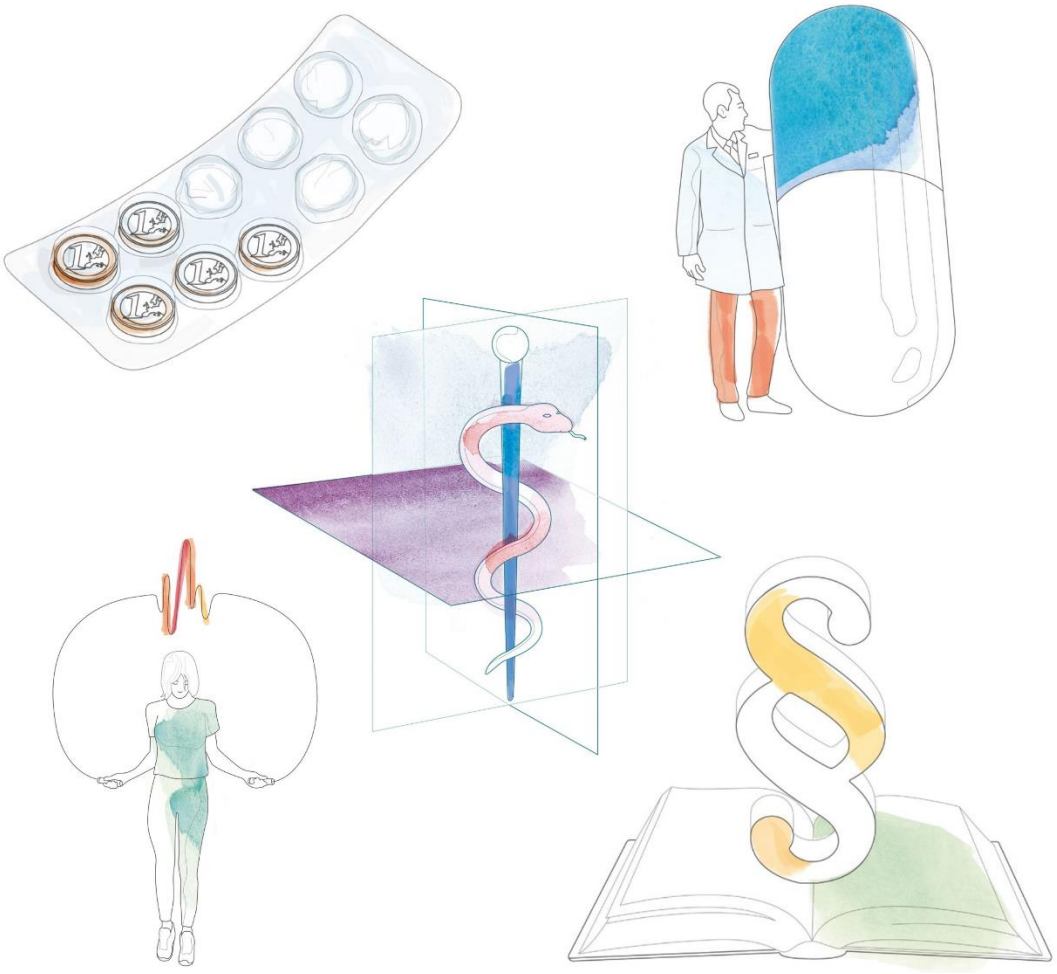
Navigating Germany's Biosimilar Policies

A road to healthcare accessibility



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Lay summary (Dutch)

Biologische medicijnen (*biologicals*) zijn geneesmiddelen waarvan de werkzame stof wordt gemaakt door een levend organisme, zoals hormonen, vaccins of producten voor gen- en celtherapie. *Biosimilars* zijn medicijnen die sterk lijken op al eerder goedgekeurde biological, die gemaakt kunnen worden als het patent op een biological is verlopen. Ze zijn daardoor goedkoper dan de originele biologicals en dragen dus bij aan het betaalbaar houden van de gezondheidszorg. Hoewel ze erg op de originele medicijnen lijken, zijn ze niet precies hetzelfde en moeten ze strenge tests ondergaan om te bewijzen dat ze net zo veilig en effectief zijn. In Duitsland worden biosimilars veel gebruikt, zelfs voor Europese standaarden. Door te kijken naar de Duitse aanpak om biosimilars te gebruiken, kunnen we dus beter begrijpen hoe we deze medicijnen het beste kunnen gebruiken in andere landen.

Biosimilars worden door de Europese Geneesmiddelenautoriteit (EMA) goedgekeurd voordat ze de markt op mogen. In 2019 is er Duitsland een controversiële wet aangenomen, genaamd GSAV, die het mogelijk maakte dat sinds 2024 de apotheker het goedkoopste passende medicijn (vaak een biosimilar) moet geven als de arts een bepaald biologisch medicijn voorschrijft. Dit proces heet automatische substitutie. Het beleid van Duitsland heeft er in de afgelopen periode voor gezorgd dat er veel geld is bespaard op dure biologicals, vooral voor bepaalde soorten medicijnen die worden gebruikt bij ontstekingen.

Het beleid over biosimilars heeft veel kritiek gekregen, vooral vanwege de automatische substitutie. Een aantal organisaties van farmaceuten, artsen, ziekenhuizen en patiënten hebben problemen met deze wetten. De organisaties die de kosten van medicijnen betalen, zoals zorgverzekeraars, zijn er juist blij mee. Als we naar het beleid van andere Europese landen kijken, kunnen een aantal positieve elementen herkennen, die mogelijk ook het Duitse beleid sterker kunnen maken, zoals stimulansen en informatievoorzieningen voor artsen of manieren om te onderhandelen over de prijs van medicijnen. Het is echter lastig om het beleid uit andere landen zomaar over te nemen, omdat elk land een ander gezondheidszorgsysteem heeft.

Er is nog steeds discussie over hoe uitwisselbaar de biosimilars zijn voor de originele biologicals. Ondanks dat sommige artsen nog steeds niet helemaal overtuigd zijn, wijzer wetenschappers erop dat biosimilars veilig en uitwisselbaar zijn. Het gebruik van ervan heeft soms wel praktische problemen, zoals het bijhouden van bijwerkingen van de medicijnen. Duitsland doet veel dingen goed als het gaat om biosimilars, zoals een hoog gebruik, een goede integratie in het zorgstelsel en snelle toegang tot nieuwe biosimilars. Er zijn echter regionale verschillen in het gebruik en kritiek op de automatische substitutie wijzen echter op gebieden die nog verbeterd kunnen worden.

Het is belangrijk om mensen te blijven inlichten over biosimilars en met alle betrokkenen te praten over hoe we deze medicijnen het beste kunnen gebruiken. Samenwerken met andere Europese landen kan helpen om ze op een nog grotere schaal te kunnen gebruiken. Kortom, hoewel Duitsland een voorbeeld kan zijn voor andere landen qua beleid rondom biosimilars, zijn er ook daar nog steeds aspecten die verbeterd kunnen worden om biosimilars in de toekomst beter in te kunnen zetten.

Abstract

Biosimilars, medicines highly similar to another already approved biological medicine, are cost-effective alternatives to biologicals and are crucial for healthcare accessibility. While similar to reference medicines, they are not identical but undergo rigorous approval processes ensuring safety and efficacy. Germany has a high uptake of biosimilars and appears as a leader in biosimilar adoption on a global scale, thus understanding Germany's approach can exemplify effective policy integration. This analysis aims to evaluate Germany's biosimilar policies, its effects on uptake and pricing, and stakeholder perceptions.

EMA established guidelines for biosimilars in 2004, outlining biosimilar assessment criteria used for market authorization. Germany adopted biosimilar use recommendations in 2008, which were further refined in 2017 and 2021. In 2019, the GSAV law enabled the Federal Joint Committee (G-BA) to regulate biosimilar interchangeability. Subsequently, the G-BA adopted guidelines for automatic substitution of biosimilars in pharmacies in 2023 (§40B to Medicinal Products Directive), which have become effective from March 15 2024. Germany's biosimilar policies have led to significant cost reductions and increased biosimilar uptake over the years, particularly in anti-TNF biologicals, though adoption rates vary regionally, with lower rates in economically disadvantaged areas.

The GSAV and subsequently automatic substitution were met with a lot of critique from pharmaceutical associations, physician and hospital associations, and patient organizations. Payers, the sick funds, did respond positively to the law. When looking at policies from other European countries, positive policy elements can be identified that could be adopted to further strengthen Germany’s policies, such as physician incentives, hospital financing mechanisms, public procurement policies, education for healthcare professionals and inclusion of biosimilars in reference price systems. However, effective policy elements are often hard to translate to other countries due to differences in healthcare systems.

Debates around Germany’s biosimilar substitution persist, especially regarding the recently implemented automatic substitution due to concerns about interchangeability. Interchangeability is crucial for biosimilar uptake, but doubts among physicians remain. Scientific evidence supports interchangeability, but practical challenges exist, including the need for a robust pharmacovigilance system. Germany's strengths include high national uptake, integration into medical practice, and proactive measures for fast adoption of new biosimilars. However, regional variations and criticisms on the mandatory substitution, indicate areas for improvement. Future perspectives emphasize the need for continued education, stakeholder engagement, and evidence-based policymaking. Collaboration with the EMA to clarify interchangeability and harmonize policies could provide beneficial to increase biosimilar uptake on a continental level. Overall, while Germany's biosimilar policies set a global example, further improvements are necessary for to integrate biosimilars better into the future healthcare system.

Content

List of abbreviations

AkdÄ	Drug Commission of the German Medical Association *(Arzneimittelkommission der deutschen Ärzteschaft)*
AMK	Drug Commission of German Pharmacists (*Arzneimittelkommission der Deutschen Apotheker*)
AM-RL	Medicines Directive (*Arzneimittel-Richtlinie)*
BAH	Federal Association of Drug Manufacturers (*Bundesverband der Arzneimittel-Hersteller)*
BÄk	Federal Medical Association *(Bundesärtzekammer)*
BfArM	Federal Institute for Drugs and Medical Devices (*Bundesinstitut für Arzneimittel und Medizinprodukte)*
BMG	Federal Ministry of Health (*Bundesministerium für Gesundheit*)
BPI	Federal Association of the Pharmaceutical Industry (*Bundesverband der Pharmazeutischen Industrie*)
CAGR	Compound annual growth rate
CHMP	Committee for Medicinal Products for Human Use (of the EMA)
ECBS	Expert Committee on Biological Standardization (of the WHO)
EEA	European Economic Area
EMA	European Medicines Agency
ERP	External reference pricing
EU	European Union
FDA	Food and Drug Administration (of United States)
G-BA	Federal Joint Committee (*Gemeinsame Bundesausschuss*)
GDP	Gross domestic product
GSAV	Law for more safety in the supply of pharmaceuticals *(Gesetzes für mehr Sicherheit in der Arzneimittelversorgung)*
HHI	Herfindahl index
HMA	Heads of Medicines Agencies
INN	International Nonproprietary Names
IQWiG	Institute for Quality and Efficiency in Health Care (*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen*)
IRP	Internal reference pricing

LÄK	Regional physician associations (*Landesärztekammer)*
LoE	Loss of Exclusivity
mAb	Monoclonal antibody
PEI	Paul Ehrlich Institute
PPP	Purchasing power parity
PRCA	Pure red-cell aplasia
Q	Quarter (of a year)
RPS	Reference price systems
SBP	Similar Biotherapeutic Product
SGB V	Fifth Book of the Social Code *(Sozialgesetzbuch Fünftes Buch)*
SHI	Statutory health insurance
TD	Treatment days
TRS	Technical report series
USA	United States (of America)
VFA	Association of Researching Drug Manufacturers (*Verband der forschenden Pharma-Unternehmen*)
VUD	Association of University Hospitals in Germany (*Verband der Universitätsklinika Deutschlands*)
WHA	World Health Assembly
WHO	World Health Organization

1. Introduction

1.1. Policy Background and Context

1.1.1. Biosimilars: what are they and why do we need them

Biosimilars form a part of the healthcare system of today and tomorrow as they are alternatives to more expensive biological medicines. Biologicals are medicines whose active substances are produced by living organisms (1). This sets them apart from small molecule medicines, which are smaller, more well-defined structures and produced through chemical synthesis. Biologicals are generally larger and more complex molecules produced by living organisms. They usually consist of proteins, carbohydrates, nucleic acids, cells, tissues, or a combination of these substances. Thus, they can for the basis for a wide range of products, such as hormones, vaccines, monoclonal antibodies or gene and cellular therapies. As a result, the therapeutic value of biologicals lies in their ability to provide innovative and effective treatments, because they are effective in targeting specific disease mechanisms. However, the high cost of biologicals forms a significant barrier to accessibility for many patients (2).

The European Medicines Agency (EMA) defines a biosimilar as a "*biological medicine highly similar to another already approved biological medicine"*. This approved medicine is also called the reference medicine, reference biological or reference biologic (1). The World Health Organization (WHO) uses a similar definition stating that they are "*products that are designed to be highly 'similar' to the corresponding licensed 'originator' biotherapeutics"* (3). WHO also mentions alternative terms for biosimilars, such as "similar biotherapeutic products", "similar biological medicinal products" and "biosimilar products" (3). In this report, the terms "biologicals" and "biosimilars" will be used, as well as "reference medicine" or "reference biological". Generic medicines for small-molecule medicines are considered identical, however biosimilars are considered similar to the drugs with no differences in terms of their clinical effects, but not completely identical (4). Box 1 shows a landmark example of a case in which small differences in biologicals can have big effects, and why similarity does not automatically mean equality.

Box 1. Epoetin-associated pure red cell aplasia.

Recombinant human erythropoietin (epoetin) was approved in France in 1988 for use in treating anemia in dialysis patients with chronic renal failure. Erythropoietin is heavily glycosylated, and this glycosylation is crucial for its biological function. However, the endogenous erythropoietin and epoetin have different glycosylation patterns, particularly concerning the sialic acid composition of oligosaccharide groups. Epoetin alfa (produced by Johnson & Johnson) and epoetin beta (produced by Roche) are manufactured using recombinant methods in Chinese-hamster–ovary cells. They exhibit slight differences in glycosylation, with epoetin alfa containing more sialic acid residues compared to epoetin beta (5).

Between the introduction of epoetin in 1988 up until 1998, three cases of antibody-associated pure red-cell aplasia (PRCA) were reported in patients undergoing epoetin therapy. However, from 1998 to 2000, France saw an increase with 13 reported cases: 12 association with the Eprex formulation of epoetin alfa, and one associated with Neorecormon, a formulation of epoetin beta (5). Between January 1998 and April 2004, there were 175 reported cases of PRCA

associated with Eprex, 11 cases with Neorecormon, and 5 cases with Epogen. The majority of these cases were concentrated in France, Canada, the United Kingdom, and Spain (6).

The increased incidence of Eprex-associated PRCA was found to be due to a simultaneous combination of factors related to the production, handling, and route of administration of epoetin (7). Changes in formulations and manufacturing processes such as freeze-drying facilitate aggregation of proteins, which can increase immunogenicity. Furthermore, a shift from intravenous administration to (often self-administered) subcutaneous administration leads to wrong storage and mishandling, furthermore inducing antibody formation, resulting in an immune response. Implementing protocols to ensure proper storage, handling, and administration of Eprex in chronic kidney disease patients led to an 83 percent decrease in exposure-adjusted incidence worldwide (6).

EMA assesses most[1] of the marketing authorization (MA) applications for biosimilars, based on the same standards applied to all biological medicines approved in the European Economic Area (EEA), to ensure their quality, safety, and efficacy. The MA application can only be made once the period of data exclusivity (the patent) has expired for the reference medicine. It will include comparability studies with the reference medicines to demonstrate their similarity and absence of clinically meaningful differences in safety, quality, and efficacy. This approach avoids unnecessary clinical trials already conducted with the reference medicine (1).

Currently, biologicals are forming an increasingly big share of the pharmaceutical market. By the end of 2022, biologicals have surpassed small-molecule new molecular entities in United States (USA) Food and Drug Administration (FDA) approvals, which is a significant milestone in their increasing prominence since the late twentieth century (8). Not only are biologicals increasing in approval number, their pharmaceutical expenditure is also increasing (see Figure 1) (9). Biologicals represent 35% of European Union (EU) pharmaceutical expenditure, with a compound annual growth rate (CAGR) of 11.3% over the past five years, as compared to 6.3% CAGR for the total market over the past five years (9). By offering different cost options for patients, biosimilars form an alternative to drive down pharmaceutical costs in a growing market of biologicals.

[1] As per Article 3(1) of Regulation (EC) No 726/2004, "*medicinal products developed by means of biotechnological processes as described in the Annex (point 1) of Regulation (EC) No 726/2004*" fall under mandatory scope of the centralized procedure for MA. This includes almost all biosimilars. Biosimilars not produced by means of biotechnological processes, for example blood products, would thus not be obliged to use the centralized procedure (117).

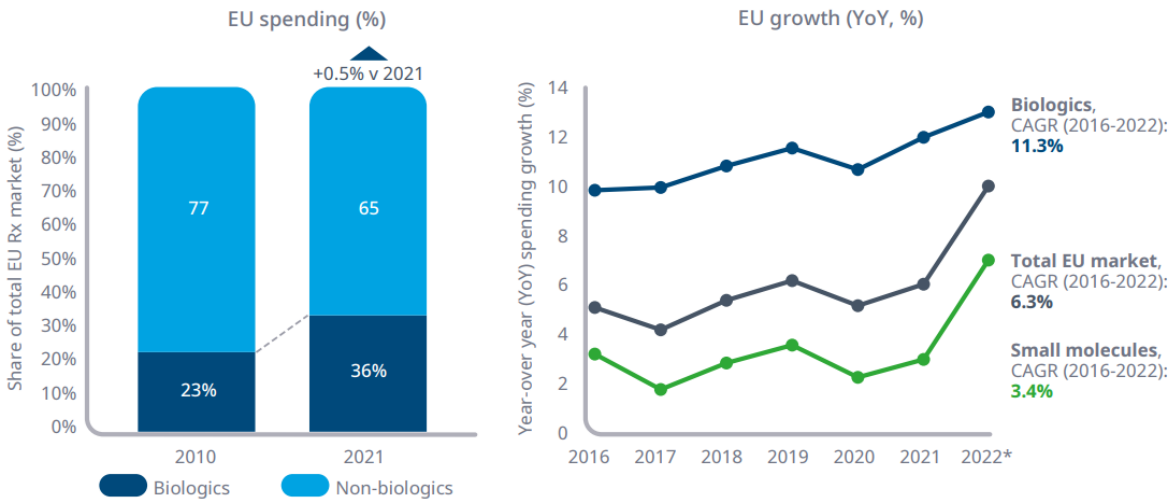


Figure 1. The EU spending and spending growth on biologicals. *Biologic market includes both reference biologicals and biosimilars. Biologic molecules exclude ATC-V medicines* (9)**.**

1.1.2. Germany's healthcare system

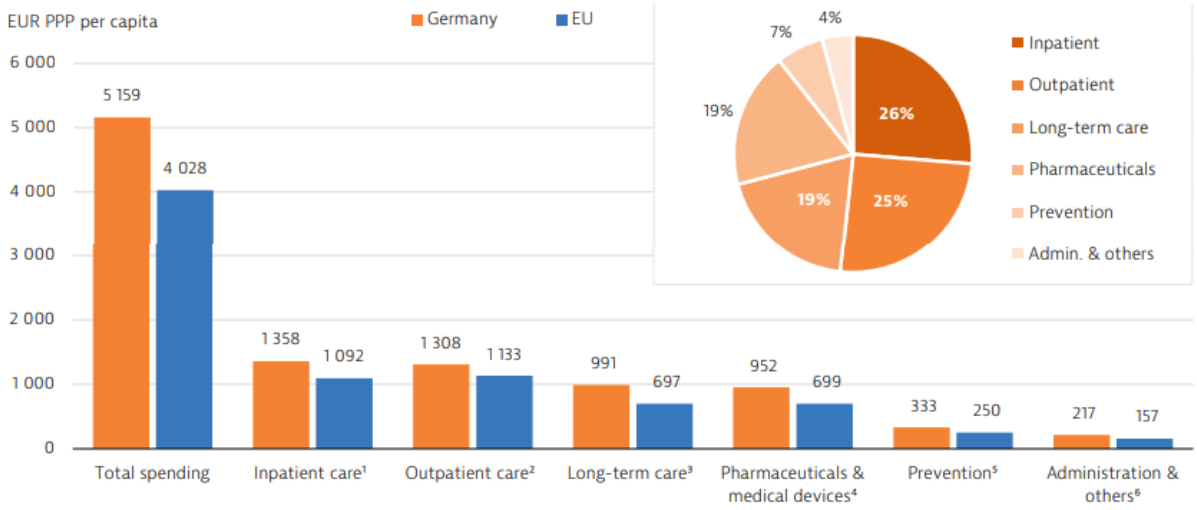
The EU is the most advanced market when it comes it biosimilars, because of its robust legislative framework and pathway for biosimilars (10). Though MA is organized centrally at EMA level, the individual EMA members have their own set of laws and regulations governing the uptake of biosimilars, resulting in varying levels of use (9–11). This can be due to differences in local pricing, reimbursement policies, stakeholder impact, and attitudes toward biosimilars. Currently, Germany and France collectively constitute over half of the biosimilars market share within the EU (10). This report will focus mostly on the policies for biosimilars in Germany, see also section 1.2 Relevance.

Germany is the biggest country in the EU based on population, representing 19.8% of the EU population (12). An overview of key demographic, socioeconomic and healthcare factors can be found in Table 1. Germany's health system is characterized by its mandatory health insurance, provided primarily through statutory health insurance (SHI, 89% of population) and private health insurance (PHI). Despite near-universal coverage, financial and administrative barriers are causing some gaps in coverage. Nevertheless, Germany's unmet medical care needs rank among the lowest in the EU. Germany's healthcare expenditure, which was 12.9% of its GDP in 2021, is the highest in the EU. This comes down to €5.159 (adjusted for differences in purchasing power) per capita, also the highest in the EU. Over 50% of healthcare spending goes towards inpatient and outpatients care, see also Figure 2. Public funding for healthcare is predominant, representing 85.5% of total expenditure. (12)

Table 1. Key demographic and socioeconomic and healthcare factors of Germany and the EU. *Data is from 2022 unless specified otherwise. GDP = Gross domestic product. PPP = Purchasing power parity.* (12–15)**.**

	Germany	**EU**
Population size	88 237 124	446 735 291
Share of population over age 65 (%)	22.1	21.1
Fertility rate[1] (2021)	1.6	1.5
GDP per capita (Euro PPP[2])	41 246	35 219
Relative poverty rate[3] (%)	14.7	16.5
Unemployment rate (%)	3.1	6.2
Total health expenditure (Million Euro; Euro per capita; % of GDP) (2021)	445 855.00; 5 599.48; 12.88	1 591 899.68; 3562.06; 10.87
Total health spending (Euro PPP per capita)	5 159	4 028
Pharmaceucitical expenditure[4] (Euro PPP per capital)	952	699
Pracisting pharmacists per 100.000 inhabitants (2020)	66.95	N/A[5]

[1] Fertility rate is defined as number of children born per woman aged 15-49.
[2] PPP is defined as the rate of currency conversion that equalizes the purchasing power of different currencies by eliminating the differences in price levels between countries.
[3] Relative poverty rate is the percentage of persons living with less than 60 % of median equivalized disposable income.
[4] Pharmaceutical expenditure consists of expenditure on pharmaceuticals and medical devices in the outpatient sector.
[5] The EU average is not available due to not all EU members having available data. The unweighted median value is 87.21 and the majority of EMA member states have a value between 65 and 130.



Notes: 1. Includes curative-rehabilitative care in hospital and other settings; 2. Includes home care and ancillary services (e.g. patient transportation); 3. Includes only the health component; 4. Includes only the outpatient market; 5. Includes only spending for organised prevention programmes; 6. Includes health system governance and administration and other spending.
Source: OECD Health Statistics 2023 (data refer to 2021, except Malta (2020)).

Figure 2. Healthcare expenditure of Germany and the EU and expenditure share of Germany (12).

A key institution in German healthcare policy is the Federal Ministry of Health (*Bundesministerium für Gesundheit*, BMG), which makes policies at a federal level. The BMG directs both the Federal Institute for Drugs and Medical Devices (*Bundesinstitut für Arzneimittel und Medizinprodukte,* BfArM) and the Paul Ehrlich Institute (PEI). The PEI is the competent higher federal authority for "sera, vaccines, blood preparations, tissue preparations, tissues, allergens, advanced therapy medicinal products, xenogeneic medicinal products and blood components manufactured using genetic engineering", and the BfArM is the competent higher federal authority for all other (bio)pharmaceuticals (16). The individual states (*Länder*) possess their own legislative authority to implement federal laws and oversee the planning and financing of inpatient care. Additionally, the *Länder* exercise supervision over municipal public health services. While SHI falls under federal jurisdiction, the *Länder* play a crucial role in supervising regional health insurance funds. Last, they oversee regional medical associations for their compliance with regulations and standards (17).

A key principle of German healthcare is its self-administration. Thus, the Federal Joint Committee (*Gemeinsame Bundesausschuss*, G-BA) is self-governing and is the highest decision-making body concerning SHI. The G-BA is also responsible for healthcare quality assurance, with support from institutions like the Institute for Quality and Efficiency in Health Care (I*nstitut für Qualität und Wirtschaftlichkeit im Gesundheitswesen*, IQWiG) (18). Lastly, physicians providing services under SHI in Germany are obliged to be members of the 17 regional physician associations (*Landesärztekammern, LÄK*). These associations negotiate collective contracts with sickness funds, perform quality assurance, and set budgets on a regional level (19). The regional physician associations are coordinated through the Federal Medical Association *(Bundesärtzekammer, BÄk*), which is informed by the Drug Commission of the German Medical Association *(Arzneimittelkommission der deutschen Ärzteschaft, AkdÄ)*. These many institutions all form relevant stakeholders the design as well as implementation of Germany's policies on biosimilars.

1.2. Relevance

Both EMA and WHO emphasize the significance of biosimilars as a cost saving alternative to biologicals (1,3). Furthermore, the WHO included a section about 'promoting the use of quality-assured generic and biosimilar medicines' in their guideline on country pharmaceutical pricing policies, with strong policy recommendations to increase the uptake of biosimilars, furthermore underpinning the relevance of biosimilars (20). Understanding Germany's policies on biosimilars is relevant, because Germany has one of the highest uptakes of biosimilars in the world as well as of the Germany's influential healthcare system and large position within the EU pharmaceutical market (11,12). Thus, understanding Germany's approach can reveal the role of the government in shaping and implementing effective policies that contribute to the successful integration of biosimilars into healthcare systems.

An additional rationale behind conducting this policy analysis stems from the WHO's objective to establish a policy observatory, tracking and analyzing pricing policies for health products worldwide. This initiative tries to understand the evolution, design, and impacts of these policies over time, and targets decisions-makers, managers, donors, civil societies, WHO staff, and researchers. By doing this, it facilitates evidence-based policy development and stimulates informed discussions on pharmaceutical pricing policies (21).

1.3. Objectives and methods

This report aims to summarize Germany's biosimilar policies, as well as its effects on uptake and pricing and potential unintended effects of these policies. Additionally the perceptions of several relevant stakeholders on the German biosimilar policies will be investigated. Furthermore, a comparison will be made with policies for biosimilars from other European countries. Ultimately, the research question can be formulated as: "What are strengths and weaknesses of Germany's biosimilar policies and what can be learned from this?".

This objective was achieved by a comprehensive search across both academic publications as well as grey literature sources. For academic publications, search engines such as PubMed, Embase and Google Scholar are used. Moreover, GaBI Journal, the leading journal specialized in biosimilars, is used. Grey literature searches included a wide range of sources, including Overton, German government websites such as bfarm.de, g-ba.de, and bundesregierung.de, as well as the websites of the EMA and WHO. News articles were also included in the search strategy and were found through Nexis Uni and Google. Key search terms used in combinations included "Germany," "EMA," "biosimilars," "biosimilar policy," "guidelines," "interchangeability," "biologicals," "biosimilars substitution," "market access," and "cost-effectiveness." Snowballing will be used to identify additional relevant sources. In general, articles from 2006 to 2023 have been included, as the first EMA-approved biosimilar marketing authorization was granted in 2006. However, to further investigate the historical perspective, articles of before 2006 can also be included. The search was conducted in English, with German being translated using tools such as Google Translate and DeepL Translate. Dutch language sources were considered if relevant for international comparisons.

2. History of the biosimilar policies

2.1. Policies and guidelines on MA, substitution and use

An overview of the policies and guidelines by WHO, EMA and Germany can be found in Figure 3.

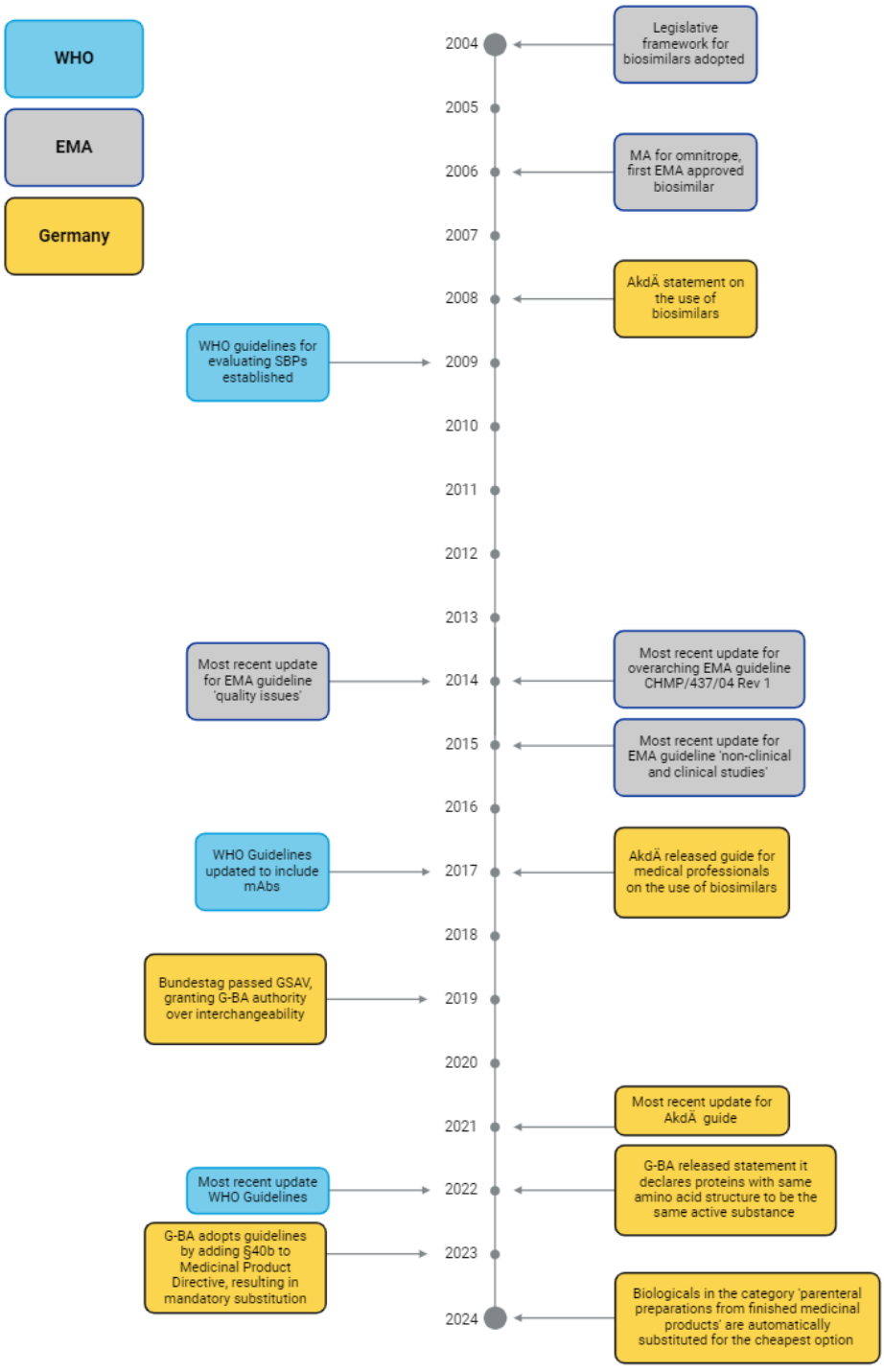


Figure 3. Timeline of the biosimilar policies and guidelines by WHO, EMA and Germany. *Created using BioRender.*

2.1.1. WHO

In 2007, WHO started an informal consultation regarding the regulatory evaluation of therapeutic biological medicinal products, specifically the status of biosimilars. In this meeting, the main topic was the status of biosimilars and existing regulatory pathways for MA, the use of International Nonproprietary Names (INN), potential immunogenicity, and WHO international standards and reference materials were also relevant topics of this consultation. The main outcome of the consultation was the need for a WHO-developed guideline. This guideline would be developed by a new WHO working group, and would work to harmonize regulatory expectations, including defining terminology and scope, addressing interchangeability, and enhancing availability of safe and effective biosimilars (22).

In 2009, the guidelines for evaluating Similar Biotherapeutic Products (SBPs) were established. They are adopted into the technical report series (TRS) of the WHO Expert Committee on Biological Standardization (ECBS), as Annex 2 of WHO TRS 977. In the guideline, the scientific principles and systematic approach for a comparability study between the biosimilar and its reference counterpart are outlined (23,24). Since 2017, the ECBS has included biosimilar monoclonal antibodies (mAbs) in the guidelines. There is a separate class-specific guideline developed for mAbs (25). The guidelines were last updated in 2022, as annex 3 of TRS 1043, aligned with World Health Assembly (WHA) resolution WHA67.21 for better access to biotherapeutics including biosimilars. The revisions aimed to increase flexibility and decrease regulatory burdens while maintaining product quality, safety, and efficacy. The updated guidelines now cover a broader range of biological products beyond biotherapeutics, such as palivizumab used prophylactically. Lastly, the term "similar biotherapeutic product" has been replaced by "biosimilar" (26,27).

2.1.2. EMA

In June 2003, EMA's Committee for Medicinal Products for Human Use (CHMP) recommended omnitrope for MA, but the European Commission rejected it because it wished the manufacturer had applied through the "essential similarity" route, rather than the "well-established medicinal use" route. The adoption of an official framework for biosimilars in the EU in March 2004 allowed for the manufacturer to seek MA through the biosimilar route in July 2004. After a second positive opinion from the EMA in January 2006, omnitrope was finally approved on April 12, 2006, following. This made omnitrope the first biosimilar that obtained MA in Europe (10,28).

The legislation of the biosimilars is defined in Directive 2001/83/EC, where the requirements for MA through the biosimilar route is laid down. It is stated that *"the general principles to be applied [for similar biological medicinal products] are addressed in a guideline taking into account the characteristics of the concerned biological medicinal product published by the Agency"* (29,30). Since its publication, the European guidelines have included a general overarching guideline for biosimilars, as well as separate general guidelines on quality, non-clinical and clinical issues. Next to this, product-specific guidelines are also available, with specific requirements for MA (22).

All current guidelines are available on EMA's website (1). The overarching guideline, CHMP/437/04 Rev 1, has last been updated in 2014 (30). Key themes from this guideline are the application of the biosimilar approach, the choice of the reference product and the principle of establishing biosimilarity. In short, the guideline covers the following: the biosimilar approach is necessary due to

the complexity of biological products, which cannot be assessed through standard bioequivalence studies; biosimilarity must be demonstrated in terms of quality, biological activity, safety, and efficacy, with particular emphasis on molecular and biological similarity to the reference product; differences in strength, formulation, or presentation require justification, but changes to improve efficacy are not compatible with biosimilarity; regulatory requirements include fulfilling quality data standards, demonstrating comparable safety and efficacy, and considering extrapolation to other indications; the choice of reference product is crucial, typically a product authorized in the EEA, although comparisons with non-EEA authorized products may be accepted under certain conditions; the development program should follow a stepwise approach, starting with physicochemical and biological characterization and progressing to clinical studies as needed; clinical data should confirm comparable performance to the reference product and cannot justify substantial differences in quality attributes; if significant differences between the biosimilar and the reference product are identified, a standalone development program may be necessary; simplified approaches to confirmatory clinical trials may be considered in specific circumstances, provided that similarity in efficacy and safety can be deduced from other data and there are no concerns regarding impurity profiles or excipients (30).

The “Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues” was last updated in 2015 and lays down requirements for non-clinical and clinical studies. For non-clinical studies this includes *in vitro* studies about target binding, signal transduction and functional activity/viability. There will also be a determination whether *in vivo* studies are needed, based on differences in relevant quality attributes, in quantitative differences in quality attributes or in formulation. The clinical segment covers the criteria for pharmacokinetic, pharmacodynamic, and efficacy studies. The last section on clinical safety and pharmacovigilance covers clinical safety studies, including immunogenicity, as well as the risk management plan (31).

The “Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues” was last updated in 2014 and covers the requirements concerning manufacturing procedures as well as several comparability exercises. Specifically it describes the selection of the reference medicinal product, the biosimilar comparability exercise and analytical considerations regarding physicochemical characterization, biological activity, immunochemical properties, purity and impurities, and quantity (32).

Currently there are product-specific guidelines available for products containing any of the following active substances: recombinant granulocyte-colony stimulating factor, low-molecular-weight heparins, recombinant human insulin and insulin analogues, interferon beta, monoclonal antibodies, recombinant erythropoietins, recombinant follicle-stimulating hormone, somatropin, recombinant interferon alpha or pegylated recombinant interferon alpha (1).

In short, EMA’s guidelines provide a framework needed for MA within the EEA. A unique feature for biosimilars is the extrapolation, that allows the authorization of the biosimilar for clinical indications of the reference medicine without conducting clinical trials in those indications. In short, the development program focuses on demonstrating similarity to the reference medicine on a quality level, with clinical data intended to confirm this similarity. Interesting to note is that the EMA

regulations do not say anything about physician-level switching or pharmacy-level substitution, making this a responsibility at EEA member state level (33,34).

2.1.3. Germany

In 2008, the AkdÄ released a statement on the use of biosimilars. At this time, biosimilar products such as erythropoietin, growth hormone and medicines containing filgrastim had been approved throughout Europe. The AkdÄ recommended that biosimilar medicinal products can be used at the start of treatment in the same way as the reference biological. If there is a substitution from the reference biological to a biosimilar, the patients must be observed during the initial period after the switch. The AkdÄ states that the safety of biosimilars is comparable to newly approved medicinal products of the same active substance class, for which the spectrum of significant adverse drug reactions is known (35).

In 2017, the AkdÄ released a guide (36) about biosimilars, which was updated in 2021 (37). This most recent version provides an analysis of the current understanding and utilization of biosimilars in medical practice. The guide aims to equip healthcare professionals with evidence-based information to facilitate appropriate treatment decisions, independent of pharmaceutical interests. Over the past 13 years, biosimilars have gained traction in the EU as comparable alternatives, garnering increased acceptance among physicians and patients. The number of approved biosimilars steadily rose since the guide's first edition, with 52 biosimilars available for 16 different active ingredients at the time of the update, including those used in oncology (37). In March 2024, this number increased to 83 biosimilars available (38). The guide covers the distinctions between biologicals and chemically synthesized medicines, the approval process for biosimilars, pharmacovigilance, and the interchangeability of reference drugs and biosimilars. The guide also explains experiences with switching patients to biosimilars, incorporating insights from switch studies, including those involving multiple switches between reference drugs and biosimilars (37).

In 2019, the German Bundestag passed a law for more safety in the supply of pharmaceuticals (*Gesetzes für mehr Sicherheit in der Arzneimittelversorgung*, GSAV) (39). This law covers drug monitoring and safety, a revenue threshold for orphan drug, better supply for patients with haemophilia and a national implementation of biosimilar quotas (39,40). With this new law, the G-BA has the authority to regulate the interchangeability of biosimilars and reference medicines, which makes it possible to implement national prescription quotas for biosimilars and give biosimilars preferred reimbursement status (39,40). The GSAV includes an amendment to paragraph 129 of the Fifth Book of the Social Code (*Sozialgesetzbuch Fünftes Buch*, SGB V), which would make future automatic substitution of biologicals possible. This law caused a lot of political discussion, see also Chapter 3. Opinions and perceptions of stakeholders.

In 2022, the G-BA released a statement regarding an amendment to the procedural rules (of Federal Gazette No. 84a of 2009, (41)): Addition of a title in the 4th chapter – Exchange of Biosimilars (42). This section outlines criteria for creating an informative overview of approval relationships for products, including biosimilars and multiple reference medicinal products in the German market. It defines the criteria for inclusion of a medicinal product based on regulatory approval, disregarding approved areas of application. Additionally, it specifies that proteins with the same amino acid sequence are considered the same active substance, even if differing in glycosylation or tertiary structure. Different

than standard procedures, a two-week period is set for the submission of statements for amending Annex VIIa to the Medicines Directive (*Arzneimittel-Richtlinie*, AM-RL) (42).

This amendment, containing acknowledgement of interchangeability, was another step towards the developments of legal guidelines for automatic substitution of biopharmaceuticals. This framework was planned to be finished for 2022, though the negative feedback on the GSAV halted its development. On June 15 2023, the G-BA adopted corresponding guidelines for substitution by the addition of paragraph 40b to the Medicinal Products Act. This had as a result that "*parenteral preparations from finished medicinal products (individually prepared injections and infusions) according to § 129 para. 1a) sentences 5, 6 of SGB V*" would be substituted automatically, starting from March 15 2024. On 16 November 2023, a small amendment was made to paragraph 40b, to further clarify on the equal status of biosimilars to their reference biologicals. Thus, currently, automatic substitution of biosimilars in pharmacies has been enabled, unless the prescribing physician has explicitly excluded it (4,42–44). An updated list of interchangeable biosimilars are found under AM-RL Annex VIIa: Biologicals and biosimilars (45).

2.2. Pricing in Germany

When it comes to the pricing policies for biosimilars, Germany does not use a price-link system between the biosimilar and biological. Germany does include biologicals in the reference price system (RPS) since 2009, and a few biosimilar are also included (4). In the inpatient sector, tendering is used by hospitals. In the outpatient (off-patent) sector, discount contracts are established between individual payers (sickness funds) and manufacturers, that resemble a form of tendering. In exchange for providing discounts on their products, manufacturers have the opportunity to enjoy exclusive distribution rights for their medicines. For biologic medications, a prevalent approach has been the utilization of "open house contracts". Under these contracts, a sickness fund extends an open offer to manufacturers specifying the discount rate in advance. Any manufacturer producing biosimilar or reference medicines that agrees to this discount rate can participate in the contract without the need for individual negotiations (4).

The 17 (regional) LÄK play a large role in the pricing and use of biosimilars, as they negotiate collective contracts with sickness funds and set the budgets to regulate healthcare spending. Since 2008, the LÄK arrange price control measures with the sickness funds, like quota setting (19). For example, rheumatologists participating in a 2018 specialist agreement with one of Germany's major health insurance funds are required to aim for a 60% prescription rate of biosimilar etanercept and 80% for infliximab and rituximab infusions. In general, the most common biosimilars for quotas are epoetins, infliximab, etanercept, rituximab and trastuzumab. Failure to adhere to biosimilar quotas may lead to recourse claims if the physician's prescribed proportion exceeds the quota (4,19). However, physicians are generally not held accountable for this violation alone. Next to the quota setting, "integrated care contracts" between individual sickness funds and healthcare providers are used to prioritize the prescription of biosimilars to individuals enrolled in those healthcare providers (4). A summary of the biosimilar policies is provided in Figure 4.

Overview of Biosimilar Policies in Germany

Guidelines	• No payer guidelines pertaining to biosimilar use published nationally • Drug guidelines published by some KVs* but not biosimilar specific • Clear position of Paul-Ehrlich-Institut regarding the use of biosimilars
Physician switch	• No authorised legislation to substitute biologics or biosimilars; switching only allowed at physician's discretion • INN prescribing not formally mandated by law
Biologic pharmacy substitution	• Biologic pharmacy substitution is not permitted • Only bioidentical** versions of four active ingredients (epoetin alpha, epoetin zeta, filgrastim, interferon beta-1b) can be substituted for each other in certain circumstances, unless the prescribing physician indicates
Pricing	• No mandatory originator list price reduction; mandatory originator net discount increase from 7 to 10% upon LoE • No specific biosimilar pricing regulation beyond standard mandatory net discounts
Reimbursement	• Hospitals financed through the G-DRG system***, with cost assignment to therapies based on disease, procedure, degree of severity and other factors • Very expensive drugs excluded from the DRG system and funded separately via insurance funds
Tenders	• Conducted through Sick Funds (ex-hospital setting) and hospitals (mostly ambulatory setting products) • Sick funds obliged to sign contracts with at least two companies to supply each region
Incentives	• Some local Sick Funds exempt patients from co-payments for preferred anti-TNFs to incentivize their uptake • Annual budget responsibility set by Sick Funds for office-based specialists, encouraging prescribing of less expensive options • Federal prescribing targets for therapy areas, including minimum prescription volume targets for several biosimilars

* Statutory insurance physicians "Kassenärztliche Vereinigungen"
** Biosimilar medicines coming from the same cell line and production site
***German diagnosis-related group

Figure 4. Overview of the German biosimilar policies. *It is important to note that since 2024, substitution has been allowed* (46).

2.3. Policy impact

Germany's biosimilar policies have had several impacts. A major outcome is the impact of biologicals on the pharmaceutical expenditure. A counterfactual analysis from 2007 to 2014, projected significant cost reductions of $258.45 million for epoetin and $143.4 million for filgrastim. However, the adoption of biosimilar somatropin incurred additional expenses amounting to $48.74 million, which is not elucidated by the researchers (19,47). Another analysis estimated that Germany saved €3.6 billion between 2015 and 2022 on anti-TNFs because of biosimilars (9). Based on the IQVIA scorecard for biosimilars (see also Figure 5), Germany performs well for anti-TNFs regarding level of competition, price evolution and volume development, though the scores for other biosimilars investigated are not consistently high across these categories (48).

MOLECULE	LEVEL OF COMPETITION	PRICE EVOLUTION	VOLUME DEVELOPMENT
	1=Low, 5=High	1=Low, 5=High	1=Low, 5=High
Anti-TNF			5
Adalimumab	5	5	5
Infliximab	5	4	5
Etanercept	5	4	5
Insulin Lispro	4	3	3
Insulin Glargine	2	3	5
Rituximab	5	3	1
Trastuzumab	5	2	1
	Indicator of the amount of competition based on the number of competitors and their respective market shares	*Net price reduction from average price of the countries in scope 1 year before first biosimilar entry*	*Change in biologic volume since biosimilar entry*

Figure 5. IQVIA scorecard for biosimilars in Germany (48)**.**

Another major outcome is the uptake of biosimilars in Germany. Germany scores particularly well on its fast access to novel biosimilars (9,48). Germany has an increased level of uptake of anti-TNF biologicals since the introduction of biosimilars (see Figure 6) (9). Furthermore, biosimilar uptake appears to increase after its market entry, though levels vary (49). Though Germany's biosimilar adoption is high on a global and even European scale (see Figure 7), the adoption rates are not equal across all regions in Germany. The adoptions rates range from 66.7% to 88.5%, with a median of 81.6%. Biosimilar adoption rates are notably lower in regions characterized by lower income and lower social and political trust, i.e. all provinces in eastern Germany (50,51).

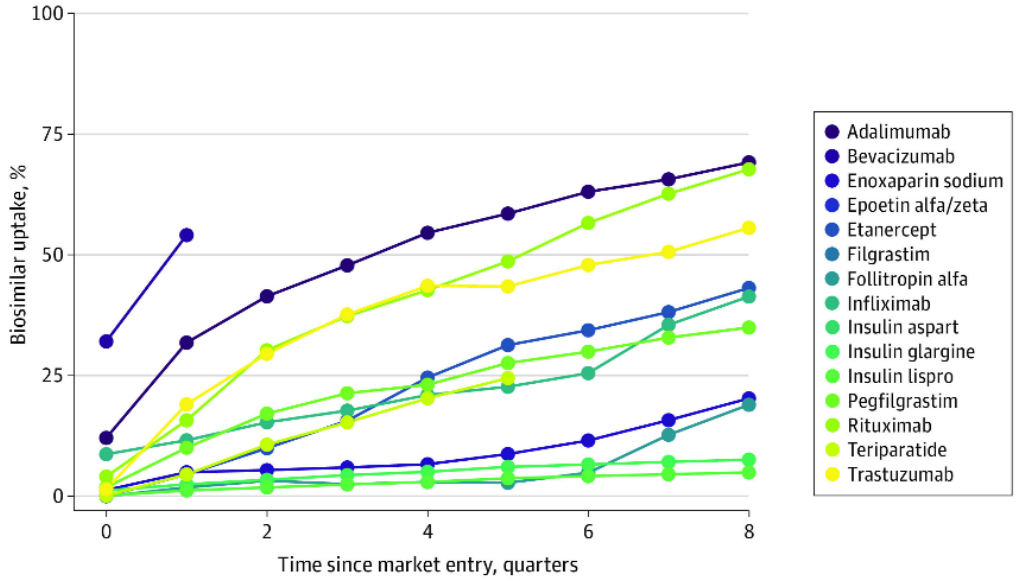


Figure 6. Biosimilar uptake since market entry in Germany (49)**.**

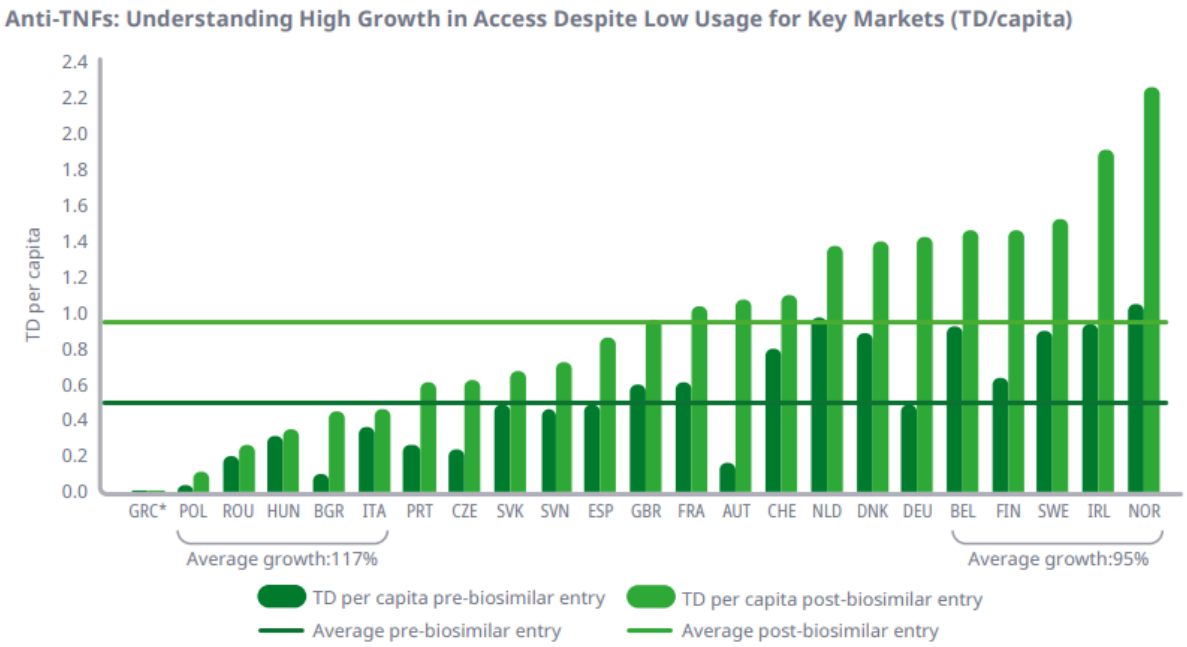


Figure 7. Uptake of anti-TNF biologicals in Europe pre- and post-biosimilar entry. *TD = Treatment days* (9)

3. Opinions and perceptions of stakeholders

3.1. The governing bodies

In 2019, the GSAV was ratified by the *Bundestag* (see also chapter 2.1.3. Germany). The German Ministry of Health lists official responses on the GSAV on its website, such as from insurance funds or associations of drug manufacturers (52). Several governing bodies responded to the GSAV. The G-BA released an assessment acknowledging the positive aspects of strengthening the interchangeability of reference biologicals and biosimilars. It argued there has been a lack of reported problems from patients who switched to biosimilars. The assessment highlighted that biosimilars would have an increased presence due to patent expirations and emphasizes the need for rigorous approval processes for biosimilars because of their complex nature. The G-BA supports the legislative aim to make biological medicinal products more affordable, and their assessment has several adjustments to the proposed legislation to ensure that regulations are appropriately targeted and effectively implemented (53).

Finally, Member of Parliament Michael Hennrich (CDU/CSU) said the following about the biosimilars in 2019:

> *We have managed to regulate the issue of biosimilars sensibly and pragmatically. We have made it clear that interchangeability by the doctor must not result in direct substitutability. It depends on a special decision by the G-BA. The transition period gives us the opportunity to continue to pursue acceptance among doctors, but above all among patients, and to create more awareness* (54).

The latest statement from the Scientific Services of the German Bundestag (2023) listed the market opening and exchange of reference biologicals and biosimilars as a solution for affordable drug supply. Lastly, the BfArM and the PEI also considered the approved biosimilars to be safe and interchangeable with their respective reference biologicals. The statement acknowledged fears from critics that automatic substitution might reduce market competition and could potentially lead to increased cost pressure for manufacturers. However, it did not make a conclusion regarding whether the current regulations are the right approach to make a contribution to cost savings while ensuring security of supply (44).

3.2. Pharmaceutical industry

Pharmaceutical companies in Germany exhibit a spectrum of attitudes towards biosimilars. On one side, the production of biosimilars allows for an emerging manufacturing industry in Germany to develop in a stimulating environment, because of Germany's high pharmaceutical engineering capabilities and the European advanced and progressive regulatory framework (55). On the other hand, pharmaceutical companies that produce reference medicines express concerns about revenue loss due to patent expirations and increased competition.

The German pharmaceutical association with the largest number of members, the Federal Association of Drug Manufacturers (*Bundesverband der Arzneimittel-Hersteller*, BAH), already expressed their concerns regarding the pharmacovigilance of biosimilars in 2016. It stated that biosimilars and their reference biologicals are not completely identical, but can have the same active

ingredient names. This would make it unclear to track whether the reference biological or biosimilar has been used, and makes the assignment of adverse events ambiguous (56).

Furthermore, the BAH released a statement expressing concerns over the GSAV in 2019. This statement opposes routine substitution of biological medicines due to safety concerns and stresses the importance of physician discretion in choosing between biologicals and biosimilars based on medical factors and patient involvement. As with the previous statement, they add the need for more robust pharmacovigilance measures to ensure traceability of medicines. The BAH argues for clear processes for prescribing biologicals and emphasizes the need to maintain the current strict guidelines (57).

The Association of Researching Drug Manufacturers (*Verband der forschenden Pharma-Unternehmen*, VFA), another large pharmaceutical association, also responded to the GSAV. They argue that the decision regarding medication choice should solely be made by the physician, and that the competition between the reference medicines and biosimilars is strong enough to not need further measures that could also compromise drug safety (58). In response to the fact that over half of the newly approved medicines in 2022 were biopharmaceuticals, the president of the VFA, Han Steutel says: *"The strong figures for biotechnology must not obscure the gloomy outlook for the entire pharmaceutical industry"*. He voices that the laws on financing statutory health insurance companies are making the work of companies more difficult (59).

Pro Generika is the association representing manufacturers of generics and biosimilars Germany, whose members produce 79 percent of the medicines consumed by the patients covered under statutory health insurances (60). In 2016, Pro Generika advocated for the introduction of regional biosimilar target. It highlighted a growing demand among physicians for comprehensive information on biosimilars, particularly the new generation of monoclonal antibodies. It notes that successful biosimilar uptake is observed in regions where health insurance funds and physician associations have agreed on target agreements, including physician education. It advocates to expand these regional initiatives nationwide, to significantly lower the financial burden on the healthcare system (61). In response to the issue of regional disparities in the uptake of biosimilars. Pro Generika attributed these disparities to various factors unrelated to the biosimilars themselves. They emphasize the importance of factors such as good information for doctors, individual consultation, and agreements on market shares in influencing biosimilar uptake (62).

However, in 2022, Pro Generika also acknowledged the controversy over the substitution of biopharmaceuticals in pharmacies has not diminished in intensity. It states that there are outstanding issues regarding ensuring therapy quality and drug therapy safety and compliance with pharmacovigilance requirements. Thus, it argues that the regulation on substitutions in pharmacies is not needed. It points out that prices in the biopharmaceutical market are already seeing significant declines, fixed prices are in place, 90% of biosimilars are covered by discount agreements, and the overall security of supply is ensured by robust and globally diversified production and supply chains (63).

Lastly, the Federal Association of the Pharmaceutical Industry (*Bundesverband der Pharmazeutischen Industrie*, BPI) acknowledged the high cost-saving potential of biosimilars in 2023, but is wary of a repeat of the excessive economization that caused supply chain problems for generics.

3.3. Healthcare professionals

In 2018, the Drug Commission of German Pharmacists (*Arzneimittelkommission der Deutschen Apotheker*, AMK) stated that there is nothing objectionable against the initial prescription of biosimilars. For reasons of medication therapy safety and pharmacovigilance, the AMK does view the exchange of biosimilars critically, in particular because of different administration systems that cause application errors upon switching. The AMK also considers that some patients are used to specific medication, and may express concerns about switching due to discount contract requirements. Similarly to the BAH, the AMK also argues that biosimilars impose high demands on the national pharmacovigilance system, particularly concerning traceability (64).

The BÄk and AkdÄ released a joint statement in response to the GSAV. While they supported the majority of the topics this law covers, they expressed concerns about the sections regarding biosimilars. Firstly, the associations mentioned that the proposed definition is difficult to understand for healthcare professionals and patients. Secondly, they opposed the extension of substitution rules to biosimilars. They argued that they have concerns about the interchangeability of biosimilars, especially if a patient has been treated with a reference medicine for an extended period. They also raised concerns about the potential impact on medication safety and patient trust (65).

In response to the GSAV, the Association of University Hospitals in Germany (*Verband der Universitätsklinika Deutschlands*, VUD) argued that the substitution of biosimilars should not be the same as substitution of generics, due to the complexity of manufacturing of biosimilars. It found that it is not possible to produce identical copies of biologicals and that there is not enough knowledge about the potential risks of substitution. The VUD also argued that people treated with biologicals are often admitted to hospitals, resulting in many switches between inpatient and outpatient care, and automatic substitution would lead to the patients often being subjected to burdensome changes in medication. Thus, it found that exchange should only happed at physician level (switching) rather than based on cost considerations dictated by the health insurance company (66).

Despite Germany being praised by IQVIA for its educational efforts regarding biosimilars (48), a study in 2021 revealed that 44.1% of investigated German pharmacists do not feel properly informed about biosimilars, and when asked only 41.7% was able to give a correct definition of biosimilars. Despite only 48.8% of the investigated German pharmacists having received training on the topic of biologicals after initial professional education, 83.3% would be interesting in receiving additional training on biologicals (67). In conclusion, there is a mixed perception of how well pharmacists are educated on biologicals and biosimilars.

3.4. Payers

According to *Barmer GEK* in 2016, a health insurance fund covering 8.7 million Germans, biosimilars can save more than billions of euros in a period between 2016 and 2021, however, prescribing physicians would need better education about these so-called biosimilars. *Barmer GEK* wants doctors to better utilize the cost-saving biosimilars (68). *AOK Bundesverband*, another health insurance fund covering 27 million Germans, stated in 2022 that doubts about the comparability of reference biologicals, are considered unfounded because of numerous so-called switch studies. *AOK Bundesverband* also stated that further prospective switch studies are not necessary and would be a big waste of clinical research resources (69).

3.5. Patients and the general population

Uptake of biosimilars is varying across the German states, and this is associated to varying levels of social trust and trust in government (50,51). In particular, in states located in former East Germany, there is a low trust, both in fellow citizens and government policymakers, which impacts the biosimilar uptake. This suggests that trust plays a significant role in patients' confidence in the safety and effectiveness of biosimilars. Despite the fact that regions with lower income levels, such as in former East Germany, may have a greater need for healthcare savings, they still exhibit lower rates of biosimilar adoption due to underlying trust issues (50). Despite this, biosimilars do have an upward trend in uptake on a nation-wide level (51).

Biosimilars occasionally made it into the newspapers. *Bild*, Germany's biggest newspaper adopted a positive opinion on their cost-saving potential in 2019, saying that biosimilars can make therapies more accessible (70). *Tagesspiegel* has released multiple critical articles, particularly around the time of the GSAV adoption discussing concerns with substitution, especially in sensitive treatments like fertility treatment, where biosimilar substitution may affect patient trust, therapy adherence, and safety (71).

The German Society for Gastroenterology, Digestive and Metabolic Diseases (*Deutschen Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten*, DGVS) showed limited approval of the automatic substitution , while the German Crohn's Disease / Ulcerative Colitis Association (*Deutsche Morbus Crohn / Colitis ulcerosa Vereinigung*, DCCV), the German Psoriasis Association (Deutscher Psoriasis Bund, DPB), the German Rheumatism League (*Deutsche Rheuma-Liga*, DRL), and the German Leukemia and Lymphoma Aid (*Deutsche Leukämie- und Lymphom-Hilfe*, DLH) all respond negatively towards automatic substitution (see also Figure 8) (72). Furthermore, the patients representation in the G-BA, consisting of four patient organizations, the German Disability Council (*Deutscher Behindertenrat*, DBR), Federal Working Group of Patient Services and Initiatives (*BundesArbeitsGemeinschaft der PatientInnenstellen*, BAGP), the German Association of Self-Help Groups (*Deutsche Arbeitsgemeinschaft Selbsthilfegruppen*, DAG-SHG) and the Federation of German Consumer Organizations (*Verbraucherzentralen-Bundesverband*, vzbv) released a statement against the automated substitution of biosimilars. They argued that there is insufficient scientific data supporting the safety and efficacy of multiple biosimilar switches and that there is a risk of patients experiencing loss of efficacy, as a result of adherence issues and application errors associated with using different preparations. The patients representation added that a one-time switched is deemed acceptable, but that multiple switches are not. They fear that the regulation for automatic substitution emphasized economic factors over safety concerns. Finally, they add that it is crucial to educate patients the implications of switching biologic preparations is crucial and to expand existing registries to ensure a better understanding of these transitions for future reference (73).

Figure 8. Response of several stakeholders towards automatic substitution. *Adapted from* (72)**.**

4. Comparative Analysis of Germany's International Biosimilar Policies

4.1. Key differences in European Biosimilar Policies

A study from 2021 compared biosimilar policies of sixteen European countries in order to provide an overview of policy measures as well as model how different scenarios could play out in the German pharmaceutical market. Several policy strategies were identified across the nations, including both supply- and demand-side measures (see also Table 2) (74).

Regulation regarding the supply-side is often done using price link policies, in which biosimilar prices have to be lower than the references, often by a certain percentage. In Germany, as well as Denmark, Sweden, the United Kingdom, and the Netherlands, the price of the reference biological is not used to determine the price of the biosimilar (74).

Another policy measure for the supply-side is tendering. While all investigated countries use tendering for the inpatient sector, often organized at hospital level, fewer than half of the investigated countries use tendering in the outpatient sector. A notable example of this is the "preference price policy" as used in the Netherlands, where health insurers launch tenders for active substances (including biosimilars), and the winning bidder's product becomes the preferred option for reimbursement, with patients paying the difference for other products (74).

Lastly, RPSs are present in most studied countries, often using internal reference pricing (IRP). IRP regulates prices by grouping products of the same active substance or therapeutically interchangeable medicines and defining a maximum reimbursement amount per group. Germany includes a few biosimilars in their RPS. Other countries that include biosimilars in their RPS are Czechia, Denmark, Spain, the Netherlands, Norway and Slovakia (74).

Policy measures on the demand-side of biosimilars can target physicians. One way to do this is by using prescribing by INN instead of the trade name of the medicine, which is done is most of the investigated countries, often on a voluntary basis. Some countries also distinguish between using INN for small molecule drugs versus biologicals (i.e. United Kingdom, Belgium and France) or even biosimilars and "bioidenticals" (i.e. Germany). Another way is to include prescribing guidelines and recommendations, which are available for all investigated countries. Examples of these are quotas (e.g. Belgium and Germany), an obligation to prescribe the most economical therapy (e.g. Austria and Finland), or a more general recommendation to switch (e.g. Netherlands and Norway) (74).

Another measure on the demand-side of biosimilar is at the pharmacy level. This can be done by substitution at the pharmacy level. This is an impactful policy that is often used for generics, but biosimilar substitution is rarely applied and not allowed in many countries. The Czech Republic does not explicitly prohibit substitution at pharmacy, but it is not recommended. As of 2022, automatic substitution is only allowed in Germany (41). Financial incentives for dispensing biosimilars are generally absent, except for France, where pharmacy margins for biosimilars are calculated based on the price of the reference medicine, thus resulting in a relatively higher margin for biosimilars (74).

Table 2. Summary of biosimilar policy measures used across sixteen European countries. *RPS = reference price system. Adapted from Vogler et al. (2021)* (74)**.**

	Supply-side policy measures				Demand-side policy measures			
	Price link	Tendering (inpatient sector)	Tendering (outpatient sector)	Biosimilars in the RPS	INN prescribing for biologicals	Prescribing guidelines and recommendations	Biosimilar substitution	Financial incentive
Austria	Yes	Yes	No	No RPS	No	Yes	No	No
Belgium	Yes	Yes	No	No	Yes	Yes	No	No
Czechia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Denmark	No	Yes	Yes	Yes	No	Yes	No	No
Spain	Yes	Yes	No	Yes	Yes	Yes	No	No
Finland	Yes	Yes	No	No	Yes	Yes	Yes[1]	No
France	Yes	Yes	No	No	No	Yes	No	Yes
Germany	No	Yes	Yes	Yes (few)	Yes	Yes	Yes[2]	No
Ireland	Yes	Yes	No	No	Yes	Yes	No	No
Italy	Yes	Yes	No	No	Yes	Yes	No	No
Netherlands	No[3]	Yes	Yes	Yes	Yes	Yes	No	No
Norway	Yes	Yes	No	Yes	Yes	Yes	No	No
Poland	Yes	Yes	No	No	Yes	Yes	No	No
Slovakia	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Sweden	No	Yes	No	No RPS	Yes	Yes	No	No
United Kingdom	No	Yes	No	No RPS[4]	No	Yes	No	No

When it comes to the outcome of the several types of policies, in 2020, IQVIA released Country Scorecards for Biosimilar Sustainability using long-term competition as way to achieve sustainability. This report looked across various European countries, and focused on three outcome measures. The first key metric was the Level of competition, gauged through the Herfindahl index, which assessed the intensity of competition based on the number of competitors and their market shares. Additionally, price evolution was looked into, factoring in starting price, list price adjustments, and rebates to calculate the net price reduction from the average list price a year prior to the first biosimilar entry. Lastly, volume development was assessed, measuring the change in biologic volume since the introduction of biosimilar competition, thereby indicating the extent of additional access generated (75).

[1] As of 2024, see Chapter 4.2.6. Finland.
[2] As of 2024, see Chapter 2.1.3. Germany.
[3] No price link system, but the price of the biosimilar must be below the price of the reference biological.
[4] The United Kingdom has set a reference price for adalimumab.

Regarding availability, in Germany the seven biosimilars most recently launched (as of 2020) were all available. Of the twelve countries investigated, this was only the case in three others, Italy, Poland and Sweden (see also Figure 9). When looking at the level of competition, Germany scored particularly high (see also Figure 10): for all biosimilars but two it received the highest score, which corresponded to a Herfindahl index of under 0.4, indicating a high level of competition. Other countries that score well are Italy, the Netherlands, Poland, Spain, Sweden and the United Kingdom. When it comes to price evolution, Germany doesn't score particularly high (see Figure 11). Only for adalimumab Germany had a ≥50% reduction of net price versus the average list price 1 year before biosimilar entry. It is to be noted for many countries pricing data was not available, but Italy, Sweden and the UK all scored better than Germany. Lastly, looking at volume development, Germany had an >25% increase in TD per capita in Quarter (Q) 1 of 2020 versus the year before biosimilar entry for four medicines, and a 10–20% increase for one (see also Figure 12). Compared to other countries, Germany scored quite well, but was outperformed by Denmark, Norway, Poland and Sweden (75).

Considering all of the factors, it seems that many countries did not consistently score well across all of the categories. For example, in Italy there was a high level of competition and a high reduction in price, but a low level of volume development. Some countries did manage to score well across all categories, such as Sweden and Poland (75).

MOLECULE	Adalimumab	Infliximab	Etanercept	Insulin Lipro	Insulin Glargine	Rituximab	Trastuzumab
Denmark	✔	✔	✔	✘	✔	✔	✔
France	✔	✔	✔	✘	✔	✔	✔
Germany	✔	✔	✔	✔	✔	✔	✔
Hungary	✔	✔	✘	✘	✔	✔	✔
Italy	✔	✔	✔	✔	✔	✔	✔
Netherlands	✔	✔	✔	✘	✔	✔	✔
Norway	✔	✔	✔	✘	✔	✔	✔
Poland	✔	✔	✔	✔	✔	✔	✔
Romania	✔	✔	✔	✘	✔	✔	✔
Spain	✔	✔	✔	✘	✔	✔	✔
Sweden	✔	✔	✔	✔	✔	✔	✔
UK	✔	✔	✔	✘	✔	✔	✔

Figure 9. Biosimilar market availability of the seven biosimilars most recently launched as of 2020 in twelve European countries (75)**.**

MOLECULE	Adalimumab	Infliximab	Etanercept	Insulin Lipro	Insulin Glargine	Rituximab	Trastuzumab
Denmark	4	1	2	N/A	2	5	3
France	3	5	4	N/A	1	4	4
Germany	5	5	5	4	2	5	5
Hungary	1	1	N/A	N/A	2	4	5
Italy	4	5	4	1	4	5	5
Netherlands	4	5	4	N/A	4	4	5
Norway	3	3	4	N/A	1	2	4
Poland	4	5	5	4	4	1	4
Romania	1	4	1	N/A	1	1	1
Spain	4	5	4	N/A	2	5	4
Sweden	4	5	4	4	4	5	4
UK	5	5	4	N/A	2	4	4

Source: IQVIA MIDAS, 12 months of data ending MAT Q1 2020. HHI calculated using volume treatment days.
Chart notes: N/A = Not applicable due to unavailability of biosimilars within a market.

Figure 10. Level of competition of biologicals biosimilars in twelve European countries (2020). *The Herfindahl index (HHI) has been converted to a scale of 1-5 as follows: (1-HHI)*10, and approximated to the nearest integer. Score 1=0-1 measurement, Score 2=2; Score 3=3, Score 4=4-5, Score 5=6-10. N/A indicates that no biosimilar was launched for a given molecule/country* (75)**.**

MOLECULE	Adalimumab	Infliximab	Etanercept	Insulin Lispro	Insulin Glargine	Rituximab	Trastuzumab
Denmark	5	5	5	N/A	2	3	5
France	3	5	3	N/A	2	2	2
Germany	5	4	4	3	3	3	2
Hungary	5	5	N/A	N/A	3	N/A	N/A
Italy	5	5	5	4	2	5	5
Netherlands	N/A	N/A	N/A	N/A	2	N/A	N/A
Norway	N/A	5	N/A	N/A	3	N/A	N/A
Poland	5	N/A	5	4	3	N/A	N/A
Romania	N/A	N/A	N/A	N/A	3	N/A	N/A
Spain	N/A	N/A	N/A	N/A	3	N/A	N/A
Sweden	5	5	5	4	3	4	N/A
UK	4	5	4	N/A	3	4	4

Figure 11. Price evolution of biologicals/biosimilars in twelve European countries (2020). *Scores are based on the percent reduction of net price per molecule versus the average list price per molecule 1 year before biosimilar entry. 1: <0% reduction of net price. 2: 1–14% reduction of net price. 3: 15–29% reduction of net price. 4: 30–49% reduction of net price. 5: ≥50% reduction of net price* (75)**.**

MOLECULE	Adalimumab	Infliximab	Etanercept	Insulin Lispro	Insulin Glargine	Rituximab	Trastuzumab
Denmark	5	5	5	N/A	5	1	5
France	4	5	1	N/A	2	1	1
Germany	5	5	5	3	5	1	1
Hungary	3	1	N/A	N/A	4	1	1
Italy	1	1	1	1	1	1	1
Netherlands	5	5	1	N/A	1	3	3
Norway	5	5	3	N/A	5	3	3
Poland	5	5	5	5	5	1	2
Romania	1	1	1	N/A	5	1	1
Spain	1	3	1	N/A	5	1	1
Sweden	5	5	5	5	5	3	3
UK	3	5	3	N/A	1	1	1

Figure 12. Volume development of biologicals/biosimilars in twelve European countries (2020). *Scores are based on the increase in treatment days per capita in Q1 2020 versus the year before biosimilar entry 1: <5% increase. 2: 5–10% increase. 3: 10–20% increase. 4: 20–25% increase. 5: >25% increase* (75)**.**

4.2. Country highlights

Six EMA member countries are selected whose biosimilar policies are highlighted further. Sweden and Poland are included because they scored very well across all categories in the IQVIA sustainability scorecard. The Netherlands is included because they do not use a price link system, but they do employ tendering in the outpatient sector. Belgium is included because of their high availability of studies involving stakeholder perspectives. Romania is selected as a poorer EU member state that did not score well in the IQVIA sustainability scorecard. Lastly, Finland is included because they have the most recent policy change (2024).

4.2.1. Sweden

In Sweden, physicians hold the responsibility for deciding between the reference medicine and biosimilar(s). They are encouraged to assess all factors, such as safety, effectiveness, and price differences. They are advised against engaging in multiple switches (74). There are no specific clinical guidelines for biosimilars (75). The Swedish Medical Product Agency recommends that naive patients should start therapy using biosimilars, that substitutions in ongoing patients should be carefully monitored, and that repeated substitutions should be avoided (76). INN prescription and pharmacy substitution of biologicals are both not allowed (74,75), but the implementation of INN prescription has been suggested (76).

Regarding pricing, there's no mandatory reduction in the list price of originator drugs after the Loss of Exclusivity (LoE), and no official discounts are mandated for biosimilars. Biosimilars are freely priced without specific pricing regulations. Additionally, there's no separate reimbursement process for biosimilars (75).

Tenders are applied either in the retail market for patient-administered medicines picked up at pharmacies, or in the hospital market for hospital-administered medicines. Both national and regional tenders exist, usually resulting in a single tender winner. One exception is infliximab, which was split between treatment-naïve and ongoing patients. The are no patient incentives for biosimilar use, but there are local prescribing guidelines within specific tender regions (75). Sweden uses a product-of-the month auction system to reduce costs on generics, however biosimilars are treated as separate substances rather than substitutable products (76).

Sweden succeeds in having a high acceptance of biosimilars as part of the medical system among payers, providers, and patients. Other positive elements are a rebate for self-injectable biosimilar purchases, which is shared between the government, the County Councils (payers) and sometimes the prescribing healthcare institution (providers), as well as Sweden's 10 tender regions which fosters market competition. Challenges include that some of the Swedish counties unnecessarily choose medicines with the highest rebates, rather than the lowest cost. Reimbursed manufacturers might also face a lower-than expected volume because of competition offering price adjustments. Lastly, limited biosimilar use in reimbursement systems favors reference product prescriptions, which might raise prices over time (77).

4.2.2. Poland

In Poland, biosimilar switching is allowed at the physician level, but not at the pharmacy level. Pharmacies are however required to inform patients about cheaper alternatives to originator

medicines. There are no specific clinical guidelines regarding biosimilar in use (75,78). Poland uses a price reduction system, in which originator drugs have a mandatory 25% price reduction when the patents expires. Furthermore, Poland uses a price referencing systems on a group-level in retail setting and on a molecule-level in hospital setting. Moreover, there is tendering at a national level as well as at a hospital level, in which there are multiple winners. Hospital-level tendering is usually done on a yearly basis (75).

Though hospitals can purchase medicines autonomously, they receive a limited reimbursement, resulting in a financial incentive to buy cheaper biosimilars. Thus, biosimilars are often prescribed to naïve patients, despite the lack of formal biosimilar quotas. Furthermore, there is a flat reimbursement rate per jumbo group for medicines in the retail setting, stimulating patients to buy biosimilars. The Polish MoH would like to increase the use of biosimilars to reduce healthcare spending (75).

Though the Polish biosimilar policy achieves a high level of competition, volume development and price reduction, there is room for improvement. The absence of a clear definition of biological medicines in the Polish legal framework creates ambiguity in law interpretation (78). There is no comprehensive training for patients or physicians and there are no treatment guidelines. Despite this, Poland does succeed in having a high acceptance of biosimilars as part of the medical system among payers, providers, and patients. Furthermore, Poland's tendering and market size is beneficial for a competitive environment. However, several policy challenges persist. Biosimilars do not automatically appear on the reimbursement list and mandatory price reductions for originators diminish the market's appeal for manufacturers. Current policies do not facilitate increased biosimilar uptake when the biological patent expires and the reimbursement system could be more efficient (79).

4.2.3. The Netherlands

In the Netherlands, naïve patients can undergo switching between biosimilars, as long as thorough clinical monitoring is provided and patients are duly informed. While the prescription of biosimilars using INN is allowed, it is not obligatory (74,75,80). The Dutch Association of Hospital Pharmacists (*Nederlandse Vereniging van Ziekenhuisapothekers*, NVZA) has developed a "biosimilars toolbox" aimed at educating hospital physicians and staff on using biosimilars within the hospital environment. It also provides guidance on the prescription of biosimilar medicines for patients (81).

There is no specific price regulation for biosimilars, such as mandatory list price reductions at LoE, though biosimilar prices must be below reference biological prices (74,75). Reimbursement for biosimilars operates within the medicines reimbursement system. There is no national tendering, but hospital tendering is allowed and sometimes done in collaboration with health insurers (75).

There are no notable incentives, such as patient incentives or financial incentives or quotas for physicians. However, physicians are encouraged by insurers to prescribe rationally, thus recommending biosimilars (75).

The Dutch biosimilar policy achieves a high level of competition as well as decent volume development, though the extent of the price reduction is not known for many of the investigated molecules. However, the Netherlands is praised for its regulatory environment and clinical guidelines, awareness and pricing rules. Furthermore, the market structure using local tenders

supports a competitive market. However, contracting is fragmented, resulting in a fragmented development of experience (82).

4.2.4. Belgium

Belgium uses a pricing system for biosimilars based on a price link mechanism: initially set at 20% lower than the reference medicine. Additional price reductions occur once after 12 years of inclusion on the reimbursement list, depending on the revenue of the active substance. There is tendering in the inpatient sector at hospital level, but no tendering in the outpatient sector (74).

INN prescription is applied in Belgium on a voluntary basis, though it is not recommended for biologicals. Theres are prescribing quota for cheap medicines, including biosimilars. An agreement between the state, some professional associations, the association of hospital pharmacists and the pharmaceutical industry has been made in 2016 to promote the use of biosimilars, as a part of the framework agreement with the pharmaceutical industry ("Pact for the future") (74,83).

Biosimilar uptake in Belgium is low compared to other Western European countries like Germany or the Netherlands, which could be explained because of low knowledge levels among both healthcare providers and patients, a weak tendering system and a lack of incentives for healthcare professionals and patients. Patients in Belgium need to be educated about biosimilar medications (84,85). Nevertheless, the majority of patients are optimistic about switching to biosimilars if they receive adequate support from their healthcare providers (86). Furthermore, there is a high necessity for education regarding both biologicals and biosimilars among Belgian community pharmacists and physicians (87). Lastly, there is a non-coherent policy framework. The Belgian government has tried to improve the biosimilar uptake with several interventions, but with variable and limited results. Thus, a more coherent policy framework is needed for a more competitive biologicals market in Belgium (84,85).

4.2.5. Romania

In Romania, patients may undergo switching at the physician's discretion, but this is not often done. There are no clinical guidelines regarding the use of biosimilars and treatment guidelines provided no clear guidance on switching. Substitution at the pharmacy level is not allowed (75).

Reference biologicals are obliged to sell at 80% of the original price upon LoE. Furthermore biosimilars should be at least 20% lower than the new price of the reference medicine, so at 65% of the original price for the reference biological. Additionally, there is external reference pricing (ERP). Romania's ERP entails that biosimilar prices must be lower than those in a basket of 12 countries (6 Eastern and 6 Western EU countries). Reimbursement is based on brand names and even allows a premium of 20% for the reference biological over the biosimilars, further limiting incentive for switching. There are no quotas or incentives for the uptake of biosimilars in place. Romania employs tendering on a hospital level, with a single winner (75).

While there is rising awareness about biosimilars in Romania, many aspects of Romania's biosimilar policies are flawed. In fact, only 17% of hospital volume (in treatment days) comprised of biosimilars (88). Thus, The law of quota or guidance, the reimbursement system favoring reference biologicals and general lack of access to biologicals hinder Romania from having a high uptake of biosimilars (89).

4.2.6. Finland

Finland uses a price link system for biosimilars, with the first biosimilar have a price initially set at 30% lower than the reference medicine. There is tendering in the inpatient sector with using common "procurement pools" of university hospitals, but there is no tendering in the outpatient sector. There is voluntary INN prescribing, and their prescribing guidelines oblige the most economical therapeutic alternative for all patients, when biosimilars are available. The prescribing of a pricier medicine requires a written justification in the patient's medical record (74).

Since 1 January 2024, a new biosimilar policy is effective in Finland allowing pharmacies to interchange biological medicines without healthcare professional supervision. This change is aimed to increase access to biosimilars (90). However, a survey revealed significant hesitancy among originator users towards switching to a biosimilar, mostly due to a lack of knowledge about biosimilars. Biosimilar users are generally more open to switching, but still have concerns regarding immune responses (90,91). To combat these challenges, the policy gives pharmacies the responsibility in guiding patients towards more cost-effective alternatives and ensuring understanding of the biosimilars.

4.3. Transferability of policies

When looking at the transferability of policies, it is impossible to directly copy a policy or set of policies from one country to another. Despite EMA member states all having the same MA for biosimilars, differences in healthcare system and current biosimilar policies, but also population and healthcare spending make transferring policies difficult. It is however possible to identify best practice elements, which could serve as an example for other countries. On the other hand, it is also possible to identify weak spots in certain policies as well, in case a certain policy sticks out for being ineffective.

Policy measures can be summarized according to the targeted stakeholder, such as physicians' incentives which include prescription quotas or targets, financial incentives or penalties, and prescription guidelines. These measures aim to influence physicians' prescription behavior towards biosimilars (92). A measure on the pharmacy-level is a substitution system such as in Germany or Finland (41,93). Hospitals' incentives are influenced by financing mechanisms, but hospital-level policies can also include tendering. Public procurement and policies to limit the impact of discounts are suggested to positively influence biosimilar adoption in hospitals. Further policies could target patients, such as the inclusion of biologicals in the reference price system and preference policies on biosimilars. The lack of transparency regarding discounts and negotiations between purchasers and providers in hospitals can hinder the uptake of biosimilars. Thus, policies can also include education healthcare professionals or patients (92).

If we compare Germany's biosimilar policies to those of other countries, we can detect rather unique elements to the German policies, but also find significant similarities. First, Germany distinguishes itself by its automatic substitution policy, a measure also embraced by Finland since 2024. Germany's lack of a price link is shared by a couple of countries, such as Denmark, the Netherlands, Sweden and the UK. Germany's system of education towards biosimilars is rather unique. While the Netherlands also shows strong educational efforts on a national level, Germany's efforts are more regionalized. The policy measures of tendering in the outpatient sector and inclusion of the

biosimilars in RPS are not unique for Germany, as they can be found in roughly half of the investigated European countries. Lastly, Germany's policy features of tendering in the inpatient sector and the lack of financial incentives at demand-side are commonly shared by almost all investigated European countries.

5. Discussion

This report revealed that Germany's biosimilar policies resulted in a high uptake of biosimilars, despite regional variant in this uptake. Germany's policies provides insightful lessons for other nations, especially regarding the effective implementation of pricing strategies, tendering policies, as well as educational campaigns aimed at promoting understanding and adoption of biosimilars. However, there is still debate surrounding Germany's recently implemented automatic substitution, due to a lack of trust in the interchangeability of biosimilars.

5.1. Interchangeability and switching of biosimilars

Interchangeability of biosimilars is a cornerstone of biosimilar uptake, because it can enable substitution and access to safe and effective alternatives to originator biologicals. Despite positive experience regarding safe use in clinical practice, many physicians still have doubts about the interchangeability of biosimilars (94). According to the EMA, interchangeability refers to the practice of changing one medicine for another that is expected to have the same clinical effect. In practice, this covers both replacing a reference biological with a biosimilar or vice versa or replacing one biosimilar with another (34). Interchangeability can enable switching (at the prescriber level) or substitution (at the pharmacy level) (94). EMA states in their overarching guideline that *"Evaluation of biosimilar medicines for authorisation purposes by the EMA does not include recommendations on whether a biosimilar should be used interchangeably with its reference medicine. Substitution policies are within the remit of the EU member states."* (30). EMA has released a statement with the Heads of Medicines Agencies (HMA) in 2022 (latest update in 2023) that "*that once a biosimilar is approved in the EU it is interchangeable [from a scientific viewpoint]*", however it stressed thar decisions about switching or substitution remain with the individual member states (95). This statement is however still not included in the overarching guidelines for biosimilars, which leads to a fragmented series of policies regarding interchangeability and substitution.

Biological products undergo manufacturing changes throughout their lifecycle, and need to be tested on comparability between new and previous versions. Despite minor differences, safety and efficacy are unlikely to be affected. The comparability approach has been used for over two decades and facilitates market introduction of new versions without notifying stakeholders, given rare adverse reactions. These comparability tests have provided a lot of knowledge for assessing potential clinical implications and associated risks during transitions between biologicals and biosimilars, which undergo more extensive comparability assessments during development (7). While more biosimilars are becoming available, careful clinician support is also crucial for successful switching. Further challenges include a robust pharmacovigilance system and multiple switches, however, biosimilar interchangeability itself appears safe and cost-effective (96).

Biosimilars and their reference products, as demonstrated in European public assessment reports, exhibit highly similar characteristics, including pharmacokinetics/-dynamics, safety, and efficacy. The theoretical variability of pharmacokinetics in individual subjects is comparable to that of generics. Moreover, biosimilars also undergo rigorous pre-approval immunogenicity assessments. While it is expected that therapeutic proteins may be recognized by the immune system, harmful

immune responses are rare (7). Literature reveals that the risk of immunogenicity when switching to a biosimilar is not greater than the risk when switching between two batches of biologicals (97,98).

A bigger concern for switching biosimilars is rather the nocebo effect[1] when patients are switched to a biosimilar (97). Though unlikely, switching to a different version or a biosimilar may provoke an immune response, potentially resulting in T-cell activation and acute hypersensitivity. However, because T-cell epitopes are linear peptides, proteins with an identical amino acid sequence to the reference biological are not expected to cause immunogenicity. Rather, immunogenicity is expected when the new version of the medicine (after a manufacturing change or creation of a biosimilar) is of lower quality, thus not truly comparable. A lower quality due to manufacturing changes is what happened during the Epoetin/PRCA-case (see box A) (7). Literature suggests that the theoretical risks of switch-related adverse effects appear exaggerated and that switching studies may not provide definitive answers. Instead, current similarity demonstration and post-marketing surveillance should be sufficient for ensuring biosimilar interchangeability (7,98).

Research indicated there is no evidence from clinical trial data or post marketing surveillance data that switching between biologicals and biosimilars leads to safety concerns, and that surveillance data indicates that EU approved biosimilars are highly similar and interchangeable with their reference products (98,99). However, it is important to consider the nocebo effect when prescribing biosimilars, and thus, healthcare providers should be properly educated on biosimilar use (94). A harmonization of terminology and unified position regarding interchangeability is needed to properly educate healthcare professionals. Scientific experience reassures the safety of biosimilars, suggesting that the biggest hurdles for interchangeability are practical, rather than scientific (100). Additionally, acknowledgement of interchangeability of biosimilars should increase physician confidence in biosimilars (97).

5.2. Strengths and limitations of the biosimilar policy

Germany's biosimilar policy has several strengths. First, Germany has had a proactive stance on biosimilars, and was generally an early adopter of biosimilars (51). This proactive stance of biosimilars still applies to the current situation, as in Germany the time from EMA approval of a new biosimilar to the first sales of that biosimilar is short. Furthermore, there is only a short time from the tender award to the first sales of that biosimilar. Lastly there is a full reimbursement from the first day, at a price set by the company (48). These measures are in line with WHO's recommendation of enabling early market entry of biosimilars as well as low patient co-payments (20). In short, Germany's policies ensure that patients have fast access to new biosimilars.

Second, on a national level uptake of biosimilars is high compared to other European countries (48). Germany has also shown a proactive stance regarding uptake, wanting to increase this despite having already high levels (101). It is found that this is due to Germany's policies, as the biosimilar quotas were associated with increased biosimilar use, especially among regular prescribers of biologic drugs. It is interesting to note that while biosimilar quotas were effective for erythropoiesis-

[1] The nocebo effect is the opposite of the placebo effect, i.e. unwanted effects or the perception of ineffectiveness due to patient's pessimistic beliefs or expectations. Negative attitudes of patients towards biosimilars can cause the nocebo effect, which can lead to a reduced adherence and heightened instances of treatment discontinuation (118).

stimulating substances and filgrastim, they had no impact on somatropin, due to a higher uncertainty in the difference of efficacy between reference and biosimilar (19,102). Biosimilar quotas were found to be more effective than priority prescribing (19).

Other positive policy elements include Germany's general acceptance of biosimilars among payers, providers, and patients and integration into appropriate medical practice. Germany's system of integrating open house contracts by sick funds is effective in achieving significant cost savings. Furthermore, clinical guidelines have been implemented to promote biosimilars as the primary choice when deemed suitable, further increasing their uptake. Lastly, the hospital tendering structure, characterized by multiple buying groups and distinct hospital chains, keeps level of competition high among various manufacturers (48). The inclusion of using multiple pricing policies, such as tendering, is agreement with WHO's policy recommendations (20).

However, though on a national level biosimilar uptake is high, there is a big regional variation in the biosimilar uptake. This regional variation cannot be explained by the structure of economic incentives, but rather by cultural differences among regional physician associations. The low levels of biosimilar uptake are linked to low levels of social trust and trust in government. It is suggested that a proper response to this variation is focus more on showing the benefits of biosimilars, thus enhancing social and political trust (50,103).

Furthermore, there is a mixed perception of how well pharmacists are educated on biologicals and biosimilars. While IQVIA indicated good educational efforts, community pharmacists do not feel properly informed about biosimilars (48,104). This indicated a possible limitation of Germany's efforts and an area for future improvement.

Another limitation on Germany's biosimilar policy is the widespread criticism on policies: both the GSAV and the mandatory substitution at pharmacy level. As discussed in chapter 3, the BÄk, the AkdÄ, the BAH, and the VFA, all responded negatively to the introduction of the GSAV and the mandatory substitution. Interesting, even Pro Generika responded negatively to the mandatory substitution, citing that this regulation would not be needed because of already-high uptake. One can argue that the uptake can still be improved in various regions of Germany, but a mandatory substitution may also have a negative effect due to lower trust with patients and physicians. However, the substitution is in line with WHO's policy's recommendations. WHO also recommends using IRP as a policy measure and while in place, only a few of Germany's biosimilars are includes in their RPS (20).

Lastly, a possible limitation that Germany will need to be mindful of potential future shortages of biosimilars. Despite being a robust production hub for biosimilars, Germany does face some risks due to increasing production migration to Asia. In the past, strong price regulations and outsourcing of generic production caused supply bottlenecks. Though this is currently not the case for biosimilars, experts stress the need for proactive measures to avoid repeating past errors (105).

5.3. Future perspectives

In 2007, Moors *et al*. identified five factors for the adoption of biosimilars: the relative advantage over existing therapy, the compatibility with the adopter, the complexity of integration, the trialability before adoption, and the observability of advantage (106).

As stated in chapter 5.1. Interchangeability and switching of biosimilars, the development of biosimilars focuses on demonstrating similarity rather than *de novo* efficacy or safety tests. This might be a reason for difficulties in accepting biosimilars by many physicians, who often have a poor understanding of biological medicines in general, increasing the complexity of integration of biosimilars into the healthcare system. Physicians often embrace innovative medicines when it is approved, but they still have a reluctance towards biosimilars. This contradiction raises questions about the adoption of new paradigms within the medical community and highlights the need for better communication and understanding of biosimilar development processes (94).

On a European level, literature also highlights that knowledge and trust towards biosimilars among healthcare professionals and patients is improving but still rather low (107). Misinformation from the originator industry also affects stakeholder trust (107,108). Proposed solutions from interviews with relevant stakeholders (physicians, hospital pharmacists, nurses, regulators, and patients/representatives) include organizing initiatives to explain biosimilars and their rationale, investing in education about biologicals and combatting misinformation, developing clear regulatory guidance on interchangeability and sharing real-world clinical data. Additionally, it is important to exchange biosimilar experiences and to provide practical product information and guidance about biosimilars. Lastly, it is recommended to organize multi-stakeholder educational activities and to have initiatives in such a way that information uptake is active. Implementation of the recommendations should increase biosimilar understanding and acceptance (107).

Next to biosimilar understanding, it is also important to improve biosimilar use in clinical practice. The beforementioned five stakeholder group proposed the following solutions: spreading evidence from (multiple) switching; providing clear regulatory guidance regarding interchangeability; design guidelines to guide switching involving multiple stakeholders and using a pragmatic approach; avoid mandatory switching. It is recommended that actions to increase stakeholder willingness of using biosimilars should focus on the benefits of biosimilars, medical prices, transparency towards where healthcare savings go, sharing of usage data and finding right incentives for stakeholders (109). To involve patients into policymaking, patient preference studies can reveal unmet needs and provide a new perspective for policymaking (110). These proposed solutions can guide policymakers to increase uptake in the clinical practice (109,110).

Some of these recommendations can be applied on a European level, while others are more suitable for a national level. On a European level, the EMA can work towards clearer guidance regarding interchangeability and practical switching or substitution guidelines. Despite EMA's statement on interchangeability, it is not included in the guidelines and leaves the implications of interchangeability up to the member state, presumably due to a desired autonomy on a national level. Thus alternatively, the EMA can also provide more support in sharing clinical data and help harmonize educational activities and combatting misinformation (107,109). A more consistent position by the EMA on interchangeability would diminish uncertainty among stakeholders about the use of biosimilars, and decrease differences in uptake across members (111).

On a national level, Germany can further focus on educating relevant stakeholders as well as involve stakeholders in future policymaking (107,109). Interestingly, Germany goes against the recommendation to avoid mandatory substitution. It will be interesting to see how uptake will develop under the new guidelines, and future research could reveal how effective this policy intervention has

been. Based on this research, Germany could either reverse this policy or inspire other countries to adopt similar policies.

Germany itself can also learn from other countries by considering to adopt successful policy aspects. As discussed in chapter 4, it is of course warranted that not any policy element can be directly copied, as it might not integrated in the German healthcare system the same way as it is in another country. Germany could consider implementing price link policies or reference price systems similar to those used in Denmark, Sweden, the UK, and the Netherlands to regulate biosimilar prices relative to reference biologicals. Germany could also adopt multi-stakeholder educational efforts similar to those of the Netherlands. A milder approach to the current mandatory substitution would also be to introduce financial incentives and substitution guidelines on a pharmacy level, such as in France. Furthermore, Sweden provides an interesting example on how to involve an incentive for multiple stakeholders in their rebate system for self-injectable biosimilars, with the government, the payers and sometimes the providers all being incentivized to use biosimilars.

Germany also provides many learning opportunities for other countries: if Germany's automatic substitution proves successful, it is a leading example and could serve as a model for other countries aiming to improve uptake. Finland has also started implementing this and could provide further data. Furthermore, countries such as Poland and the Netherlands could learn from Germany's experience with tendering in both the inpatient and outpatient sectors to increase competition and drive down prices. Germany can also serve as an example in educational efforts, for countries such as Belgium or Romania.

The most relevant countries that can adapt from Germany's biosimilar policies are those that fall under the same market authorizations by the EMA, though Germany (and Europe) are setting an example on a global scale as well. For example, the USA can improve by letting competition drive prices and by having reasonable market expectations. Furthermore, they can learn from Europe by having better biosimilar education, sharing clinical data, creating incentives for uptake and having a flexible regulatory framework that allows for new knowledge to be incorporated. From Germany specifically, the USA can learn on how the physicians' associations can use discussion to build trust in biosimilars, but also seek to Germany for local examples of provider incentives, or look towards Germany's substitution regulation (112). These relevant lessons of course extend beyond the USA, and set an example for many countries around the world.

5.4. Strengths and limitations of the study

By covering various aspects of biosimilar regulation, such as EMA's marketing authorization, but also Germany's policies on switching and substitution, the study offers insight into the German biosimilar landscape. Additionally, the study can offer a nuanced perspective on the implementation of biosimilar policies in Germany, as it includes real-world experiences by policymakers through stakeholder opinions. Furthermore, because other European countries are included, relevance of the study is increased, as it provides cross-country insights on potential policy transferability. Last, the study can offer a comprehensive insight by including a mix of academic publications from multiple databases, as well as policy documents, stakeholder reactions, local news, and other grey literature sources. Thus, this study provides a concise overview of EMA's and Germany's biosimilar policies, and brings valuable insights into the regulatory framework, stakeholder perspectives, and comparisons with policies in other countries.

One limitation of the study is its short timeframe, which may have restricted the depth of analysis. Furthermore, the fragmented nature of Germany's biosimilar policies presented a challenge in data collection, that could have resulted in data gaps, potentially limiting the study's completeness. This limitation has been mitigated by including both academic and grey literature from a wide range of sources. Though the study has included comparisons with policies with several other European countries, not all possible relevant nations could have been investigated. Thus, there is the possibility of overlooking important policy elements or best practice examples from countries not included in the analysis. A potential limitation is the language barrier regarding German-language sources, though many German sources were relatively easily navigated using online translation. The study relied on online translation, potentially resulting in misinterpretation of sources and missing out on relevant sources. A last limitation is the recency of key changes in Germany's biosimilar policy, such as the automatic substitution fully coming into effect. Because of this, the effects of this policy cannot be fully understood yet. In conclusion, this study mitigates several limitations in its study design and provides a valuable overview of the regulatory framework, though future research may bring more insight into its implications.

5.5. Conclusion

In conclusion, this study revealed the importance of biosimilars as a part of the modern healthcare system and several strengths and weaknesses of Germany's biosimilar policies. Biologicals form a growing market in the pharmaceutical sector and biosimilars provide a safe and cost-effective alternative to reference biologicals. Furthermore, the importance of biosimilars is stressed by the WHO, the EMA and the German government. The German biosimilar policies are designed with a proactive stance of the stakeholders and are aimed at ensuring fast access to new biosimilars while also maintaining high standards of safety and efficacy. However, the discussion surrounding interchangeability and switching of biosimilars stresses the importance of clearer regulatory guidance and robust pharmacovigilance systems. Scientific evidence does support the safety and effectiveness of biosimilar interchangeability, with concerns primarily revolving around practical challenges rather than scientific uncertainties.

The strengths of Germany's biosimilar policy include fast access to biosimilars, a high uptake in general and an effective integration into medical practice. However, regional variations in uptake and criticism of certain policy elements, such as mandatory substitution, highlight areas for improvement. Germany's experience offers valuable lessons for other countries, particularly in terms of implementing pricing strategies, tendering policies, and educational initiatives to enhance biosimilar understanding and adoption. With Germany's recent implementation of policies, more research is needed to investigate the impact of the automatic substitution. Looking ahead, there is a strong need for continued education, stakeholder engagement, and evidence-based policymaking to further promote biosimilar uptake. EMA should develop a clearer stance on the interchangeability to achieve these goals, as well as collaborate with nations to facilitate knowledge sharing and harmonize policies. Thus, while European and German biosimilar policies are a leading example on a global scale, further improvements are still necessary to integrate biosimilars better in the healthcare system of the future.

6. Sources

1. European Medicines Agency. EMA. 2023 [cited 2024 Feb 7]. Biosimilar medicines: Overview. Available from: https://www.ema.europa.eu/en/human-regulatory-overview/biosimilar-medicines-overview

2. Makurvet FD. Biologics vs. small molecules: Drug costs and patient access. Med Drug Discov. 2021 Mar 1;9:100075. DOI:10.1016/J.MEDIDD.2020.100075

3. World Health Organization. Biosimilars [Internet]. [cited 2024 Feb 12]. Available from: https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/sbp

4. Vogler S, Schneider P, Zuba M, Busse R, Panteli D. Policies to Encourage the Use of Biosimilars in European Countries and Their Potential Impact on Pharmaceutical Expenditure. Front Pharmacol. 2021 Jun 25;12. DOI:10.3389/fphar.2021.625296

5. Casadevall N, Nataf J, Viron B, Kolta A, Kiladjian JJ, Martin-Dupont P, et al. Pure red-cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin. N Engl J Med. 2002 Feb 14;346(7):469–75. DOI:10.1056/NEJMOA011931

6. Bennett CL, Luminari S, Nissenson AR, Tallman MS, Klinge SA, McWilliams N, et al. Pure red-cell aplasia and epoetin therapy. N Engl J Med. 2004 Sep 30;351(14):1403–8. DOI:10.1056/NEJMOA040528

7. Kurki P, van Aerts L, Wolff-Holz E, Giezen T, Skibeli V, Weise M. Interchangeability of Biosimilars: A European Perspective. BioDrugs. 2017 Apr 1;31(2):83–91. DOI:10.1007/S40259-017-0210-0/METRICS

8. Senior M. Fresh from the biotech pipeline: fewer approvals, but biologics gain share. Nat Biotechnol. 2023 Feb 1;41(2):174–82. DOI:10.1038/S41587-022-01630-6

9. IQVIA, Troein P, Newton M, Stoddart K, Arias A. The Impact of Biosimilar Competition in Europe - December 2022. 2022.

10. Farhat F, Torres A, Park W, Lopes G de L, Mudad R, Ikpeazu C, et al. The Concept of Biosimilars: From Characterization to Evolution—A Narrative Review. Oncologist. 2018 Mar 1;23(3):346. DOI:10.1634/THEONCOLOGIST.2017-0126

11. Grabowski H, Guha R, Salgado M. Biosimilar competition: lessons from Europe. Nat Rev Drug Discov. 2014 Feb;13(2):99–100. DOI:10.1038/NRD4210

12. European Commission. State of Health in the EU, Germany. OECD/European Observatory on Health Systems and Policies [Internet]. 2021 [cited 2024 Feb 12];1–23. Available from: https://ec.europa.eu/health/sites/health/files/state/docs/2019_chp_be_english.pdf

13. Eurostat. Health care expenditure by financing scheme. 2023. DOI:10.2908/hlth_sha11_hf

14. OECD. Pharmaceutical spending [Internet]. 2024 [cited 2024 Mar 14]. Available from: https://data.oecd.org/healthres/pharmaceutical-spending.htm

15. Eurostat. Health personnel (excluding nursing and caring professionals) - historical data (1980-2021). 2022. DOI:10.2908/HLTH_RS_PRS1

16. Medicinal Products Act (Arzneimittelgesetz – AMG) [Internet]. [cited 2024 Mar 13]. Available from: https://www.gesetze-im-internet.de/englisch_amg/englisch_amg.html#p1636

17. Bundesministerium für Gesundheid. The German Healthcare System [Internet]. Berlin; 2020. Available from: https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/5_Publikationen/Gesundheit/Broschueren/200629_BMG_Das_deutsche_Gesundheitssystem_EN.pdf

18. Institute for Quality and Efficiency in Health Care. Health care in Germany: The German health care system [Internet]. Informed Health Online; 2018 [cited 2024 Feb 12]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK298834/

19. Blankart KE, Arndt F. Physician-Level Cost Control Measures and Regional Variation of Biosimilar Utilization in Germany. 2020 Jun 1;17(11):1–14. DOI:10.3390/IJERPH17114113

20. World Health Organization. WHO Guideline on Country Pharmaceutical Pricing Policies [Internet]. 2020 [cited 2024 Mar 17]. Available from: https://www.who.int/publications/i/item/9789240011878

21. World Health Organization. Concept note for an observatory of country pharmaceutical and health product pricing policies [Internal, Draft]. 2021.

22. Headquarters WHO. Health (San Francisco). 2007 [cited 2024 Feb 19]. p. 19–20 Meeting Report WHO Informal Consultation on Regulatory Evaluation of Therapeutic Biological Medicinal Products. Available from: https://www.who.int/publications/m/item/therapeutic-biological-medicinal-products

23. World Health Organization. Biosimilars [Internet]. [cited 2024 Feb 12]. Available from: https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/sbp

24. World Health Organisation. WHO Expert Committee on Biological Standardization Sixtieth report [Internet]. 2009 [cited 2024 Feb 12]. Available from: https://www.who.int/publications/i/item/9789241209779

25. World Health Organization. Annex 2: Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs) [Internet]. WHO ECBS 67. 2013 [cited 2024 Feb 19]. Available from: https://www.who.int/biologicals/biotherapeutics/WHO_TRS_1004_web_Annex_2.pdf?ua=1

26. Kang HN, Wadhwa M, Knezevic I, Ondari C, Simao M. WHO guidelines on biosimilars: Toward improved access to safe and effective products. Ann N Y Acad Sci [Internet]. 2023 Mar 1 [cited 2024 Feb 13];1521(1):96–103. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/nyas.14965DOI:10.1111/NYAS.14965

27. World Health Organization. WHO TRS. 2022 [cited 2024 Feb 12]. WHO Expert Committee on Biological Standardization Seventy-fifth report. Available from: https://www.who.int/publications/i/item/9789240057081

28. Committee for Medicinal Products for Human Use. Omnitrope EPAR: Background information on the procedure. 2006;(July 2004):2006. Available from: https://www.ema.europa.eu/en/documents/procedural-steps/omnitrope-epar-procedural-steps-taken-authorisation_en.pdf

29. European Parliament, Council of the European Union. Official Journal L. 2004 [cited 2024 Feb 15]. p. 67–128 Directive 2001/83/Ec. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32001L0083&from=en

30. Committee for Medicinal Products for Human Use. EMA. 2014 [cited 2024 Feb 15]. Guideline on similar biological medicinal products. Available from: https://www.ema.europa.eu/system/files/documents/scientific-guideline/wc500176768_en.pdf

31. European Medicines Agency. CHMP Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues [Internet]. 2014 [cited 2024 Feb 15]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active-substance-non-clinical-and-clinical-issues-revision-1_en.pdf

32. European Medicines Agency. CHMP Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1). 2012 [cited 2024 Feb 15]; Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active-substance-quality-issues-revision-1_en.pdf

33. Schiestl M, Zabransky M, Sörgel F. Ten years of biosimilars in Europe: development and evolution of the regulatory pathways. Drug Des Devel Ther. 2017 May 16;11:1509–15. DOI:10.2147/DDDT.S130318

34. European Medicines Agency. Biosimilars in the EU - Information guide for healthcare professionals [Internet]. 2019 [cited 2024 Feb 12]. Available from: https://www.ema.europa.eu/system/files/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en_1.pdf

35. Der Bundesärztekammer F. Stellungnahme der Arzneimittelkommission der deutschen Ärzteschaft zu Biosimilars. [cited 2024 Feb 16]; Available from: www.akdae.de

36. Arzneimittelkommission der Deutschen Apotheker. Leitfaden Biosimilars - version 1 [Internet]. 2017 [cited 2024 Feb 16]. Available from: https://biosimilarsverband.at/wp-content/uploads/2018/04/leitfadenakd.pdf

37. Arzneimittelkommission der Deutschen Apotheker. Leitfaden Biosimilars - version 2 [Internet]. 2021 [cited 2024 Feb 16]. Available from: https://www.akdae.de/fileadmin/user_upload/akdae/Arzneimitteltherapie/LF/PDF/Biosimilars.pdf

38. Gemeinsamer Bundesausschuss. AM-RL. 2024 [cited 2024 Mar 20]. Anlage VIIa zum Abschnitt M der Arzneimittel-Richtlinie Stand (letzte Änderung in Kraft. Available from: https://www.g-ba.de/downloads/83-691-877/AM-RL-VIIa-Biosimilars_2024-03-15.pdf

39. Mehr Sicherheit in der Arzneimittelversorgung - BMG [Internet]. [cited 2024 Feb 26]. Available from: https://www.bundesgesundheitsministerium.de/gsav

40. Evidera. PPD. 2018 [cited 2024 Feb 26]. GSAV - A New Law for More Safety in the Supply of Pharmaceuticals in Germany. Available from: https://www.evidera.com/wp-content/uploads/2019/11/201911-GSAV-FINAL.pdf

41. G-Ba. Verfahrensordnung 84a [Internet]. 2018 [cited 2024 Feb 16]. Available from: https://www.g-ba.de/downloads/62-492-1614/VerfO_2018-03-16_iK-2018-07-05.pdf

42. Gemeinsamer Bundesausschuss. AM-RL. 2022 [cited 2024 Feb 16]. Beschluss AM-RL § 40b. Available from: https://www.g-ba.de/downloads/39-261-5758/2022-12-06_AM-RL_Einstellung-Verfahren_Biologika-Apotheke.pdf

43. Joline Schmidt K, Konstanski M, Schepis Martinez J, Hall C. Xcenda HTA Quarterly. 2023 [cited 2024 Mar 15]. Navigating the road to successful biosimilar uptake in Europe – Still some way to go? Available from: https://www.xcenda.com/insights/htaq-spring-2023-the-road-to-successful-biosimilar-uptake-in-europe

44. Wissenschaftliche Dienste des Deutschen Bundestages. Deutscher Bundestag. 2023 [cited 2024 Feb 26]; Available from: https://www.bundestag.de/resource/blob/958060/3e214dc926a30f919fdde9130fdb8801/Biosimilars.pdf

45. BfArM - Types of approval - Interchangeability of biosimilars [Internet]. [cited 2024 Feb 16]. Available from: https://www.bfarm.de/DE/Arzneimittel/Zulassung/Zulassungsarten/Austauschbarkeit-Biosimilars/_artikel.html

46. IQVIA Institute for Human Data Science. Country Scorecards for Biosimilar Sustainability: Methodology Appendix [Internet]. 2020 [cited 2024 Feb 17]. Available from: https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/country-scorecards-for-biosimilar-sustainability/iqvia-institute-scorecards-appendix-orb2520.pdf

47. Morton S, Dora Stern A, Stern S. The Impact of the Entry of Biosimilars: Evidence from Europe Citation Terms of Use Share Your Story. Rev Ind Organ. 2018;53(1):173–210. DOI:10.1007/s11151-018-9630-3

48. IQVIA. Biosimilar Scorecard 2020 Germany. 2020 [cited 2024 Feb 17]; Available from: www.iqviainstitute.org/biosimilarscorecards

49. Carl DL, Laube Y, Serra-Burriel M, Naci H, Ludwig WD, Vokinger KN. Comparison of Uptake and Prices of Biosimilars in the US, Germany, and Switzerland. JAMA Netw Open. 2022 Dec 2;5(12):E2244670. DOI:10.1001/JAMANETWORKOPEN.2022.44670

50. Robinson JC. Social trust and regional variation in the adoption of biosimilars in Italy and Germany. GaBI J. 2022;11(3). DOI:10.5639/gabij.2022.1103.015

51. Moorkens E, Lacosta TB, Vulto AG, Schulz M, Gradl G, Enners S, et al. Learnings from Regional Market Dynamics of Originator and Biosimilar Infliximab and Etanercept in Germany. Pharmaceuticals [Internet]. 2020 Oct 1 [cited 2024 Feb 19];13(10):1–20. Available from: /pmc/articles/PMC7590006/DOI:10.3390/PH13100324

52. Bundesministerium für Gesundheid. Statements on the draft bill GSAV [Internet]. 2019 [cited 2024 Feb 22]. Available from: https://www.bundesgesundheitsministerium.de/service/gesetze-und-verordnungen/guv-19-lp/stellungnahmen-refe/gsav.html

53. Gemeinsamer Bundesausschuss. Stellungnahme der hauptamtlichen unparteiischen [Internet]. 2019 [cited 2024 Feb 24]. Available from: https://www.g-ba.de/downloads/17-98-4779/2019-04-04-PA-AfG-SN-GSAV-G-BA.pdf

54. Deutscher Bundestag. 104. Sitzung 06.06.2019 [Internet]. Berlin; 2019 [cited 2024 Feb 22]. Available from: https://dserver.bundestag.de/btp/19/19104.pdf

55. Pyka A, Buchmann T, Vermeulen B. Biosimilars in Germany: the emergence of a new industry in the light of the varieties of capitalism approach. Technol Anal Strateg Manag. 2017 Mar 16;29(3):276–89. DOI:10.1080/09537325.2016.1262022

56. Bundesverband der ArzneimittelHersteller. BAH. 2016 [cited 2024 Feb 27]. Stellungnahme des Bundesverbandes der Arzneimittel-Hersteller e.V. zum Regierungs-Entwurf eines Vierten Gesetzes zur Änderung arzneimittelrechtlicher und anderer Vorschriften (u.a. des Arzneimittelgesetzes). Available from: https://www.bundestag.de/resource/blob/422080/7fe39477e5fc493419c7a2ae789611f7/bundesverband-der-arzneimittel-hersteller-e--v---bah--data.pdf

57. Deutscher Bundestag. Stellungnahme des Bundesverbands der Arzneimittel-Hersteller e . V . (BAH) zum Entwurf der Bundesregierung für ein Gesetz zur Zusammenführung von Krebsregisterdaten [Internet]. Vol. 19. 2021. Available from: https://www.bundestag.de/resource/blob/633874/970cfaf06735187ab4a8b11b7a9b275f/19_14_0068-13-_BAH_Arzneimittelversorgung_19-8753.pdf

58. Verband der forschenden Pharma-Unternehmen (VFA). Stellungnahme zum Gesetzentwurf der Bundesregierung [Internet]. 2019 [cited 2024 Feb 23]. Available from: https://www.vfa.de/de/wirtschaft-politik/stellungnahmen

59. Schlieker K. Rekord bei Arzneien mit Gentechnik; Biopharmazeutika stellen 59 Prozent aller neu zugelassenen Medikamente - die Branche ist trotzdem pessimistisch. Starkenburger Echo. 2023 May 27;

60. Pro Generika. Our positions [Internet]. 2007 [cited 2024 Feb 22]. p. 1–6. Available from: https://www.progenerika.de/the-association/our-positions/?lang=en

61. Pro Generika. Stellungnahme von Pro Generika zum „Entwurf eines Gesetzes zur Stärkung der Arzneimittelversorgung in der GKV“ [Internet]. 2016 [cited 2024 Feb 23]. p. 12. Available from: https://www.bundestag.de/resource/blob/482500/6b0857a81da6b5e24df18b03871f1272/18_14_0223-1-_AMVSG_progenerika.pdf

62. Deutscher Bundestag. Ausschuss für Gesundheit. 2016 [cited 2024 Feb 24]. Wortprotokoll der 98. Sitzung. Available from: https://www.bundestag.de/resource/blob/514414/1c1b39b33efe5051c7311166fbc2eec0/098_14-12-2016_GKV-AMVSG.pdf

63. Pro Generika. Stellungnahme zum Referentenentwurf eines Gesetzes zur finanziellen Stabilisierung der Gesetzlichen Krankenversiche-rung (GKV-Finanzstabilisierungsgesetz-GKV-FinStG) [Internet]. Berlin; 2022 [cited 2024 Feb 22]. Available from: https://www.progenerika.de/app/uploads/2022/07/Stellungnahme-Pro-Generika-GKV-FinStG_120722.pdf

64. AMK. STELLUNGNAHME der Arzneimittelkommission der Deutschen Apotheker (AMK) zum Referentenentwurf eines Gesetzes für mehr Sicherheit in der Arzneimittelversorgung (GSAV) [Internet]. Berlin; 2018 [cited 2024 Feb 22]. p. 6. Available from: https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/3_Downloads/Gesetze_und_Verordnungen/Stellungnahmen_WP19/GSAV/AMK_Apotheker.pdf

65. Bundesärztekammer (BÄK) & Arzneimittelkommission der deutschen Ärzte- schaft (AkdÄ). Gemeinsame Stellungnahme der Bundesärztekammer und der Arzneimittelkommission der deutschen Ärzteschaft zum Gesetzentwurf der Bundesregierung Entwurf eines Gesetzes für mehr Sicherheit in der Arzneimittelversorgung (BT-Drs. 19/8753) [Internet]. bundesaerztekammer.de. Berin; 2019 [cited 2024 Feb 22]. Available from: http://121daet.baek.de/dev_baek_public/index.phpDOI:10.1007/s12285-011-0275-6

66. VKU. Vorläufige STELLUNGNAHME zum Referentenentwurf des BMG “Gesetz für mehr Sicherheit in der Arzneimittelversorgung (GSAV)” [Internet]. 2018 [cited 2024 Mar 14]. Available from: https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/3_Downloads/Gesetze_und_Verordnungen/Stellungnahmen_WP19/GSAV/VUD.pdf

67. Arnet I, Verbeek M, Almarsdóttir Anna B, Barbier L, Clifford R, Eickhoff C, et al. Community pharmacists’ preparedness for substituting biologics and dispensing biosimilars – Lessons learned from a multinational survey. Exploratory Research in Clinical and Social Pharmacy. 2021 Dec 1;4:100084. DOI:10.1016/J.RCSOP.2021.100084

68. Wiesbadener Tagblatt. Krankenkasse sieht hohe Einsparpotenziale; GESUNDHEIT GEK-Report fordert stärkeren Einsatz von Nachahmerpräparaten biotechnologisch hergestellter Arzneimittel. Wiesbadener Tagblatt. 2016 Jun 15;

69. AOK-Bundesverband. Stellungnahme des AOK-Bundesverbandes zum Entwurf eines Gesetzes zur finanziellen Stabilisierung der gesetzlichen Krankenversicherung (GKV Finanzstabilisierungsgesetz – GKV FinStG) Bundestags-Drucksache 20/ 3448. 2022 [cited 2024 Feb 24];1–84. Available from: https://www.aok-bv.de/imperia/md/aokbv/positionen/stellungnahmen/20220922_gkv-finstg_stellungnahme_aok-bundesverband.pdf

70. Klostermann R. Welt-Rheuma-Tag: Das sind die neuen Medikamente. Bild [Internet]. 2019 [cited 2024 Feb 26]; Available from: https://www.bild.de/ratgeber/gesundheit/gesundheit/welt-rheuma-tag-das-sind-die-neuen-medikamente-65261410.bild.html

71. Hoffmann M. Biosimilar-Substitution – ein Irrweg. Tagesspiegel Background Gesundheit & E-Health [Internet]. 2022 May 16 [cited 2024 Feb 26]; Available from: https://background.tagesspiegel.de/gesundheit/biosimilar-substitution-ein-irrweg

72. IQVIA Institute for Human Data Science. FOKUS BIOSIMILARS [Internet]. 2022 [cited 2024 Mar 14]. Available from: https://www.iqvia.com/-/media/iqvia/pdfs/germany/publications/fokus-biosmilars/newsletter-fokus-biosimilars-07.pdf

73. Sander C. Unklares Risiko für Patientinnen und Patienten: G-BA ebnet Weg für Austausch von Biosimilars untereinander allein aus Kostengründen. Berlin; 2020.

74. Vogler S, Schneider P, Zuba M, Busse R, Panteli D. Policies to Encourage the Use of Biosimilars in European Countries and Their Potential Impact on Pharmaceutical Expenditure. Front Pharmacol [Internet]. 2021 Jun 25 [cited 2024 Feb 17];12:625296. Available from: www.frontiersin.orgDOI:10.3389/FPHAR.2021.625296/BIBTEX

75. IQVIA Institute for Human Data Science. Country Scorecards for Biosimilar Sustainability.

76. Pharmaceutical Pricing and Reimbursement Information. PPRI Pharma Profile Sweden 2023. 2023;

77. IQVIA Institute for Human Data Science. Biosimilar Scorecard 2020 | Sweden [Internet]. 2020 [cited 2024 Feb 2]. Available from: https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/country-scorecards-for-biosimilar-sustainability/iqvia-biosimilar-scorecard-sweden.pdf

78. demosEUROPA. Biologics in the Polish health system. 2015 [cited 2024 Mar 6];3–40. Available from: https://www.infarma.pl/assets/files/innowacje/Biologics_in_the_Polish_health_system.pdf

79. IQVIA Institute for Human Data Science. Biosimilar Scorecard 2020 Poland. 2020;

80. College ter Beoordeling van Geneesmiddelen (CBG - MEB). Extra medische informatie voor zorgverleners: Verschillen tussen biologische medicijnen en biosimilars [Internet]. [cited 2024 Mar 6]. Available from: https://www.cbg-meb.nl/onderwerpen/medicijninformatie-

originele-biologische-medicijnen-en-biosimilars/extra-medische-informatie-voor-zorgverleners

81. NVZA. NVZA Toolbox Biosimilars Een praktische handleiding voor succesvolle implementatie van biosimilars in de medisch specialistische zorg. 2017 [cited 2024 Mar 6];(april):1–38. Available from: https://nvza.nl/wp-content/uploads/2017/04/NVZA-Toolbox-biosimilars_7-april-2017.pdf

82. IQVIA Institute for Human Data Science. Netherlands Biosimilar Scorecard 2020 IQVIA. 2020 [cited 2024 Mar 6]; Available from: https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/country-scorecards-for-biosimilar-sustainability/iqvia-biosimilar-scorecard-netherlands.pdf

83. de Block M. Convention sur la relance des médicaments biosimilaires en Belgique [Internet]. Brussel; 2016. p. 57. Available from: https://www.inami.fgov.be/SiteCollectionDocuments/convention_medicaments_biosimilaires_belgique.pdf

84. Barbier L, Simoens S, Declerck P, Vulto AG, Huys I. Biosimilar Use and Switching in Belgium: Avenues for Integrated Policymaking. Front Pharmacol. 2022 Jul 12;13:821616. DOI:10.3389/FPHAR.2022.821616/BIBTEX

85. Vandenplas Y, Simoens S, Van Wilder P, Vulto AG, Huys I. The impact of policy interventions to promote the uptake of biosimilar medicines in Belgium: a nationwide interrupted time series analysis. Health Res Policy Syst. 2023 Dec 1;21(1):1–11. DOI:10.1186/S12961-023-01015-4/TABLES/4

86. Vandenplas Y, Barbier L, Simoens S, Van Wilder P, Vulto AG, Huys I. Perceptions About Biosimilar Medicines Among Belgian Patients in the Ambulatory Care. Front Pharmacol. 2022 Jan 5;12. DOI:10.3389/FPHAR.2021.789640/FULL

87. Barbier L, Vandenplas Y, Simoens S, Declerck P, Vulto AG, Huys I. Knowledge and perception of biosimilars in ambulatory care: a survey among Belgian community pharmacists and physicians. J Pharm Policy Pract. 2021 Dec 1;14(1):1–16. DOI:10.1186/S40545-021-00330-X/FIGURES/6

88. KMPG. Improving healthcare delivery in hospitals by optimized utilization of medicines: a study into 8 european countries. KPMG International Cooperative [Internet]. 2019 [cited 2024 Mar 15];150. Available from: https://www.medicinesforeurope.com/wp-content/uploads/2019/10/20190903_Hospital-Reform-Study_final.pdf

89. IQVIA Institute for Human Data Science. Romania scorecard biosimilars 2020 IQVIA. 2020 [cited 2024 Mar 6]; Available from: https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/country-scorecards-for-biosimilar-sustainability/iqvia-biosimilar-scorecard-romania.pdf

90. Government proposes generic substitution of biological medicines by pharmacies - Ministry of Social Affairs and Health [Internet]. [cited 2024 Mar 22]. Available from: https://stm.fi/en/-/government-proposes-generic-substitution-of-biological-medicines-by-pharmacies

91. Pölkki M, Prami T. Biosimilars Would Reduce Health Care Costs But Are Yet Poorly Known – Patient Survey Study Among Biological Medicine Users. Integr Pharm Res Pract. 2024 Feb;Volume 13:9–16. DOI:10.2147/IPRP.S440888

92. Bocquet F, Paubel P, Fusier I, Cordonnier AL, Sinègre M, Le Pen C. Biosimilar Versus Patented Erythropoietins: Learning from 5 Years of European and Japanese Experience. Appl Health Econ Health Policy. 2015 Feb 1;13(1):47–59. DOI:10.1007/s40258-014-0125-6

93. Ministry of Social Affairs and Health. Valtioneuvosto. 2022 [cited 2024 Mar 6]. Government proposes generic substitution of biological medicines by pharmacies. Available from: https://valtioneuvosto.fi/en/-/1271139/government-proposes-generic-substitution-of-biological-medicines-by-pharmacies

94. Barbier L, Vulto AG. Interchangeability of Biosimilars: Overcoming the Final Hurdles. Drugs. 2021 Nov 1;81(16):1897–903. DOI:10.1007/S40265-021-01629-4/METRICS

95. European Medicines Agency, Heads of Medicines' Agencies. Statement on the scientific rationale supporting interchangeability of biosimilar medicines in the EU [Internet]. 2023 [cited 2024 Mar 21]. Available from: https://www.ema.europa.eu/en/documents/public-statement/statement-scientific-rationale-supporting-interchangeability-biosimilar-medicines-eu_en.pdf

96. Moore GT, Keung C. Biosimilars: is interchangeability the proof of the pudding? Medical Journal of Australia. 2021 Feb 1;214(3):124–5. DOI:10.5694/MJA2.50912

97. Ebbers HC, Schellekens H. Are we ready to close the discussion on the interchangeability of biosimilars? Drug Discov Today. 2019 Oct 1;24(10):1963–7. DOI:10.1016/j.drudis.2019.06.016

98. Kurki P, Barry S, Bourges I, Tsantili P, Wolff-Holz E. Safety, Immunogenicity and Interchangeability of Biosimilar Monoclonal Antibodies and Fusion Proteins: A Regulatory Perspective. Drugs. 2021 Nov 1;81(16):1881–96. DOI:10.1007/S40265-021-01601-2/TABLES/7

99. Ebbers HC, Muenzberg M, Schellekens H. The safety of switching between therapeutic proteins. Expert Opin Biol Ther. 2012;12(11):1473–85. DOI:10.1517/14712598.2012.711308

100. Barbier L, Vandenplas Y, Lacosta TB, Vulto AG. Bioprocess Online. 2022 [cited 2024 Mar 7]. Biosimilar Interchangeability: Regulatory & Practical Considerations. Available from: https://www.bioprocessonline.com/doc/biosimilar-interchangeability-regulatory-practical-considerations-0001

101. GaBi Journal. GaBI Journal. 2014 [cited 2024 Mar 8]. p. 13–4 Germany wants to increase biosimilars penetration Biosimilars. Available from: https://gabi-journal.net/news/germany-wants-to-increase-biosimilars-penetration

102. GaBi Journal. GaBI Journal. 2020 [cited 2024 Mar 8]. p. 1–2 Quotas improve biosimilar use in Germany Posted. Available from: https://gabionline.net/biosimilars/research/Quotas-improve-biosimilar-use-in-Germany

103. Moorkens E, Lacosta TB, Vulto AG, Schulz M, Gradl G, Enners S, et al. Learnings from regional market dynamics of originator and biosimilar infliximab and etanercept in Germany. Pharmaceuticals [Internet]. 2020 Oct 21 [cited 2024 Mar 8];13(10):1–20. Available from: https://www.mdpi.com/1424-8247/13/10/324/htmDOI:10.3390/ph13100324

104. Arnet I, Verbeek M, Almarsdóttir Anna B, Barbier L, Clifford R, Eickhoff C, et al. No Title. Exploratory Research in Clinical and Social Pharmacy. 2021 Dec 1;4:100084. DOI:10.1016/j.rcsop.2021.100084

105. Pro Generika. Experten diskutieren über Lieferketten von Biosimilars [Internet]. 2023 [cited 2024 Feb 24]. Available from: https://www.progenerika.de/news/interview-abwanderung-biosimilarproduktion/

106. Moors E. Challenges for the adoption of future biosimilars. Biopharmaceuticals EJHP Practice [Internet]. 2017 [cited 2024 Mar 9]; Available from: https://www.researchgate.net/publication/233779729_Challenges_for_the_adoption_of_future_biosimilars

107. Barbier L, Simoens S, Vulto AG, Huys I. European Stakeholder Learnings Regarding Biosimilars: Part I—Improving Biosimilar Understanding and Adoption. BioDrugs. 2020 Dec 1;34(6):783–96. DOI:10.1007/s40259-020-00452-9

108. Cohen HP, McCabe D. The Importance of Countering Biosimilar Disparagement and Misinformation. BioDrugs. 2020 Aug 1;34(4):407–14. DOI:10.1007/s40259-020-00433-y

109. Barbier L, Simoens S, Vulto AG, Huys I. European Stakeholder Learnings Regarding Biosimilars: Part II—Improving Biosimilar Use in Clinical Practice. BioDrugs. 2020 Dec 1;34(6):797–808. DOI:10.1007/s40259-020-00440-z

110. Janssens R, Barbier L, Muller M, Cleemput I, Stoeckert I, Whichello C, et al. How can patient preferences be used and communicated in the regulatory evaluation of medicinal products? Findings and recommendations from IMI PREFER and call to action. Front Pharmacol. 2023;14. DOI:10.3389/fphar.2023.1192770

111. Barbier L, Mbuaki A, Simoens S, Declerck P, Vulto AG, Huys I. Regulatory Information and Guidance on Biosimilars and Their Use Across Europe: A Call for Strengthened One Voice Messaging. Front Med (Lausanne). 2022 Mar 9;9:820755. DOI:10.3389/fmed.2022.820755

112. Brill A, Robinson C. Matrix Global Advisors. 2020 [cited 2024 Mar 10]. p. 13 Lessons for the United States from Europe's Biosimilar Experience. Available from: https://biosimilarscouncil.org/wp-content/uploads/2020/06/EuropeBiosimilars_June_2020.pdf

113. European Medicines Agency. Ema.Europa.Eu. 2024 [cited 2024 Mar 29]. Search (filters: Human, Medicine, Biosimilar, Authorized). Available from: https://www.ema.europa.eu/en/search

114. Generics and Biosimilars Initiative. GaBI Journal. 2023 [cited 2024 Mar 19]. p. 7–10 Biosimilars approved in Europe. Available from: http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Europe

115. Sander A. Rote-Hand-Brief Inhixa (Enoxaparin-Natrium) Injektionslösung [Internet]. Berlin; 2018 [cited 2024 Mar 19]. Available from: https://www.bfarm.de/SharedDocs/Risikoinformationen/Pharmakovigilanz/DE/RHB/2018/rhb-inhixa.html#:~:text=Die Firma Techdow Pharma Germany,nicht mehr appliziert werden kann.

116. Brouwers JRBJ, Roeters van Lennep JE, Beinema MJ. Biosimilars of low molecular weight heparins: Relevant background information for your drug formulary. Br J Clin Pharmacol. 2019 Nov 1;85(11):2479. DOI:10.1111/BCP.14081

117. European Medicines Agency. Biosimilar medicines: marketing authorisation [Internet]. [cited 2024 Mar 13]. Available from: https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/biosimilar-medicines-marketing-authorisation

118. Sheridan M, Massich M, Ashourian N. Biosimilars: From Production to Patient. Journal of Infusion Nursing. 2024 Jan 1;47(1):19. DOI:10.1097/NAN.0000000000000528

7. Appendix 1

German biosimilar policies (2006-2024)

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What was the policy?

- Included in the policy are biosimilar products [1, 2]
- There is automatic substitution (pharmacy-level) of 'parenteral preparations from finished medicinal products (individually prepared injections and infusions) according to § 129 para. 1a) sentences 5, 6 of SGB V' [1-3]
- Tendering in inpatient sector through hospitals [4]
- Tendering in outpatients sector through sick funds, using open house contracts [4]
- INN prescribing allowed, but not mandatory [4]
- A few biologicals are included in external reference price system [4]
- Regional physician associations negotiate with sick funds, set budgets for healthcare spending and set prescription quota for physicians [5]

Prior policies: Previously biosimilars could not be substituted, but only switched under physicians' control. This was encouraged using prescribing quotas [4,5].

Why was the policy established?

- Policy established to improve biosimilar supply, increase biosimilar uptake and decrease regional variation in uptake [1]
- Increased biosimilar uptake is associated to cost-saving and improved access to biological medicines [6]
- Politico-legal environment reflected ongoing debates and discussions surrounding pharmaceutical regulation, particularly interchangeability [7]

Purpose: Biosimilars should come into supply more quickly. Increased biosimilar uptake decreases healthcare costs.

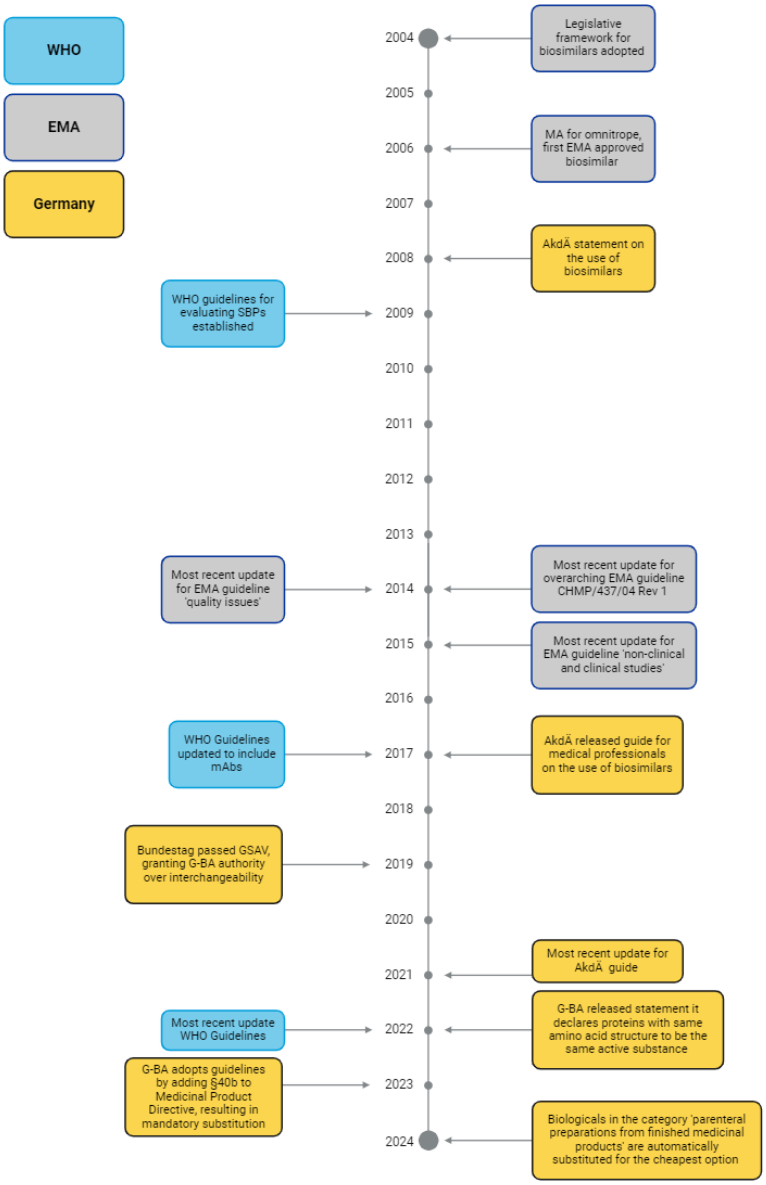
When and how was it implemented?

- Bundestag ratified a law for more safety in the supply of pharmaceuticals (Gesetzes für mehr Sicherheit in der Arzneimittelversorgung, GSAV) in 2019 [1]
- G-BA adopted guidelines for automatic substitution in 2023, effective from March 15 2024 (§40B to Medicinal Products Directive) [8]
- The G-BA is the responsible authority regarding the operation of the policy [8]
- Implementation of the policy should result in cost-saving for the sick funds, needing no further funds.

What were the reported outcomes?

- Previous biosimilar policies led to an increased biosimilar uptake, significant cost reductions in pharmaceutical expenditure, and improved access to novel biosimilars in Germany [9].
- Speed of access was reported to be high in Germany (2021) [9]
- An unintended consequence of Germany's previous policies was a strong regional variation in uptake, with former East Germany having significantly lower biosimilar uptake [10]
- Most recent policy changes do not have reported outcomes yet, due to the recent nature of the changes.

Policy development and implementation timeline



Created using Biorender

Related policies

〉 Germany is a member of the EMA. As a result, marketing authorization for biosimilars (and biologicals) is organized centrally within the EMA, as per Directive 2001/83/EC [11]

Main references

1. Mehr Sicherheit in der Arzneimittelversorgung - BMG [Internet]. [cited 2024 Feb 26]. Available from: https://www.bundesgesundheitsministerium.de/gsav
2. Wissenschaftliche Dienste des Deutschen Bundestages. Deutscher Bundestag. 2023 [cited 2024 Feb 26]; Available from: https://www.bundestag.de/resource/blob/958060/3e214dc926a30f919fdde9130fdb8801/Biosimilars.pdf
3. SGB 5 - nichtamtliches Inhaltsverzeichnis [Internet]. Gesetze-im-internet.de. [cited 2024 Mar 22]. Available from: https://www.gesetze-im-internet.de/sgb_5/
4. Vogler S, Schneider P, Zuba M, Busse R, Panteli D. Policies to Encourage the Use of Biosimilars in European Countries and Their Potential Impact on Pharmaceutical Expenditure. Front Pharmacol. 2021 Jun 25;12. DOI:10.3389/fphar.2021.625296
5. Blankart KE, Arndt F. Physician-Level Cost Control Measures and Regional Variation of Biosimilar Utilization in Germany. 2020 Jun 1;17(11):1–14. DOI:10.3390/IJERPH17114113
6. World Health Organization. WHO Guideline on Country Pharmaceutical Pricing Policies [Internet]. 2020 [cited 2024 Mar 17]. Available from: https://www.who.int/publications/i/item/9789240011878
7. Bundesministerium für Gesundheid. Statements on the draft bill GSAV [Internet]. 2019 [cited 2024 Feb 22]. Available from: https://www.bundesgesundheitsministerium.de/service/gesetze-und-verordnungen/guv-19-lp/stellungnahmen-refe/gsav.html
8. G-BA. Arzneimittel-Richtlinie [Internet]. G-ba.de. 2024 [cited 2024 Mar 22]. Available from: https://www.g-ba.de/downloads/62-492-3400/AM-RL-2023-06-15_iK-2024-03-15_AT-13-02-2024-B3.pdf
9. IQVIA Institute for Human Data Science. Country Scorecards for Biosimilar Sustainability: Methodology Appendix [Internet]. 2020 [cited 2024 Feb 17]. Available from: https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/country-scorecards-for-biosimilar-sustainability/iqvia-institute-scorecards-appendix-orb2520.pdf
10. Robinson JC. Social trust and regional variation in the adoption of biosimilars in Italy and Germany. GaBI J. 2022;11(3). DOI:10.5639/gabij.2022.1103.015
11. European Medicines Agency. EMA. 2023 [cited 2024 Feb 7]. Biosimilar medicines: Overview. Available from: https://www.ema.europa.eu/en/human-regulatory-overview/biosimilar-medicines-overview

8. Appendix 2. Overview of the biologicals and biosimilars in Germany

This table is a list of biologicals approved in Germany, along with 83 approved biosimilars, according to Annex VIIa of the AM-RL by the G-BA, most recently updated on 15 March, 2024 (38). The therapeutic areas of the biosimilars are included, as are the authorization dates of the biosimilars (113,114). The G-BA lists subcutaneous or intravenous applications of the same active ingredient separately, however the EMA does not (38,113).

Three EMA-approved biosimilars are not found in Annex VIIa: inhixa (active ingredient: enoxaparin sodium) and uzpruvo (active ingredient: ustekinumab) and rimmyrah (active ingredient: ranibizumbab). Ranibizumab itself, as well as its reference biological Lucentis and three biosimilars, is found in the overview of the G-BA. For uzpruvo and inhixa, neither the active ingredient nor the reference product are included in the list of biologicals by the G-BA (113). G-BA does not mention the reason for the absence of these biologicals and biosimilars. Uzpruvo and rimmyrah have received MA on 5th of January, 2024, and will likely be included in the next iteration of the list. Inhixa is used in Germany (115), but it could fall outside of G-BA's definition of a biosimilar. Interestingly, low molecular weight heparins, such as onaxaparin, are classified as generics rather than biologicals by the FDA (116).

Table S1. Overview of biologicals and biosimilars approved in Germany, as well as therapeutic area and authorization date of biosimilars.

Active ingredient	**Original/ reference medicinal product**[1]	**Essentially identical biotechnologically manufactured biologicals, approval according to Article 10(4) of the Directive 2001/83/EC (biosimilars**	**Therapeutic area of biosimilar (MeSH)**[2]	**Authorization date biosimilar**
Adalimumab	Humira	Amgevita	Ankylosing spondylitis; Crohn's disease; Juvenile rheumatoid arthritis; Psoriasis; Psoriatic arthritis; Rheumatoid arthritis; Ulcerative colitis	21/03/17
		Amsparity	Ankylosing spondylitis; Hidradenitis Suppurativa; Crohn's disease; Juvenile rheumatoid arthritis; Psoriasis; Psoriatic arthritis; Rheumatoid arthritis; Ulcerative colitis; Uvetis	13/02/20
		Hefiya	Ankylosing spondylitis; Hidradenitis suppurativa; Juvenile rheumatoid arthritis; Psoriasis; Uveitis	26/07/18

[1] The trademarks of the trade names are not shown in the appendix; the trademark rights remain unaffected by this.

[2] Different biosimilars of the same active substance can have MA for different therapeutic areas, e.g. Amgevita is not used for uvetis, while Amsparity is.

Active ingredient	Original/ reference medicinal product[1]	Essentially identical biotechnologically manufactured biologicals, approval according to Article 10(4) of the Directive 2001/83/EC (biosimilars	Therapeutic area of biosimilar (MeSH)[2]	Authorization date biosimilar
		Hukyndra	Ankylosing spondylitis; Crohn's Disease; Hidradenitis suppurativa; Psoriasis; Psoriatic arthritis; Rheumatoid arthritis; Ulcerative Colitis; Uveitis	15/11/21
		Hulio		17/09/18
		Hyrimoz	Ankylosing spondylitis; Crohn's Disease; Hidradenitis suppurativa; Juvenile rheumatoid arthritis; Papulosquamous skin disease; Psoriatic arthritis; Rheumatoid arthritis; Ulcerative Colitis; Uveitis	26/07/18
		Idacio	Ankylosing spondylitis; Arthritis; Crohn's Disease; Hidradenitis suppurativa; Psoriatic arthritis; Psoriasis; Rheumatoid arthritis; Ulcerative colitis; Uveitis	02/04/19
		Imraldi		24/08/17
		Libmyris	Ankylosing spondylitis; Crohn's Disease; Hidradenitis suppurativa; Psoriasis; Psoriatic arthritis; Rheumatoid arthritis; Ulcerative Colitis; Uveitis	12/11/21
		Yuflyma	Axial spondyoarthritis; Crohn's Disease; Juvenile idiopathic arthritis; Hidradenitis suppurativa; Psoriatic arthritis; Psoriasis; Rheumatoid arthritis; Ulcerative colitis; Uveitis	11/02/21
Aflibercept	Eylea	Yesafili	Macular Edema; Retinal Vein Occlusion; Diabetic Retinopathy; Myopia, Degenerative; Diabetes Complications	15/09/23
	Zaltrap			
Agalsidase	Replagal (agalsidase alfa)			
	Fabrazyme (agalsidase beta)			
Bevacizumab	Avastin	Abevmy	Breast cancer; Carcinoma of the cervix;	21/04/2021
		Alymsys		26/03/21

Active ingredient	Original/ reference medicinal product[1]	Essentially identical biotechnologically manufactured biologicals, approval according to Article 10(4) of the Directive 2001/83/EC (biosimilars	Therapeutic area of biosimilar (MeSH)[2]	Authorization date biosimilar
			Colon cancer; Fallopian tube cancer; Non-small-cell lung carcinoma; Ovarian cancer; Peritoneal cancer; Renal cell cancer	
		Aybintio	Breast neoplasms; Colorectal neoplasms; Fallopian tube neoplasms; Non-small-cell lung carcinoma; Ovarian neoplasms; Peritoneal neoplasms; Renal cell carcinoma; Uterine cervical neoplasms	19/08/20
		Mvasi	Breast neoplasms; Fallopian tube neoplasms; Non-small-cell lung carcinoma; Ovarian neoplasms; Peritoneal neoplasms; Renal cell carcinoma	15/01/18
		Onbevzi	Breast neoplasms; Colorectal neoplasms; Fallopian tube neoplasms; Non-small-cell lung carcinoma; Ovarian neoplasms; Peritoneal neoplasms; Renal cell carcinoma; Uterine Cervical Neoplasms	11/01/21
		Oyavas	Breast cancer; Carcinoma of the cervix; Colon cancer; Fallopian tube cancer; Non-small-cell lung carcinoma; Ovarian cancer; Peritoneal cancer; Renal cell cancer	26/03/21
		Vegzelma	Breast neoplasms; Colorectal neoplasms; Non-small-cell lung carcinoma; Ovarian neoplasms; Renal cell carcinoma	17/08/22
		Zirabev	Breast neoplasms; Colorectal neoplasms; Non-small-cell lung carcinoma; Renal cell carcinoma; Uterine cervical neoplasms	14/02/19
Denosumab	Prolia			

Active ingredient	Original/ reference medicinal product[1]	Essentially identical biotechnologically manufactured biologicals, approval according to Article 10(4) of the Directive 2001/83/EC (biosimilars	Therapeutic area of biosimilar (MeSH)[2]	Authorization date biosimilar
	Xgeva			
Eculizumab	Soliris	Bekemv	Atypical haemolytic uraemic syndrome (aHUS) Paroxysmal nocturnal haemoglobinuria (PNH)	24/02/23
		Epysqli	Paroxysmal nocturnal hemoglobinuria: adult and children	26/05/23
Epoetin	Erypo (epoetin alfa)	Abseamed (epoetin alfa)	Anaemia; Cancer; Chronic kidney failure	27/08/07
		Binocrit (epoetin alfa)	Anaemia; Chronic kidney failure	28/08/07
		Epoetin Alfa Hexal (epoetin alfa)	Anaemia; Cancer; Chronic kidney failure	27/08/07
		Retacrit (epoetin zeta)	Anaemia; Autologous blood transfusion; Cancer; Chronic kidney failure Anaemia; Autologous blood	18/12/07
		Silapo (Epoetin zeta)		
	NeoRecormon (epoetin beta)			
	Biopoin (epoetin theta), Eporatio (Epoetin theta)[3]			
Etanercept	Enbrel	Benepali	Axial spondyloarthritis; Psoriatic arthritis; Plaque psoriasis; Rheumatoid arthritis	13/01/16
		Erelzi	Ankylosing spondylitis; Juvenile rheumatoid arthritis; Psoriasis; Psoriatic arthritis; Rheumatoid arthritis	23/06/17
		Nepexto	Ankylosing spondylitis; Juvenile rheumatoid arthritis; Psoriasis; Psoriatic arthritis; Rheumatoid arthritis; Spondylarthropathies	25/05/20
Filgrastim	Neupogen	Accofil	Neutropenia	17/09/14
		Filgrastim Hexal	Cancer; Haematopoietic stem cell transplantation; Neutropenia	06/02/09
		Grastofil	Neutropenia	17/10/13
		Nivestim		07/06/10

[3] Starting materials and manufacturing process of Biopoin and Eporatio do not differ.

Active ingredient	Original/ reference medicinal product[1]	Essentially identical biotechnologically manufactured biologicals, approval according to Article 10(4) of the Directive 2001/83/EC (biosimilars	Therapeutic area of biosimilar (MeSH)[2]	Authorization date biosimilar
		Ratiograstim	Cancer; Haematopoietic stem cell transplantation; Neutropenia	15/09/08
		Tevagrastim		15/09/08
		Zarzio		06/02/09
Follitropin	Gonal-f (follitropin alfa)	Bemfola (follitropin alfa)	Anovulation (IVF)	26/03/14
		Ovaleap (follitropin alfa)		27/09/13
	Puregon (follitropin beta)			
	Recovelle (Follitropin delta)			
Infliximab	Remicade (intravenous application)	Flixabi	Ankylosing spondylitis; Crohn's disease; Psoriatic arthritis; Psoriasis; Rheumatoid arthritis; Ulcerative colitis	26/05/16
		Inflectra		10/09/13
		Remsima		10/09/13
		Zessly		18/05/18
	Remicade (subcutaneous application)[4]	Remsima (subcutaneous application)		
Insulin aspart	NovoRapid	Insulin aspart Sanofi	Diabetes mellitus	25/06/20
		Kirsty		05/02/21
	NovoMix	Truvelog Mix 30		01/04/22
	Fiasp			
Insulin glargine	Lantus	Abasaglar	Diabetes mellitus	09/09/14
		Semglee		28/03/18
	Toujeo			
Insulin human	Actraphane, Mixtard[5]			
	Actrapid			
	Human insulin			
	Insulatard, Protaphane[6]			
	Insuman			
Insulin lispro	Humalog, Liprolog[7]	Insulin lispro Sanofi	Diabetes mellitus	18/07/17
	Lyumjev			

[4] Remicade (subcutaneous application) is not mentioned in Appendix VII to Section M of the Drug Guideline, despite Remsima (subcutaneous application) being listed as a biosimilar.
[5] Authorization on the basis of an application within the meaning of Article 10c of Directive 2001/83/EC using the Actraphane dossier.
[6] Authorization on the basis of an application within the meaning of Article 10c of Directive 2001/83/EC using the Insulatard dossier.
[7] Authorization on the basis of an application within the meaning of Article 10c of Directive 2001/83/EC using the Humalog dossier.

Active ingredient	Original/ reference medicinal product[1]	Essentially identical biotechnologically manufactured biologicals, approval according to Article 10(4) of the Directive 2001/83/EC (biosimilars	Therapeutic area of biosimilar (MeSH)[2]	Authorization date biosimilar
Interferon beta	Avonex (interferon beta-1a)			
	Rebif (interferon beta-1a)			
	Betaferon (interferon beta-1b), Extavia[8] (interferon beta-1b)			
Natalizumab	Tysabri (intravenous application)	Tyruko	Multiple Sclerosis, Relapsis-Remitting; Multiple Sclerosis	22/09/23
	Tysabri (subcutaneous application)			
RDR	BeneFIX (Nonacog alfa)			
	Rixubis (Nonacog gamma)			
Octocog alfa	Advate			
	Covaltry			
	Recombinate			
Pegfilgrastim	Neulasta	Cegfila	Neutropenia	19/12/19
		Fulphila		20/11/18
		Grasustek		20/06/19
		Nyvepria		18/11/20
		Pelgraz		21/09/18
		Pelmeg		20/11/18
		Stimufend		24/03/22
		Ziextenzo		22/11/18
Ranibizumab	Lucentis	Byooviz	Diabetes complications; Diabetic retinopathy; Macular edema; Wet macular degeneration	18/08/21
		Ranivisio		25/8/22
		Ximluci		9/11/22
Rituximab	MabThera (intravenous application)	Blitzima	Non-Hodgkin lymphoma; Chronic B-cell lymphocytic leukaemia	13/07/17
		Rixathon	Chronic B-cell lymphocytic leukaemia; Microscopic polyangiitis; Non-Hodgkin Lymphoma; Rheumatoid arthritis; Wegener granulomatosis	15/06/17
		Riximyo		15/06/17

[8] Authorization according to Article 10c of Directive 2001/83/EC using the Betaferon dossier.

Active ingredient	Original/ reference medicinal product[1]	Essentially identical biotechnologically manufactured biologicals, approval according to Article 10(4) of the Directive 2001/83/EC (biosimilars	Therapeutic area of biosimilar (MeSH)[2]	Authorization date biosimilar
		Ruxience	Chronic lymphocytic leukaemia; Granulomatosis with polyangiitis; Microscopic polyangiitis; Non-Hodgkin Lymphoma; Rheumatoid arthritis; Pemphigus vulgaris	01/04/20
		Truxima	Chronic lymphocytic leukaemia; Granulomatosis with polyangiitis; Microscopic polyangiitis; Non-Hodgkin's lymphoma; Rheumatoid arthritis	17/02/17
	MabThera (subcutaneous application)			
Semaglutide	Ozempic (subcutaneous application)			
	Rybelsus (oral application)			
Simoctocog alfa	Nuwiq, Vihuma[9]			
Somatropin	Genotropin	Omnitrope	Pituitary dwarfism; Prader-Willi syndrome; Turner syndrome	12/04/06
	Humatrope			
	Norditropin			
	NutropinAq			
	Saizen			
	Zomacton			
Teriparatide *(there are also generic approvals)*	Forsteo	Kauliv, Livogiva, Movymia, Sondelbay, Terrosa	Osteoporosis; Postmenopausal Osteoporosis	20/11/23
		Livogiva	Osteoporosis	27/08/20
		Movymia		11/01/17
		Sondelbay		24/03/22
		Terrosa		04/01/17
Tocilizumab	RoActemra (intravenous application)	Tyenne (intravenous application)	Rheumatoid arthritis; Cytokine Release Syndrome; Juvenile rheumatoid arthritis; COVID-19 virus infection; Giant Cell Arteritis	15/09/23
	RoActemra (subcutaneous application)	Tyenne (subcutaneous application)		

[9] Authorization according to Article 10c of Directive 2001/83/EC using the Nuwiq dossier.

Active ingredient	Original/ reference medicinal product[1]	Essentially identical biotechnologically manufactured biologicals, approval according to Article 10(4) of the Directive 2001/83/EC (biosimilars	Therapeutic area of biosimilar (MeSH)[2]	Authorization date biosimilar
Trastuzumab	Herceptin (intravenous application)	Herwenda	Stomach Neoplasms; Breast Neoplasms	15/01/23
		Herzuma	Early breast cancer; Metastatic breast cancer; Metastatic gastric cancer	08/02/18
		Kanjinti		16/05/18
		Ogivri		12/12/18
		Ontruzant		15/11/17
		Trazimera	Stomach Neoplasms; Breast Neoplasms	26/07/18
		Zercepac		27/07/20
	Herceptin (subcutaneous application)			
Tremelimumab	Imjudo, tremelimumab AstraZeneca[10]			

[10] Starting materials and manufacturing process of Imjudo and Tremelimumab AstraZeneca do not differ.