biosimilars, their market uptake as well as interchangeability policies are left to Member States(1).

The geographical focus of this research is on Central and Eastern Europe, hereinafter CEE. While there are contentious definitions of this region, for the purpose of this study, we will include the following countries, subdivided thusly. CEE countries that are EU members and thus under EMA jurisdiction, namely, Poland, Czech Republic, Slovakia, Hungary, Bulgaria, Romania, Slovenia, Croatia. The three Baltic states, Estonia, Latvia and Lithuania will also be considered in this category. Additionally, the so-called Western Balkan States, namely Albania, Bosnia and Herzegovina, North Macedonia, Serbia, Kosovo*[1] and Montenegro will be included. While these countries are under different jurisdictions and influences, they exhibit commonalities in the development and organisation of their healthcare systems. Furthermore, the differing state of those healthcare systems can provide for useful comparators of policy. The intention is to include the EU member states of the former Eastern Bloc,

* This designation is without prejudice to positions on status, and is in line with UNSC 1244 and the ICJ Opinion on the Kosovo Declaration of Independence

which are comparatively poorer and with lower healthcare expenditure than Western EU Member States, as well states that are in varying degrees of EU accession (Western Balkans) and exhibit regulatory reliance on the EMA, as well as a degree of legal alignment with the EU as part of EU accession.

Having defined biosimilars, several key theoretical concepts and the geographical scope of the study and having observed the place of biosimilars in increasing access to biologic therapies, this study aims to explore various factors of access to biosimilars in CEE including the regulatory framework, pricing and reimbursement policies as well as prescribing of biosimilars. This literature review will try to ascertain what factors contribute to and what factors are prohibitive towards access to biosimilars and draw comparisons between selected states.

# II. Methods

The method of this study is literature review. Peer-reviewed academic articles and publicly available documents were found using academic search engines and on institutional web pages. Academic literature was screened for on Google Scholar and Pub Med, accessed through the Utrecht University library, using queries such as “access to biosimilars”, “biosimilars in Central and Eastern Europe”, “regulation of biosimilars”, “healthcare systems of Central and Eastern Europe”. Selection criteria for the academic articles included recency of publication, and relevance, as demonstrated by publication in reasonably high-impact, peer-reviewed academic journals. Supplementary information about legal documents, treatment and other guidelines and policy were obtained from official websites of institutions such as the EMA, the WHO and local ministries of health and drug regulatory agencies (“grey literature”). For Western Balkan states, searches were performed both in English and Serbian-Croatian-Bosnian (SCB). The analysis of the literature was partially guided by the Bigdeli et al(3) article on Access to Medicines.

# III. Development and Regulation of Biosimilars in the EU

In order to better understand biosimilars, I will first turn to the EU policies governing biosimilar regulation, and examples of other biosimilar policies from (Western) EU Member States, which will serve as a starting point for analysing access in CEE. As the global leader and the region with the most expansive experience with biosimilars, the EU has the most extensive set of regulations of biosimilars which serve as the blueprint for other regions.

## 3.1. Biosimilar Regulation in the EU

The advent of biosimilar development can be traced to the EU, and a guideline that first postulated the possibility of copying a biological product in 2003 (7). The European authorities distinguished between generic products and biosimilars (officially, "similar biological medicinal products") in 2005, and the first biosimilar product was approved in the EU in 2006 (7). In terms of regulatory pathways in the EU, we distinguish between 4 procedures, the centralized marketing authorisation procedure, as well as the decentralised, mutual recognition and national marketing authorisation procedure. Given that almost all biosimilars and biologics are biotechnology-derived proteins which legally must be approved via the centralized procedure (7). It is also pertinent to note that virtually all innovative products undergo the centralized procedure. The fact that all biosimilars undergo the same procedure for all EU and EEA members allows for uniformity, and for a good overview of policies applied over this very large market that serves a significant population.

Before delving into the guidelines and procedures that govern biosimilars and key regulatory challenges, we turn to two key elements of biosimilar "philosophy": *comparability* and *biosimilarity*. A certain, predetermined amount of inherent variability between batches is permitted in biologic medicines, given that living cells are the source of biotechnological medicinal products. Furthermore, the manufacturing process of such products is the key determinant of their features, and it may have severe implications for the quality process of the product (7). Manufacturers are therefore required to establish that safety and efficacy of their product remain unchanged with manufacturing changes. This so-called comparability exercise can be quite extensive, both with regards to biosimilars, and biologics, and when changes in quality profile are detected, non-clinical and even clinical bridging studies may be required(7). While a change in quality profile does not necessarily mean a change in clinical performance of a therapeutic, stringent requirements are put in place to ensure this in case of uncertainty. These principles of *comparability* guide the way similarity is demonstrated for biosimilars(7). *Biosimilarity* is established using highly-sensitive analytical methods, and followed up by non-clinical and clinical studies. The active substance of the biosimilar is a close copy of the active substance of the reference product(7). Due to the complexity of the biological products, and the high impact of the specificities of manufacturing, some degree of variation is expected and minor differences in quality attributes are expected (7). In case of proteins, biosimilarity requires identical primary structure (the amino acid sequence) and folding pattern (tertiary structure) (2).

A comprehensive set of scientific guidelines governs the development and assessment of biological products, including biosimilars in the EU (2), (7). All existing regulation for biologics applies to biosimilars. Furthermore, there is a hierarchically organised set of guidelines applied to biosimilar specifically. There is one umbrella guideline which outlines general principles for all biosimilars, under

it two general guidelines one quality and other on non-clinical and clinical issues. Finally, a set of product-class specific guidelines that provide guidance for non-clinical and clinical issues constitute the last layer of the guidelines (7). The regulatory assessment of biosimilars is the same as for any new innovative products under the centralised procedure. The goal of the assessment is to ensure that the biosimilar and reference product are indeed similar (7). Marketing Authorisation Applications (MAAs) for biosimilars (and all centrally approved product) are referred to the Committee for Human Medicinal Products (CHMP), that nominates two members as rapporteurs, while the Post-authorisation Risk Assessment Committee (PRAC) nominates one of its members to be the rapporteur for the Risk Management Plan (RMP) (8). The expert teams under the rapporteurs will work independently to asses the MAA dossier and provide questions for the respondent. The respondent is given 3 months to submit responses. Usually after 3 rounds of questions and responses, the CHMP will provide an opinion. The PRAC simultaneously assess the RMP. The two assessments are finally referred to the executive body of the European Union, the European Commission (EC) that grants the Marketing Authorisation. The presence of elaborate guidelines and the stringent assessment leads us to conclude that the biosimilar approval process in the EU is robust and transparent (7,8).

## 3.2. Development and Approval of Biosimilars

The active substance of a biosimilar needs to be similar to the referent product so much so that it can be called a different version of the same active substance. Furthermore, while for the development of an innovative product, the manufacturer needs to establish acceptable quality, non-clinical pharmacology and toxicology, PK, PD and finally safety and efficacy in all therapeutic indications, in biosimilar development the goal is to demonstrate an acceptable level of comparability of quality, efficacy and safety. Once demonstrated, the manufacturer can refer to the reference product (7). The EMA recommends that the biosimilar development process start with careful analysis of the reference product, including the understanding of batch-to-batch variability of the product. Based on this analysis a QTTP, quality target product profile is developed. The QTTP guides biosimilar development. Then, the manufacturer establishes the manufacturing process for the biosimilar. Once established, a side-by-side pivotal comparability analysis of the biosimilar and the reference needs to be performed (7), (9). The regulator can conclude 3 different outcomes from the comparability exercise. Firstly, that the analytical similarity is convincingly demonstrated and that no further analyses are required. The second possibility is that significant differences are noticed, and the candidate cannot be regarded as a biosimilar. The third scenario is that similarity is demonstrated for most attributes, but additional information and testing is necessary to ensure similar clinical performance in all indications (7).

The non-clinical analyses, according to the EMA guidance are designed with the view to taking into consideration possible differences in physicochemical and structural analyses, and to provide basis for

clinical studies (7). There may sometimes be reasons to perform non-clinical in vivo studies to demonstrate differences. Immunogenicity needs to be studied for the biosimilar, much like for any biologic molecule, and due to a lack of standardized assays, immunogenicity studies must always be present in comparative studies (7). Immunogenicity is a key area of concern for biologics, and comparatively different immunogenicity is a possibility with biosimilars In the EU, applicants are required to present the anti-drug antibody (ADA) strategy (7). This is because small differences in protein structure may result in different (higher) immunogenicity potential for biosimilars. While bioequivalence is sufficient for concluding efficacy and safety of generics, the EMA guidance for biosimilars prefers pivotal single-dose PK studies in healthy volunteers. For establishing safety and efficacy, the clinical comparability is usually ascertained in a randomized clinical trial (9). The aim of safety and efficacy studies is to confirm clinical comparability, not re-demonstrate the efficacy and safety of the biosimilar. Finally, all new medicinal products in the EU, including biosimilars, require a risk management plan tailored to the product, which includes the description of the applicant's pharmacovigilance system (7).

## 3.3. Pharmacovigilance of Biosimilars

Safety signals for any newly approved medicine need to be systematically and continually monitored, detected and evaluating. In the case of biosimilars, the concern is the potential impact of intrinsic differences in immunogenicity among products (10). The EMA requires biosimilar applicants to implement rigours pharmacovigilance systems and an RMP. The applicable EMA guidance postulates that a proposed biosimilar pharmacovigilance system needs to include "qualified staff responsible for pharmacovigilance, identification of the organization and locations of the principal pharmacovigilance activities and databases, documented procedures for data protection, processing and mandatory reporting and databases compatible with electronic reporting" (10). While the introduction of biosimilars has largely been successful, there are important challenges to the healthcare system that include tracking and tracing adverse events (AEs) in relation to a specific product. The identification of a biologic only by the shared non-proprietary name, that may be familiar to the reporting physician in AE reporting has a potential to erroneously attribute the biosimilar-specific AE to the reference product. The current pharmacovigilance system is heavily reliant on spontaneous and voluntary AE reporting. We, however, recognize that only a minority of AEs are reported in such systems. Another important issue in biosimilar and biologic pharmacovigilance is that AEs are attributed to product name but not available product information such as batch number (10).

## 3.4. Interchangeability

While the approval of biosimilars is under the guise of the European Union centrally, interchangeability decisions, as well as the majority of other biosimilar-related policies are under the jurisdiction of the Member States. The EU currently has no official policy on interchangeability, and does not distinguish between a biosimilar and interchangeable medicine. The United States Food and Drug Administration (USFDA), however does distinguish between the two categories and requires specific interchangeability studies for a biosimilar to be declared interchangeable biosimilar(1). Several National Regulatory Authorities (NRAs), such as those of the Netherlands, Finland, Ireland and Germany have taken national positions and endorsed the interchangeability of biosimilars under the supervision of the prescriber (6). While interchangeability is not universally defined, the EMA definition (see Introduction) predicts the possibility of switching a medicine for an adequate substitute, it does not distinguish between "switching" driven by the prescribers, and automatic substitution of biosimilars at the pharmacy level without consulting the prescriber, which are both possible, and may take place for biosimilars.

Despite the fact that the medical community has expressed concerns about interchangeability, especially regarding immunogenicity of biosimilars, there is consensus in literature is that undesirable immunogenicity is unlikely to be triggered by biosimilar products (6). As biosimilars share the mechanism of action, highly similar physicochemical and functional properties and have comparable pharmacokinetics and pharmacodynamics with the reference medicine, it is unlikely that they would behave differently in patients. Despite it not being expected, harmful immunogenicity cannot be fully ruled out in switches (6).

## 3.5. Access to Biosimilars

In the EU, decisions about reimbursement of medicines are taken at the national level. Health Technology Assessment (HTA) is often used to inform reimbursement and/or pricing decisions (e.g. in France or Italy). Most EU countries used multiple instruments applied to different segments of the pharmaceutical market to regulate prices of medicines. External reference pricing (ERP) is used by all but one EU MS (Sweden), but there is large variation in how it is actually used. For example, in Denmark it only applies in the hospital sector, while in Germany it exists as a legal category but is not used in practice(11). The pricing point obtained through EPR which is usually used for new products serves as a starting point for public payers to further negotiate agreements and reach a more affordable price. EPR can negatively impact the access to innovative products, by for example a lower income country referencing the prices of a higher income country for price high enough to represent a barrier. Increasingly, European countries have been turning to managed entry agreements (MEAs)

as a means of entry. Such agreements take many forms and can be based on sophisticated performance-based or health outcome-based schemes where the price of the product is linked to observed health outcomes. They may be confidential (e.g. France) or publicly available (e.g. Belgium) (11).

Policies that incentivise the penetration of biosimilars to the market can be classified as physician's incentives: prescription budgets, quotas, monitoring of prescription patterns, financial incentives, guidelines, switching, prescribing by the International non-proprietary name (INN), education; pharmacist's incentives i.e. substitution, financial incentives, education; and finally patient's incentives such as co-payment and education (12). Specific policies to encourage the uptake of biosimilars diverge from policies that encourage uptake of generic medicines. Prices of biosimilars are often linked to the price of the reference (originator) prices, and there may a required difference in price between the originator and the biosimilars (12). This difference is overall lower than the difference in price for generics. Additionally, while generic substitution has been in wide use across Europe, similar policies have not been yet fully developed for biosimilars(13). Reimbursement is also a matter of national policy, and in some countries, such as Italy, even regional authorities may be involved. In a majority of EU countries, reimbursement is granted for all indications authorised, and not only those for which a clinical trial was conducted (13).

Demand-side policies are policies that e.g. target physicians to prescribe biosimilars. These may include the requirement to use INN prescribing, including biosimilars usually for treatment-naïve patients. In Belgium, for example, as part of the wider national initiative to ameliorate access to innovative products, physicians are encouraged to prescribe at least 20% biosimilars for treatment-naïve patients. In Germany, there are quotas for some biosimilars at a regional level (13). Quotas for prescribing low-cost or most cost-effective medicines are in place in some countries (e.g. Austria) and biosimilars may be part of those quotas. In countries with a more privatised healthcare system, such as the Netherlands, limitations on prescribing the originator product may be in place after the biosimilar has enter the market due to enforcement by insurance companies. Additional demand-side policies are education initiatives implemented across countries, such as local initiatives by doctors in hospitals or ambulatory care. Prescribing and therapeutic guidelines can also inform physicians. Countries like the Netherlands or Portugal organize education activities, usually put together by health authorities, to educate all stakeholders on biosimilars. While less reported in literature, patient education on biosimilars does take place, mainly via patient organizations (13).

Specific substitution policies also influence the uptake of biosimilars. For example, in France, legislation has been introduced with regards to substitution, limited to treatment-naïve patients.

Germany, however, has a special category of bioidenticals defined for some biologicals, where pharmacist substitution is allowed, unless specifically prohibited by the prescribing doctor (13).

An example of good biosimilar practice is Norway, which is not an EU MS but a part of the EEA[2], where several policies such as pricing, uptake enhancement and education is used. Norway uses tendering through a public procurement agency for public hospitals, and works closely with clinical practitioners to educate and stimulate them to prescribe cheaper tendered medicines. This has led to impressive results, namely discounts of up to 80% between the originator and biosimilar medicines (13).

# IV. Biosimilars in CEE EU Member States and the Baltics

## 4.1. Rationale for Biosimilar Use in CEE

Overall, countries in CEE have a greater unmet medical need for more advanced therapies, given the overall shorter life expectancy and worse overall health status of the population when compared to high-income Western member states (14) . Due to the status of their economies, there is more economic strain on those countries, especially when external price referencing is taken into account, since prices of new medicines are adjusted to prices set in higher-income economies. Launch strategies of pharmaceutical companies are also carefully sequenced to avoid price erosion, therefore lower-income economies are selected for later launch dates (15). *Au contraire*, the cost of health services in CEE are significantly lower than those in Western Europe. New medicines, which may be cost-effective in the West, are not necessarily cost-effective in CEE. However, there is strong and understandable pressure on CEE health systems to provide access and reimbursement for such medicines. Therefore, CEE countries are coming up with any number of cost-containment measures. These measures may include confidential price reductions, delayed reimbursement of biologic medicines, restricting the volume of patients being reimbursed the price biologics, limiting treatment duration, introduction of waiting lists and narrowing the reimbursed indication that is specified in the specific medicine's MAA. These measures are rather contrarian, and while their impact in terms of economic policy may be debated, combined they do create a significant access barrier to innovative therapies (15).

Having established this, we turn to the rationale for the use of biosimilars, especially in CEE markets, which is completely analogous to the one for using generics, especially keeping in mind that more and more biologics are soon to or have already lost patent protection (on the so-called *patent-cliff*), and

[2] EEA: European Economic Area (Island, Lichtenstein, Norway + EU28) , medicines approved by EMA are approved in both the EU and the EEA

we are, according to literature in a biosimilars "boom" (15). Biologics are naturally not a solution that allows full access to innovative therapy comparable to the one in the West for CEE patients, not only because they are significantly more expensive and complicated to produce, register and reimburse than generics, but also because biosimilars are themselves biologics, which carry with them issues to administer, monitor and manage in lower-income healthcare settings. What is apparent from a review of the existing literature on the subject is that, in fact, all above-mentioned bottlenecks and attempts at restriction do show up in some CEE countries (15), (16). However, all CEE countries seem to have some policies that aim at increasing biosimilar uptake and lowering their prices. For that end, I will attempt to document the following aspects: the presence of legislation specific to biosimilars, the current rules for pricing and reimbursement, provide an overview of the availability of main categories of biosimilars (where available) and finally attempt to identify any demand-side policies implemented in each of the CEE countries.

## 4.2. Country-specific policies

### *4.2.1. The V4 Countries*

The countries of the Visegrád group (the V4) : Poland, Hungary, Czech Republic and Slovakia share cultural and political ties, and represent a distinct block within the EU. Tesar et al.(17) analysed the reimbursement status of biosimilars in the V4 countries. At the time of the publication (2020), 54 biosimilars were approved by the EMA, and of the total group, 54% were available in the Czech Republic, 52% in Poland, 50% in Hungary and 44% in Slovakia, in the total range between 29 and 24 biosimilars. Here we define available as reimbursed by the respective reimbursement schemes for those countries. Kawaletz et al (18) investigated the reimbursement status of biologics for a list of reference active substances in 2016 as well as policies in place for reimbursement of biologics. In these countries, reimbursement criteria were similar to those for generic products. Specific price discount for first and subsequent discounts are in place in all of them. While all countries do have legislative frameworks for biosimilars, none of those seem to predict therapeutic substitution as a possibility, and in some cases it may be prohibited. The richest literature reporting is found for the V4 countries, and they serve as a good example of high variation between specific countries.

In **Hungary**, the first biosimilar to enter the market has to offer a price reduction of 30% compared to the ex-factory price of the reference product, in accordance with the ESzCsM Decree, meaning that there is specific legislative framework for biosimilars. The second product needs to offer an additional 10% reduction compared to the first biosimilar, and the third one an additional 10% compared to the second biosimilar. Hungary uses tendering to set the prices, and the main criterion for tendering is price. Inpatient drugs, such as filgrastim, etanercept, infliximab, epoetin alfa and zeta products are

reimbursed 100%, however Hungary has a prescription fee per unit of 300 HUF (approx. 1 EUR). The timelines for pricing and reimbursement decisions in Hungary vary between 60 days for the simplified and 90 days for the standard procedure, which is well within the limit of the EU Directive on Transparency that limits the deadline for such decisions to 180 days. This literature search was unable to identify specific demand-side policies currently or previously enacted, or proposed in Hungary, which does not exclude the possibility that they exist (13,17,18).

In the **Czech Republic**, the biosimilar pricing policy is set by the Amendment to Act No. 48/1997 Coll., on Public Health Insurance (1st April 2017). The price and reimbursement of the first biosimilar is at 30% of the price of the reference product. The statutory price of the reference product remains the same, but the reimbursement level is lowered to the price of the biosimilar. The maximum price is determined via ERP, which accounts for all EU members except Bulgaria, Estonia, Luxembourg, Germany, Austria, Romania, Cyprus and Malta. Substitution is not allowed. In Czechia, biosimilars have represented 17,7% of the share of pharmaceutical expenditures in 2015. The impact of biosimilars is also known for Czechia, and the average price reduction of biologics was at 50% at 2015, among the highest in the EU, likely due to introduction of new policies regarding biosimilars at the time. Furthermore, tenders are rarely established by the State Institute for Drug Control (SUKL) or health insurance funds due to a mandated reassessment of the reimbursement level for all products within a reference group. There seem to be demand-side policies enacted in Czechia, but specifics are not present in reviewed academic literature (13,17,18).

**Slovakia** implements an internal reference system, whereby the absolute level of the reimbursement for a standard daily dose of a medicine with specific active substance is linked to the least expensive alternative in that internal reference group, meaning that in Slovakia, biosimilars have a significant capacity to downsize the cost of medication (19). New regulations were in place since 2019. Until 2018, only 14 reimbursement dossiers were submitted in Slovakia. Since 2019, the first biosimilar to come to market should bring a 25% initial price reduction, and the second another 5% compared to the first and the third yet another 5% compared to the second biosimilar. Furthermore, the peculiar new legislation considers new types of packages of biosimilar as new medicinal products, and the 3-step price reduction is applied to such a change. Slovakia has no biosimilars available for epoetin zeta, etanercept and somatropin, and has a very low level of penetrations of biosimilars for follitropin alfa, infliximab and insulin glargin. Original products are, however, available. No demand-side measures are in place in Slovakia, and it appears that there is a proposal for increasing the penetration of biosimilars through state-lead incentives at the stage of public debate (19).

In **Poland**, the first biosimilar is priced with a 25% reduction compared to the reference product, and the second biosimilar needs to be cheaper than the first, at an unspecified rate. Limit groups to exist where the cheapest is the limit for the whole group. Substitution for biosimilars is allowed within reference groups, and the substitution is to be discussed by the pharmacist with the patient. Drugs are tendered with the price as the main criterion. If the original drug or another biosimilar is already on the reimbursement list, there is no need for a full HTA assessment, and a simplified Budget Impact Analysis is sufficient. The highest expenditure among the V4 for biologics is observed for Poland. Demand-side policies are implemented, including education, and the fact that pharmacist substitution is allowed. Physicians are not mandated to prescribe by INN, but may decide to opt for a biosimilar in treatment-naïve patients (13,18)

### *4.2.2. The Baltic States*

The Baltic States of Estonia, Latvia and Lithuania have among the highest levels of economic development and GDP per capita in the CEE region, and by some standards may be classified as Northern European, and not CEE countries.

In **Estonia**, prices of biosimilars are negotiated. In case of ambulatory use, the price has to be at least 15% lower than for the reference product. No such requirement exists for hospital use. Estonia is one of the rare CEE countries with a defined substitution policy. Doctors are required to prescribe by INN, and consequently, both treatment-naïve and existing patients receiving biologics are subject to substitution. Pharmacists inform patients about the cheapest alternatives. Physicians can prevent substitution on medical grounds by providing justification. Patients retain the right to refuse substitution, but the price difference between the biosimilar and the original drug is then paid for out-of-pocket. Estonia had an 8% rate of reimbursement of biosimilars in 2014, lowest at the time for CEE, but this level appears to have increased by instituting new policies, such as mandatory substitution. There appear to be other incentives for prescribing biosimilars in terms of demand-side policies, but they remain unspecified in literature (13,18).

Just like Estonia, **Latvia**, has a substitution policy. In Latvia, biosimilars are evaluated by the principles applied to generics, unobserved in other countries of interest, the first biosimilar has to be at least 30% reduced price compared to the reference product, the second and third biosimilars at least 10% cheaper than the first or second biosimilar and all subsequent biosimilars at 5% further decrease. No other incentives to prescribe have been observed. The price is capped and cannot be higher than the third lowest price in Czech Republic, Romania, Slovakia, Hungary and Denmark, and not higher than the price in Estonia and Lithuania. Substitution at the pharmacy level is allowed, unless the prescribing physician indicates otherwise on the prescription, the pharmacist has a duty to inform the patient of

the cheapest alternative. Substitution can be refused, but much like in Estonia, the difference is paid out-of-pocket. Newly diagnosed patients, however, do not have that choice, INN prescribing has to be used and the pharmacist has the duty to dispense the cheapest reimbursable product, conforming to name, pharmaceutical form and strength. The patients cannot choose.

**Lithuania** had the highest level of reimbursement of biosimilars at 32.4% of total biologics mix in 2015, and no more recent data seems available. Tendering is applied only to inpatient, but not ambulatory care. There is a specific price negotiation procedure for outpatient care, with a specific pricing pathway. First biosimilar is discounted 30% and the subsequent 15%. In 2015, substitution was not allowed, neither was interchangeability. HTA assessments are not required for previously reimbursed drugs, when a biosimilar enters the market (18). There is comparatively less data available for Lithuania than for the other Baltic and V4 countries.

#### *4.2.3. Slovenia, Bulgaria, Romania and Croatia*

Out of these 4 states, Slovenia entered the EU in 2004, together with all the previously listed CEE states. Bulgaria and Romania followed in 2007, and Croatia was the last to enter in 2013.

In **Slovenia**, the smallest country in CEE, biosimilars are tightly regulated, namely if the same biosimilar medicinal product is available in one of the reference countries or in any other country in the EU/EEA, the price is respectively at 92% of the lowest price of the biosimilar in the reference countries, which are Austria Germany and France, or a 92% median price in other EU/EEA countries. However, if the biosimilar is not on the market in any of these countries, biosimilar is at 68% of the price of the reference product. The local NRA determines maximal prices for all medication, including biosimilars. Prices are negotiated by the reimbursement body, hospitals themselves or in public procurement. No demand-side policies are observed in Slovenia, and substitution is not in the existing framework (13,18).

**Croatia** also uses ERP, with reference countries being Italy, Slovenia, Czech Republic and France. The first biosimilar needs to be 15% cheaper compared to the reference product, and all next biosimilars 10% less than the previous biosimilars. A specificity unobserved in other CEE countries is that reimbursements for biosimilars are granted not for all indications listed in the SmPC but only for those where a clinical trial was conducted. Tenders are not used. Substitution and interchangeability are allowed at the discretion of the physician, not at the level of the pharmacy. The deadline for reimbursement decisions is 90 days. HTA evaluation is required in some cases, but usually a BIA is sufficient. In 2015, Croatia had among the lowest shares of biosimilar reimbursement as opposed to other CEE countries (13,18).

**Romania** has a flat discount of 20% for biosimilars. Tenders are not used. Substitution and interchangeability are allowed at the discretion of the physician. Romania requires full HTA to reimburse biosimilars (18).

**Bulgaria** ranks as one of the poorest EU members, with the lowest GDP per capita (Eurostat). Discounts for prices of biosimilars exist but are confidential. If the reference drug is reimbursed, HTA is not required, only a pharmaco-economic evaluation of the biosimilar (20). Substitution and interchangeability are allowed at the discretion of the physician. A total of 180 days is the required timeline for decisions on reimbursement, and for next drugs only 60 days. Tachkov at al. (20) have published a paper detailing the impact of biosimilars on the price and utilization of biologic disease-modifying anti rheumatic drugs (bDMARD) in Bulgaria. They have observed that only a half of biosimilar products approved in the EU are reimbursed in Bulgaria. They did observe a positive impact of biosimilars on the price of biosimilars, namely a decrease of 50% for INNs where biosimilars were introduced. Their statistical analysis did not rule out the possibility of other factors contributing to the price decrease. Finally, they observed that the entry of biosimilars into the country is relatively slow (20).

*Table 1 Results Summary - EU countries: presence/absence of specific components of biosimilars policy*

| Country | Stepwise discount | Tenders used | ERP used | (mandatory) substitution | Demand-side policies in place |
|---|---|---|---|---|---|
| **Hungary** | ✓ | ✓ | ✓ | X | X |
| **Poland** | ✓ | ✓ | N/A[3] | ✓ [4] | ✓ |
| **Czech Rep.** | ✓ | X | ✓ | X | ✓ |
| **Slovakia** | ✓ | N/A | X | X | X |
| **Estonia** | X | N/A | X | ✓[5] | ✓ |
| **Latvia** | ✓ | N/A | ✓ | ✓ | X |
| **Lithuania** | ✓ | ✓ | N/A | X | N/A |
| **Slovenia** | ✓ | X | ✓ | X | N/A |
| **Croatia** | ✓ | X | ✓ | ✓[6] | N/A |
| **Bulgaria** | X | ✓ | N/A | ✓[7] | X |
| **Romania** | X | X | N/A | ✓[8] | X |

[3] N/A= not identifiable from available literature
[4] By prescribing physician
[5] Mandatory prescription by INN
[6] Allowed at discretion of the physician
[7] Ibid.
[8] Ibid.

# V. Biosimilars in the Non-EU Western Balkans States

Countries in the so called Western Balkans (political, not geographical term), namely Serbia, Bosnia and Herzegovina, North Macedonia, Montenegro, Albania and Kosovo*, unlike other CEE countries, are not members of the EU, however, they are all in some phase of EU accession, and as part of that process are harmonizing their legislation with the EU. Furthermore, due to their proximity to the EU pharmaceutical market, they all express some level of regulatory reliance on the decisions of the EMA. As such, they can be compared with EU Member States. Nevertheless, the regulatory element of access to biosimilars, which does not exist in CEE countries that are EU members exists here. Biosimilars are among the regulatory topics that are somewhat nascent in these countries. Therefore, it is useful to also examine the presence of e.g. scientific guidelines or other demonstrators of regulatory capacity to independently review biosimilars, which in turn, may among other factors influence the willingness of manufacturers to enter these markets.

In terms of medical need, majority of the countries have old populations and significantly lower healthcare expenditure when compared to the rest of the EU. The incidence of diseases for the treatment of which biosimilars are used is more or less comparable(21) . The rationale for market entry of biosimilars as a facilitator of access in these countries is the same as for other CEE countries, however other factors remain.

## 5.1. Serbia

In Serbia, the regulation of medicines is done by the Agency for Medicines and Medicinal Devices (*Agencija za lekove i medicinska sredstva – ALIMS)*. As per the search of the agencies website, there are no specific scientific guidelines available. Multiple biosimilars are on the market in Serbia, with marketing authorisations generally several years behind those from the EMA. Some professional associations of physicians have recommended that only biosimilars approved by the EMA or the FDA be approved by ALIMS, and this is mostly done in practice, presumably to rely on those regulatory agencies heightened capacities to assess biosimilars (22) . Biosimilars are registered only for an indication for which clinical trials have been performed, no extrapolation for other indications is allowed (13,23).

Biosimilars can be procured by national tender for brand names. The Republic's Fund for Health Insurance (*Republički fond za zdravstveno osiguranje – RFZO)* is in charge of pricing and covering the costs of medicines. Internal reference pricing is in place. The first biosimilar is discounted at 30% on

the reference product and sets the reference rate. The second biosimilar has to be 10% off the first biosimilar, and the third one 10% on the second. The price is capped by External Reference Pricing, at the maximum of 90% of the average price of the corresponding biosimilar in Slovenia, Croatia and Italy. Biosimilars are reimbursed only for indications for which clinical trials have been conducted. Automatic substitution does not take place and the treating physician can make the decision to switch to biosimilar. There is no automatic introduction of biosimilars for treatment-naïve patients. Demand-side policies have been observed in Serbia, in terms of physician education (12).

## 5.2. Montenegro

In Montenegro, the regulatory agency, CInMED (Institut za ljekove I medicinska sredstva Crne Gore) approves biosimilars, and also participates in setting the reimbursement prices. The CInMED relies in part on EMA decisions for novel medications, and is currently in a twinning project with the Croatian (EU Member) national medicines agency HALMED (*Hrvatska agencija za lijekove i medicinske proizvode)*. There are no specific guidelines for biosimilars. No specific pricing scheme is in place for biosimilars, and pricing is done through external references with reference countries being Slovenia, Croatia and Serbia. There are two biosimilars are on the market and the national reimbursement list: somatropin and filgrastim. Substitution is done on the recommendation of the treating physician (24).

## 5.3. Bosnia and Herzegovina (BiH)

The NRA of BiH is the ALIMBiH (*Agencija za lijekove i medicinska sredstva Bosne i Hercegovine).* This agency covers the entirety of BiH, both of its entities and Brcko district. It has adopted specific regulatory guidelines for the approval of biosimilar medicines. It is recommended that approvals are issued only when clinical trials have been performed for any recommendation. There have been recommendations issued on including biosimilars into treatment guidelines for relevant diseases such as Inflammatory Bowel Diseases. Tenders by brand name take place in procurement. Automatic substitution does not take place. There are 3 separate funds for public insurance, one for each of the entities (Republic of Srpska and Federation of Bosnia and Herzegovina) and another for Brcko district. This may mean that there are differences in access between the regions (25,26).

## 5.4. North Macedonia, Albania, Kosovo

Biosimilars are present on the market in North Macedonia and Albania, as per the websites of their respective regulatory agencies. The regulatory system of Kosovo is more nascent and upon examination of publicly available data, it is not clear whether biosimilars are present on the market in Kosovo. North Macedonia and Albania both use external reference pricing for all medicinal products(27) . No specific biosimilar policies were detected.

*Table 2 Results Summary Table - non-EU countries: Overview of present biosimilar policies*

| Country | Stepwise discount | Tenders used | ERP used | (mandatory) substitution | Demand-side policies in place | Biosimilar regulatory guidelines adopted | Reimburse only when a RCT was performed for specific indication |
|---|---|---|---|---|---|---|---|
| **Serbia** | ✓ | ✓ | ✓ | X | X | ✓ | ✓ |
| **Montenegro** | | | ✓ | X | X | X | N/A[9] |
| **Kosovo** | N/A | N/A | ✓ | X | X | X | N/A |
| **Albania** | N/A | N/A | ✓ | N/A | X | X | N/A |
| **North Macedonia** | N/A | N/A | ✓ | N/A | X | X | ✓ |
| **Bosnia and Herzegovina** | N/A | N/A | ✓ | N/A | X | X | ✓ |

# VI. Discussion

Having described policies set in place in Central and Eastern European countries that pertain to the regulation and pricing of biosimilars, we will be moving towards the analysis of their impact and needs for improvement from a broader perspective of access to medicines. The study determined that most countries use a step-wise discount system for establishing the externally-referenced prices of biosimilars, and that a majority of countries procures them by tender. Demand-side policies were observed in a handful of CEE countries.

For countries in CEE, which on average have lower incomes as opposed to the Western European countries, the biosimilars may not necessarily be cost-effective. This has been attributed to external price referencing (EEP), as well as the use of parallel trade by some higher income EU countries (e.g..the Netherlands), which prevent manufacturers of originator biologic medicines from reducing the price of their high-cost products in lower income markers(28). As observed, the majority of CEE countries, both EU members and non-EU states, use external price referencing. Additionally, on the list of reference countries, most have at least one high-income Western EU MS. However, as mentioned before, there is a significant level of pressure on health care decision makers from patient advocacies, politicians, the pharmaceutical industry and clinicians themselves for an increased uptake

[9] Not determinable through available literature

of biosimilars. This is evident in the development of biosimilar pricing policies, but also restrictions put in place on prescribing and using biosimilars. Barriers to access are then created as a product of the interaction between high demand and inability to sustainably fund biosimilars and biologics (28).

Barriers to treatment can be at an institutional, prescriber or patient level (28). At the institutional level, volumes of biosimilars can be capped, and sometimes the number of institutions where they are prescribed can also be limited. At the level of the prescriber, prescription guidelines in CEE are often financially motivated and may impose restrictions or require that biologic or biosimilar products be used only as the second line of treatment. Treatment duration of any biologic or biosimilar may be reduced as opposed to the duration predicted in the SmPC. Restrictions directed to patients have also been reported, such as waiting lists, or special procedures for the reimbursement of medicines. The existence of these barriers allows for the biosimilars to be aimed at CEE markets in two distinct ways. If restrictions are in place on volume or number of patients treated, and the countries have reference biologics on the market, the entry of the biosimilar should aim at treating more people within the same, limited budget. The second scenario is that the reference biologic medicine is not reimbursed, and the entry of the biosimilar would then allow for treatment of patients that was previously impossible (28).

Benefits from the introduction of biosimilars that have been described in literature are predominantly savings for the entire healthcare system, which positively impact the patients, payers and healthcare providers (29). These benefits have primarily been characterized for high-income countries in the West, at this point. Despite them currently not being as cost-effective in CEE, it is safe to assume that the entry of biosimilars, however gradual, will eventually provide similar benefits for patients and the entire health systems in CEE.

The large majority of studies cited in this research are either results of key informant interviews with policy makers, or analyses of publicly available data on reimbursement lists. While mapping biosimilar policies is an important first step in evaluating access to biosimilars, the real use of biosimilars is difficult to ascertain by these conventional methods. As such, while we are able to understand the policy maturity of the region, real influences on patients remain elusive. Having mapped out the policies, we are also able to observe that biosimilars have significantly shaped the reimbursement systems of countries in the CEE (18). The environment of reimbursement is highly dynamic, and the real world practices may differ from the policies here observed. The wide-spread presence of incentive policies is an encouraging sign. It is also encouraging that, while some analogies do exist, CEE countries do not have identical policies for biosimilar as generics (12).

This, however, is applicable mostly to the EU member states in CEE. The selected group of non-EU member states in CEE, i.e. the ones in Western Balkans remain with a specific set of challenges towards biosimilar uptake. A lower number of biosimilar policies was observed in these countries, despite researching both academic and grey literature. Furthermore, without the formal backing of the EMA, these countries have an additional institutional layer, the regulatory approval as a barrier of access. These countries would benefit not only from the introduction or refinement of national policies, but also from the highest-level factors that impact access to medicines, namely the international sphere. In the very specific spot, being economically and otherwise tied to Europe, their regulatory systems would be strengthened by the introduction and refinement of global regulatory policies regarding biosimilars, e.g. at the level of the World Health Organisation.

Increasing the uptake of biosimilars is demonstrably more likely to happen with demand-side policies in place. This primarily refers to physician education policies as well as to a lesser extent to patient-lead efforts. These policies are difficult to detect at the national level, and appear not to be wide spread. Doctors in CEE share concerns of their colleagues worldwide about the use of biosimilars, especially related to interchangeability and also effectiveness of biosimilar alternatives. While existing research has mostly cleared these concerns, it is questionable how much has that awareness dissipated into clinical practice. On a more encouraging note, patients' associations in CEE countries that are not EU members, appear to be leading the charge in putting pressure on the healthcare systems for an increased uptake of biosimilars (22). They have also created policy papers and other sources of information, both for patients and clinicians. Finally, all CEE countries appear to have some level of awareness of biosimilars, and appear to be trending upwards in biosimilar uptake and rational use, at the level of the whole healthcare systems.

## Limitations

This literature review was performed mainly in English, as well as local languages of several countries (Serbia, BiH, Croatia, Montenegro, Macedonia, Slovenia, Croatia), however, there was a language barrier towards grey and alternative literature sources when it came to most other CEE countries, potentially leaving gaps in knowledge. Furthermore, literature about biosimilars in CEE is scarce, and it remains difficult to keep it up to date, given the dynamic nature of policy. Additionally, real world conditions are impossible to assess using literature research. The principles of biosimilar uptake policies and their impacts have only been studied for high-income economies, making inferences about CEE, predominantly composed of lower-income economies impossible to make. Finally, this study excluded a portion of what can be considered CEE, namely Russia and the CIS due to an inability to find any relevant literature about biosimilars in those countries.

### Future Research

Future research on the subject of access to biosimilars in CEE should focus on expanding the knowledge to the entirety of the region. Furthermore, studies aimed at determining real world use of biosimilars, and the impact of the implemented policies should be conducted.

## VII. Conclusion

This literature review aimed at exploring access of biosimilars for the countries of Central and Eastern Europe. A number of policies has been observed, in CEE countries, both members and non-members of the EU. In the EU CEE countries, the regulation of biosimilars is done by the EMA. However, the EMA does not make decisions regarding interchangeability, nor does the Union set policies for reimbursement. All of EU CEE countries have policies in place regulating the reimbursement of biosimilars, mostly using a step-wise system of capped discount vis-à-vis the price of reference drug. Other CEE countries are also tasked with regulatory approval of biosimilars and appear to have less developed policies set in place for reimbursement of biosimilars. Despite the presence of these policies, the market uptake of biosimilars in the CEE region is highly heterogenous between various countries. The real-world use of biosimilars in indeterminable by this method of study. Nevertheless, all CEE countries have some level of understanding of biosimilars, and with time, there seems to be more biosimilars present at their markets, available to patients. A bettered access to biosimilars is one way that CEE countries can increase the quality of care delivered and bring complex biologic medications to patients in need. Globally, biosimilars are still in the emerging stages, and the CEE region can and does benefit from the proximity or membership with the EU, a global leader in that regard. While a number of reimbursement policies are in place in all CEE countries, a number of barriers remain to access to biosimilars. Finally, this issue needs to be observed from the perspective of the entire health systems and all complex factors that contribute to Access to Medicines. Such a perspective reveals that while a lot has been done, there is still much room for improvement of access to biosimilars in Central and Eastern Europe.

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