Unlocking the Potential of Biosimilars

A Roadmap for Biosimilar Policy Sustainability

Biosimilar Policy Landscape & Sustainability Assessment

Germany

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Introduction

The adoption of biosimilars can offer significant benefits to stakeholders yet has not been a uniform and equal process across countries. Biosimilar uptake has shown large discrepancies across (and sometimes within) countries.[i, ii] For example, in 2020 the uptake of infliximab biosimilars was 89% in the UK versus 6% in Japan.[iii] Biosimilar utilization can also vary significantly within countries. For example, in a 2021 US study, practice setting (outpatient hospital department vs office practice, and for-profit vs not-for-profit) was found to be a key driver in biosimilar use.[iv] A country's policy environment likely affects the variation in biosimilar success. Assessing the current biosimilar policy landscape and the extent to which current policies support long-term sustainability for biosimilars is critical to understanding the drivers of success, inefficiency and risk areas of biosimilars in any given country.

Methodology

This study presents a global analysis of the biosimilar-specific policies across a wide range of countries. Country-specific policy landscapes are summarised according to an assessment framework of nine policy areas depicted in **Table 1**. Country-specific desk research was conducted to draft policy landscapes and were subsequently validated through 1:1 interviews with country experts.

Table 1 - Policy area assessment framework

	**Manufacturing and R&D**	Policies incentivising local/regional manufacturing or investing in biosimilar R&D
	**Regulatory Approval**	Policies ensuring streamlined or accelerated regulatory pathways at national or regional level
	**Health Technology Assessment**	Policies allowing for reduced or differentiated HTA requirements for biosimilars
	**Pricing & Reimbursement**	Policies mandating price reductions for biosimilars or originator products or affecting reimbursement
	**Contracting**	Policies governing purchasing, including national/sub-national tendering and procurement of biosimilars
	**Biosimilar Education & Understanding**	Policies or initiatives supporting biosimilars education
	**Prescribing**	Policies affecting physician uptake and prescribing
	**Dispensing**	Policies at pharmacy level affecting dispensing of biosimilars
	**Monitoring**	Policies ensuring monitoring of safety and efficacy of biosimilars

Source: CRA

During 1:1 interviews, a sustainability assessment of each policy area was conducted to provide a 'biosimilar sustainability rating'. Based on a literature review, a scorecard was developed and tested with biosimilar policy experts. The scorecard summarises the potential multi-stakeholder benefits of biosimilars using a 5-point 'star rating' scale. (See **Table 2**). In addition to country-specific documents, a cross-country summary and global analysis of the long-term sustainability of biosimilar policies is published in the White Paper 'Unlocking the Potential of Biosimilars: A Global Roadmap for Biosimilar Policy Sustainability'.[v]

Table 2 – 5-point 'star rating' scale

★★★★★	The policy area is considered to be sustainable **for all stakeholders**
★★★★☆	Some **minor areas** for improvement were identified to result in a fully sustainable environment, however no unsustainable policies impact the area
★★★☆☆	Some **major areas** for improvement were identified to result in a fully sustainable environment, however no unsustainable policies impact the area
★★☆☆☆	There are sustainable policies in place which are being negated by the **presence of unsustainable policies** in the same/different policy area
★☆☆☆☆	The (lack of) policies in place are considered to **actively contribute to an unsustainable policy environment** for the majority of stakeholders

Source: CRA

Summary

	Manufacturing and R&D	No specific manufacturing incentives in Germany were identified. Manufacturing follows the EMA GMP guidelines to ensure quality and safety and manufacturing can begin ahead of originator LoE as is standard across markets.	★★★★★	Biosimilars are held to the same manufacturing standards as originator products therefore quality is maintained. Manufacturing can begin before originator LoE facilitating supply at launch while still observing the full exclusivity period of the originator product.
	Regulatory Approval	Germany follows the regulation (EC) No 726/2004 for centralised marketing authorization from the European Parliament, streamlining evidence requirements	★★★★☆	European regulatory approvals for biosimilars are streamlined to an extent but still require clinical comparative effectiveness trials which have been shown to not always be required. This generally, results in an accelerated process and efficient access.
	Health Technology Assessment	Germany's standard HTA process (AMNOG) does not apply to biosimilars and hence, these products are not required to undergo an additional benefit assessment	★★★★★	In the context of a country that values Bx medicines, no HTA required leads to multistakeholder benefits including immediate access for patients (therefore encouraging continued competition and innovation) with no negative effects on sustainability such as a lack of understanding of the value of biosimilars.
	Pricing & Reimbursement	Once a biosimilar has obtained marketing authorisation, under German law it must be reimbursed. Reference price groups can be established to limit the reimbursed price of biosimilars in the retail setting and originator products must increase their rebate from 7% to 10% upon biosimilar launch.	★★★★★	Due to transparency in EMA marketing authorisation process, immediate reimbursement does not place unexpected supply constraints on the manufacturer or existing products. Originators are not required to discount price (but must increase rebates at a sustainable level) upon biosimilar launch and RPGs are only established in some cases thus enabling market dynamics to be the primary influence on pricing.
	Contracting	Regional, multi-winner, open-house rebate contracts are used, these are not negotiated and are currently awarded solely on price. GSAV introducing exclusive contracting and negotiations as well as additional decision criteria for tenders.	★★★☆☆	Currently, multi-winner tenders without the ability to enter into exclusive contracts maintains competition and avoids supply issues. Tenders are currently awarded based on pricing, but supply commitments are made with insurers. Sub-national contracting and 24-month contracts can delay uptake and patient access to both existing and newly launched

				biosimilar products. Exclusive contracts introduced by GSAV in the near future may increase cost pressure and destabilise domestic biologic supply.
	**Public Health Education**	Training programmes, education materials and events have been organised for German pharmacists and physicians.	★★★★★	National educational efforts targeted at HCPs and pharmacists have likely contributed to the wide use and broad uptake of biosimilar products. Further, European-level education efforts led by EMA are seen to be a gold-standard regional approach.
	**Prescribing**	It is recommended that naïve patients should be initiated on the least expensive treatment. Across therapy areas quotas are set and sometimes linked to financial incentives and/or penalties if use of higher-cost treatment options cannot be justified	★★★★☆ *	Biosimilar switching is recommended but not mandated thus allowing physicians to have choice and flexibility in prescribing. Incentives in place encourage uptake however financial penalties, although not widely applied, have been criticised. While patients are not directly consulted, they are informed of switching. *Rating may change depending on the implementation of proposed legislation regarding automatic substitution
	**Dispensing**	Enforcement of the GSAV in mid-2022 will introduce automatic substitution for non-bioidentical biosimilars unless explicitly stated by physicians in prescription.	★★★☆☆	Currently, automatic substitution at the pharmacy-level is not permitted. Introduction of new measures through the GSAV in 2022 will allow this practice for biosimilars deemed interchangeable by the G-BA. This could reduce physician autonomy over prescribing.
	**Monitoring**	No specific German policies have been identified differentiating biosimilar monitoring from other pharmacovigilance efforts.	★★★★☆	European guidance on biosimilar monitoring ensures batch-level traceability and reliable AE-reporting. Manufacturers are required to commit to supply during open-house rebate tenders ensuring some level of transparency in supply and usage across Germany is well documented.

Key Successes, Areas for Improvement & Risk Areas

Key Biosimilar Policy Successes
▲ Reference price groups force price erosions from the high benchmarks established by originators
▲ Multi-winner tenders promote competition amongst manufacturers
▲ Gain-sharing agreements increase physician biosimilar prescribing
▲ Automatic substitution will drive increased use of biosimilars from 2022
Key Biosimilar Policy Areas for Improvement
► Prescription quotas are supportive of biosimilar use, although their impact is diminished by poor enforcement and limited use of penalties
► Wider use of gain sharing agreements will support greater uptake of biosimilars
► National tendering could support more rapid uptake of biosimilars, through increased physician familiarity
Key Biosimilar Policy Risks
▼ Policies driving aggressive price erosion might diminish incentives for manufactures to launch biosimilars in Germany, reducing competition and reducing overall sustainability within the biosimilar landscape
Key Biosimilar Policy Priorities to Achieve Long-Term Sustainability in Australia
1. Although regulatory approvals are streamlined and hence, accelerated in most cases, further streamlining (e.g. through the removal of comparative clinical effectiveness requirements) would further accelerate patient access to new biosimilars
2. Current contracting policy involves use of multiple sub-national tenders to select biosimilars across regions, although this process may be more efficiently run at the national level
3. Introduction of the GSAV might support the use of exclusive contracting practices providing anti-competitive opportunities for originator manufacturers to limit biosimilar use
4. Similarly, GSAV introduction may lead to use of automatic substitution, restricting physician's autonomy over determining patient treatment

Policy Landscape Assessment

Manufacturing and R&D

No biosimilar-specific manufacturing policies in Germany were identified however EU legislation applies.

Manufacturing Exemption Waiver

The manufacturing of biosimilars (and generics) can begin prior to the expiry of the originator's patent exclusivity in a similar manner to that permitted by EU legislation.

European Good Manufacturing Practices

No national or European-level policies incentivising local manufacturing of biosimilars were identified however, Good Manufacturing Practice (GMP) legislation is in place to govern biosimilar manufacture with some additional conditions versus small molecule manufacturing.

The manufacture of biological medicines tends to be more complex than for chemically-derived molecules. For biological medicines, some of the GMP requirements have been adapted to take into account their specific nature (e.g., use of appropriate aseptic techniques, refrigeration and other storage conditions, stability, transport etc.).[vi]

Any changes to the manufacturing process must be approved by the regulators and the extent to which subsequent comparability studies are requires will depend on the expected impact of quality, safety and efficacy of the medicine. Most often, analytical and functional data are sufficient, and clinical trials to prove safety and efficacy are not needed.

Regulatory Approval

Streamlined evidence requirements

Although there are no specific German policies, as an EU Member State and member of the European Economic Area (EEA) Germany follows the regulation (EC) No 726/2004 for centralized marketing authorization from the European Parliament.[vii]

The centralised procedure for granting regulatory approval of biosimilars was first introduced by the EMA in 2004 (Regulation n. 726/2004).[viii, ix] The Committee for Medicinal Products for Human Use (CHMP) regulates the authorization of biologics. The process aims at **providing enough evidence to demonstrate a high degree of similarity between the biosimilar and its reference product.** Therefore, no data needs to be acquired in terms of clinical benefit, as this is already provided by the reference product.[x]

The process to demonstrate biosimilarity consists of three different steps. Firstly, thorough physic-chemical and biological analyses are developed to demonstrate proper quality of the product, as well as its toxicology. This is followed by a second step of non-clinical (pre-clinical) trials to compare pharmacodynamics and pharmacokinetics. The final step aims at demonstrating clinical comparability between the biosimilar and the reference product, and is developed via clinical trials to demonstrate safety, efficacy and immunogenicity.[xi,xii]

Immunogenicity data needs to be collected for one year before the CHMP allows marketing authorisation, and maintained later on for long-term pharmacovigilance purposes.[xiii] Immunogenicity

factors are listed in the guidelines (e.g., anti-drug antibodies (ADAs)) but risk assessments are encouraged to be developed on a product-specific basis, as immunogenicity is hard to foresee.[xiv] **Extrapolation of indications is permitted by the EMA once biosimilarity has been demonstrated for at least one, when the scientific justification is granted**.[xv]

Health Technology Assessment

No biosimilar HTA requirements

Germany's standard HTA process (AMNOG) does not apply to biosimilars and hence, these products are not required to undergo an additional benefit assessment.[xvi] Following marketing authorisation from the European Medicines Agency (e.g. via the centralised procedure), the biosimilar will immediately be available in Germany.

Pricing & Reimbursement

Full coverage vs. partial coverage

Unlike other countries, the basket of treatments reimbursed by statutory health insurance funds is not defined by a positive list, instead all drugs that launch in Germany are reimbursed unless they are specifically excluded (e.g. over-the-counter medications) as defined by §34 SGB V. Therefore, once a biosimilar has attained a marketing authorisation – e.g. through the EMA's centralised procedure – under German law it must be reimbursed and available for use.

Reference pricing

In accordance with §35 Sozialgesetzbuch V (SGB V), reference price groups can be established to limit the reimbursed price of biosimilars.[xvii] These reference prices only apply in the retail setting and only to certain biosimilars determined on a case-by-case basis by the Federal Joint Committee (G-BA) at a national level. For example, inclusion of infliximab-containing products into a reference price group drove a 22% reduction in Remicade's selling price by the end of 2018.[xviii]

Contracting

Multi-winner contracts

In Germany, "open-house rebate contracts" are used for biosimilar contracting, since tenders are not often used in the retail setting by insurance companies (KKs). Given their "open" nature, these contracts can be signed by multiple manufacturers, including manufacturers of both the originator and biosimilars, assuming they are satisfied with the conditions defined by the statutory health insurers – e.g. mandatory net discounts.[xix]

Future changes mandated by the Act for Greater Security in the Pharmaceutical Supply System (Gesetzes für mehr Sicherheit in der Arzneimittelversorgung (GSAV)) will enter into force in mid-2022 and may limit the extent of competition between manufacturers. Importantly, this provides the opportunity for additional

exclusive contracting, alongside the existing tenders, between KKs and manufacturers, which unlike open-house contracts, facilitate exclusive discount agreements. [xx]

Contract decision criteria

Currently, these "open-house rebate contracts" are only based on price and the magnitude of discount.[xxi] Although, following the enforcement of the GSAV, exclusive contracts may involve additional criteria.

Supply considerations

Where manufacturers enter "open-house rebate contracts" with insurers, they make a supply commitment. Consequently, if this cannot be met, they face penalties.[xxii]

Contract length

Contracts currently have a duration of 24-months and they are not required to reopen following the launch of a new biosimilar competitor.[xxiii]

Scope of contracts

Contracts will be established with each health insurer individually, hence there is a sub-national scope.[xxiv] A consequence of the lack of national contracting is slower biosimilar uptake, in part due to lower initial familiarity, and hence prescribing, of biosimilars. This is exemplified by the 100% uptake of infliximab biosimilars, 12-months post-launch, observed in Denmark (single winner, national tenders) when compared to the ~20% 12-months post-launch, observed in Germany/France (multiple winner, regional tenders).[xxv]

Public Health Education

HCP educational programs

In addition to guidelines/recommendations published by various societies in Germany (e.g. Paul Ehrlich Institute), education and (voluntary) training programmes are provided to physicians in order to familiarise them with biosimilar prescribing.[xxvi]

The EMA's official webpage includes information about biosimilars and document to properly educate HCPs. Such documents were last updated in September 2019 and are currently available in 23 different languages. The information has been created gathering opinions from EU scientific experts (e.g., Doctors, nurses, pharmacists).[xxvii, xxviii]

Pharmacist educational programs

Similarly, education materials and events are organised for German pharmacists, with the goal of sharing information regarding biosimilars. Alongside existing promotional websites, information campaigns have been organised, where workshops are held and educational materials (workbooks/videos) are distributed.[xxix] Stakeholders involved in education include pro-generic societies, such as Pro Generika, and patient advocacy groups.

Patient educational programs

Although there have not been direct government efforts to educate patients on biosimilars, less formalised patient education efforts have occurred in the past education programmes. In Germany, physicians remain as the main figure to educate patients and explain the implications for treatment switch, so educational

campaigns targeted to this stakeholder group is believed to play a less important role. However, it has been reported in Germany that a lack of patient education may drive reluctance to switch to biosimilars.[xxx]

Additional to the online documents available in the EMA's webpage, other patient-friendly resources are available. An animated video was created, also in a wide scope of languages, clarifying key factors for these medicines for patients.[xxxi] The European Commission has also created manuals to raise patient awareness around biosimilars.[xxxii]

Prescribing

Clinical guidelines and prescriber-initiated switching

The GSAV which was enacted in August 2019, provides guidelines for physician biosimilar prescribing. They suggest that treatment naïve patients should be initiated on the least expensive treatment (often the biosimilar) and that physicians should investigate whether previously treated patients can be switched. Switching of a previously treated to a biosimilar would not be recommended if a physician expected the patient experience adverse effects.[xxxiii]

Currently, patients do not have to be directly consulted on their preference, although physicians would inform patients of a potential switch.

Prescription quotas

Annually, the National Association of Statutory Health Insurance Funds (GKV-SV) and the National Association of Statutory Health Insurance Physicians (KBV) define prescribing targets across therapy areas. These targets are non-binding and act as a guideline for the formation of quotas at the regional level. Regional physician associations (KVs) can then define their own quotas based on this, leading to significant variation across regions. Generally, these quotas are binding and some are even more stringent than the national prescribing targets.[xxxiv]

Financial incentives linked to biosimilar prescribing

Gain-sharing mechanisms have been introduced between some insurers and groups of physicians, enabling payer savings to be shared between groups of, and individual, physicians. An example is the BioLike initiative launched by the sick fund Barmer GEK with groups of gastroenterologists and rheumatologists, which allowed for >50% penetration in the tumour necrosis factor α inhibitor market by sharing savings realized between the sick fund and the physician association.[xxxv]

Financial penalties for physicians

Monitoring and enforcement of prescription quotas varies across regions, even where quotas are binding, but is meant to be enforced by the KV. Generally, where clinicians are audited and they cannot justify their use of higher-cost options, they may face reduced remuneration.[xxxvi] However, these policies do not apply in private practices.

Dispensing

Automatic substitution

Enforcement of the GSAV in mid-2022 will introduce automatic substitution for non-bioidentical biosimilars.[xxxvii] This will enable pharmacy-level biosimilar for biosimilars determined to be interchangeable as per the G-BA's positive list, unless doctors explicitly state that this is not possible.[xxxviii]

Monitoring

Pharmacovigilance measures

No specific German policies have been identified differentiating biosimilar monitoring from other pharmacovigilance efforts.

EMA's pharmacovigilance requirements for biosimilars are no different than those for biologics. The "list of medicines under additional monitoring" include both biosimilars, as well as those biologics approved after 2011 (and other groups of medicines). The products included in this list need to be labelled with an inverted black triangle in their documentation (e.g., Summary of Product Characteristics (SmPC) and label), and their manufacturer needs to provide a post-marketed pharmacovigilance system when applying for marketing authorisation, as well as the so-called "Risk Management Plan".[xxxix, xl]

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