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SEPTEMBER 2018

Advancing Biosimilar Sustainability in Europe

A Multi-Stakeholder Assessment

Introduction

A growing number of biologic medicines have been developed and approved over the past decade, improving the lives of patients worldwide. Although these have been effective at treating numerous diseases, patient access has been limited, partly due to their relatively high cost. As biologics lose their patent-protection, many biosimilars are becoming available across Europe, and manufacturers are seeking to bring additional biosimilar products to market. These are expected to bring with them the opportunity to generate competition for biologic therapies and thereby lower costs and increase patient access. However, some biosimilar policies and purchasing mechanisms limit participation of competitor products in specific markets, apply increasing price pressure or push physicians to switch patient product use. These current dynamics have raised questions about the sustainability of the biosimilars market in the long-term.

This report puts forth a framework for the evaluation of sustainability in the biosimilars market, seeking to identify the key elements that influence sustainability for all stakeholders. Based on these criteria, current policies and market dynamics are assessed to identify risks and challenges to the current and future biosimilars market, with the aim to identify best practices that can be leveraged to support long-term sustainability in Europe.

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Executive summary

Biosimilars are now an integral part of the market for biologics, which overall accounted for $277 (€238) billion in sales globally in 2017 and is projected to reach $452 (€388) billion by 2022[1]. In ten developed markets alone[i], $45 (€38) billion of biotech spending is now estimated to be exposed to biosimilar competition, and another $52 (€44) billion is expected to go off patent from 2019 to 2022.[2] By 2027, 77% of current biotech spending is expected to be subject to some form of competition[2]. A large and diverse group of manufacturers—numbering 184 globally[3]—are investing in the development and commercialisation of biosimilars, bringing with this investment the promise of high-quality biologic therapies at a lower cost.

In Europe, more than 45 biosimilar products (for 15 biologic medicines) are now approved and registered—treating a variety of diseases within oncology, autoimmune disorders, diabetes and fertility[4]. Frameworks to facilitate, and mechanisms to encourage, the use of biosimilars have been established at the European and country level, and have consistently emphasised the role biosimilars can play in expanding biologics access for patients while lowering treatment costs.

With the potential for biosimilar use to offer savings of more than €10 billion between 2016 and 2020 in the EU5 countries alone[5], payers are likely to experience some relief of budgetary constraints or the ability to reallocate funds, depending on the policy priorities of each country. However, to sustain the market for biosimilars in the long-term, ongoing benefits for all stakeholders must be ensured. A multi-faceted view of sustainability therefore comprises elements including providing patient access, physician prescription choice, a means to manage existing healthcare budgets for payers, the safeguarding of a healthy level of competition and supply, and product safety and quality. Metrics that can gauge trends in these individual elements of sustainability are useful tools to monitor progress and the impact of policy decisions.

To analyse the sustainability of current policies, a set of seven countries with differing approaches to biosimilar utilisation and a set of seven molecules with different purchasing and use characteristics that had biosimilars approved between 2013 and 2017, serve as a useful basis for study. Specific elements of sustainability can then be measured across these varying types, helping to identify where it may be at risk in the future and how hypothetical changes may impact these areas.

In the European market, biosimilars have increased patient access to biologic medicines, raising utilisation of the molecule (i.e., all variants of the same biologic medication, including the originator and biosimilar products) across countries. The current regulatory environment and clinical guidelines are positive toward sustainability by creating a neutral or positive climate for biosimilars relative to originator biologics (i.e., the first, branded variant of any biologic medication). Additionally, product-related sustainability elements have been maintained across countries: biosimilars have proven to be safe, quality products, and manufacturers have provided a reliable supply to markets.

Different levels of biosimilar uptake, price erosion and competitor concentration among manufacturers occur based on the setting of care in which biosimilars are prescribed and used, and the payer purchasing mechanisms in place. In the retail setting—where physician incentives to switch patients to biosimilars may formally exist but with lenient implementation, and patients are familiar with the products and may even be attached to them—biosimilar uptake is slower than in the hospital channel, where different payer purchasing mechanisms—which include tendering

i Developed markets include: U.S., Japan, Germany, France, Italy, U.K., Spain, Canada, South Korea, Australia

and contracting—and different types of incentives, provided by or enforced by payers, drive higher levels of uptake. Price competition among manufacturers in response to different payer purchasing mechanisms results in different levels of price erosion, with single-winner tenders exerting maximum pressure on price but negatively affecting sustainability.

Some of the key elements of a sustainable system were found to potentially be at future risk due to payer-driven switch (where a patient's treatment is switched by the treating physician but influenced by payer decisions, incentives and prescribing barriers) and purchasing systems. For physicians, sustainability means being able to consistently deliver the best healthcare for patients and to maintain their freedom to prescribe relevant treatments of choice[5]. However, payer-driven switch reduces physician prescription choice and patient involvement in the treatment decision, limiting or changing product selection for the patient by removing some as possible options for physicians to select without adding significant work-burden. Overall, the impact of these policies is expected to be greater for patients whose disease requires chronic treatment (e.g., diabetes). In addition, payer-driven switch, especially if enforced though negative physician incentives, provides a means to manage healthcare budgets in the short term but jeopardises sustainability by disrupting market forces and bringing uncertainty to manufacturers of whether they will be locked out from selling product in a market for a duration of time.

Although single-winner tenders were found to achieve greatest price reduction on biologic molecules when biosimilar competition exists, they were also found not to support long-term sustainability as they disrupt market forces and competition by excluding non-winner manufacturers from the market for the duration of the tender contract. Additional evidence suggests single-winner tenders do not always optimise savings, since physicians can still use non-preferred product at a higher price; whereas multi-winner tenders offer price reductions on all contracted products. They also eliminate the incentive for biosimilar manufacturers to innovate in areas to support patients and providers when they select on price only.

An increased focus on a number of areas is necessary in order for payers and policy makers to help strengthen sustainability in the long-term and ensure biosimilars continue to improve access to safe and high-quality biologic treatments in Europe. Firstly, safeguarding the interest of patients and serving their needs in the best way possible remains a critical consideration for health authorities and will become even more so as a greater number of new biosimilars coming to market will be able to be self-administered. Secondly, while creating incentives that promote biosimilar uptake, it is necessary to ensure that physicians retain prescription freedom to offer the best product selection for a specific patient. Thirdly, careful design of purchasing mechanisms is important, with tenders and contracts designed to have multiple winners and include criteria other than price, as they allow greater prescription and product choice for physicians and patients respectively, as well as sustain healthier levels of competition as compared with single-winner tenders.

Overall, in an environment that fosters sustainability, both originator biologic and biosimilar manufacturers will be incentivised and encouraged to continue innovating in differentiation areas for their products outside price and to continue the development of new biologic products, including biosimilars, thus further supporting the sustainability of the biologics market and finding new ways to assist in the needs of all stakeholders.

Sustainability in the biosimilars marketplace

- Biosimilars are now an integral part of the market for biologics (both original and biosimilars), which accounted for $277 billion in sales globally in 2017 and is projected to reach $452 billion by 2022.
- Forty-five biosimilars (for 15 biologic medicines) are now approved and registered across Europe. They treat a broad variety of diseases within oncology, autoimmune disorders, diabetes and fertility.
- A large and diverse group of manufacturers – 184 in total globally – are investing in the development and commercialisation of biosimilars.
- Mechanisms to facilitate biosimilar use have been established at the EU and country level. These have consistently emphasised the role biosimilars can play in expanding biologics access for patients while lowering patient treatment costs.
- A multi-faceted view of sustainability includes elements affecting all stakeholders including patient access, physician prescription choice, a means to manage existing healthcare budgets, and the safeguarding of healthy levels of competition, supply and product safety and quality.
- Metrics that can gauge trends in individual elements of sustainability are useful tools to monitor progress and the impact of policy decisions.
- A set of seven countries with differing payer approaches to biosimilars management, and different utilisation of seven molecules that recently faced biosimilar competition, provide a useful basis for studying the elements of sustainability.
- A route to sustain the market for biosimilars will ensure ongoing benefits for all stakeholders in the long-term.

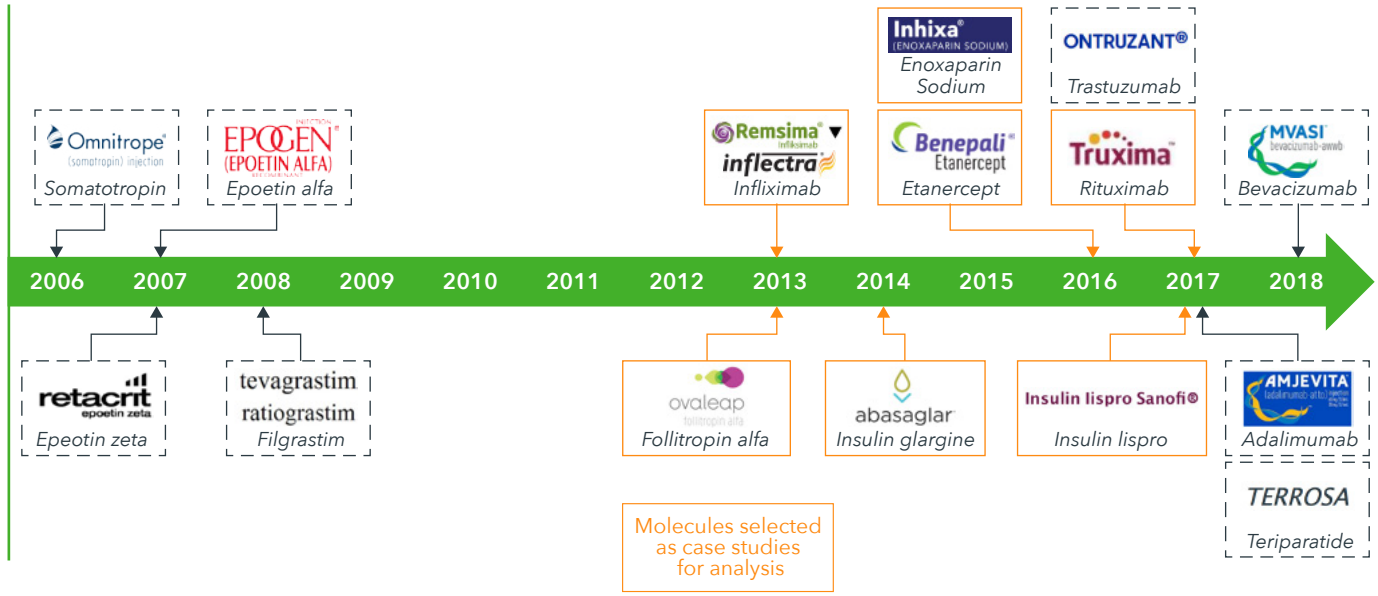
AVAILABILITY OF BIOSIMILAR PRODUCTS

Over the past 12 years, biosimilars have transformed the marketplace for biologic medicines. To date, 45 biosimilars for 15 biologic molecules have been approved and registered by the European Medicines Agency (EMA)[4], treating a variety of diseases within oncology, autoimmune disorders, diabetes and fertility (see Exhibit 1). Biosimilars are now an integral part of the total market for biologics, which accounted for $277 (€238) billion in sales globally in 2017 and is projected to reach $452 (€388) billion by 2022[1].

In ten developed markets alone[7], $45 billion of biotech spending is now estimated to be exposed to biosimilar competition, and another $52 billion is expected to go off patent from 2019 to 2022[2]. By 2027, 77% of current biotech spending is expected to be subject to some form of competition[2].

As more original biologic patents expire, a large and diverse group of manufacturers – 184 in total globally[3] – are investing in the development and commercialization of biosimilars. A growing number of biosimilars are therefore expected to undergo the approval process and reach the market in the upcoming years, particularly in oncology and autoimmune disease. As an example, in addition to the two rituximab biosimilars already approved for use in Europe by the EMA, there were 25 more in development at the end of 2017. Similarly, over 40

Exhibit 1: Availability of Biosimilars in Europe



Source: EMA List of Biosimilars, May 2018[4]; IQVIA Global Consulting Services, Jul 2018
Notes: Molecules were selected as research case studies based on availability of data. Only the first biosimilar approved per molecule is presented.
Total number of biosimilars approved by the EMA is 45 as of August 2018.

adalimumab biosimilars are in varying stages of development by manufacturers in Europe, North America and Asia Pacific[6] – a number that raises the question of whether markets can support all of these competitors, although this topic is not addressed in this report.

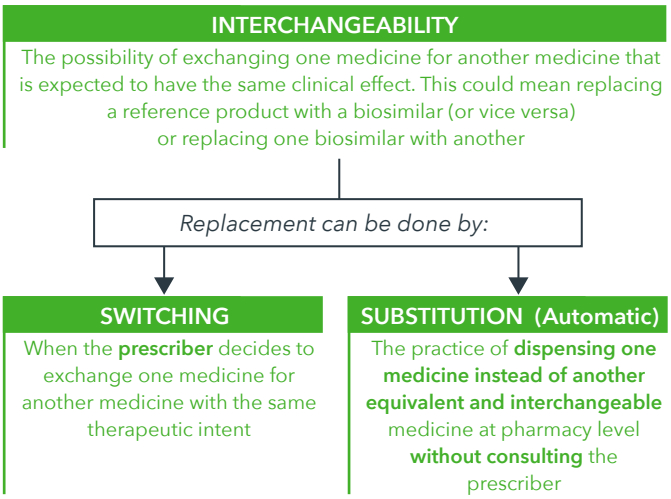
EUROPEAN POLICIES AND FRAMEWORKS FOR BIOSIMILARS

The establishment of policies and regulatory frameworks for biosimilars at the European and country levels reflect considerable efforts to facilitate biosimilar use and to emphasise the role they can play in expanding patient access to biologic medicines while lowering treatment costs. At the European level, the establishment of a centralised procedure for the evaluation and regulatory approval of biosimilars with clear guidelines for manufacturers provided the first step in improving patient access to biosimilars. As part of this procedure, biosimilar manufacturers are required to submit an abbreviated dossier, which is assessed according to standard approval timelines, such as those for original molecules. Biosimilar medicines can be awarded the same indications as the respective reference originator biologic, once biosimilar comparability has been demonstrated.

The EMA regulatory process excludes from their remit the topic of interchangeability (a fundamental element of biosimilar policies) and instead leaves interchangeability decisions to individual countries as part of national policy. Within this report, interchangeability, switch and substitution are defined according to the EMA[7], which highlights the difference between switch, based on physician and patient joint decision-making, and substitution, done at the pharmacy-level automatically without consulting the prescribing physician (see Exhibit 2).

To date, switch decisions remain with the physician; automatic substitution by the pharmacy without physician consent is generally not allowed, although in some cases hospitals and hospital pharmacists will informally push physicians to switch[8]. Moreover, clinical guidelines at the European and individual country level do not discriminate between originator or biosimilar, placing all products on an equal playing field.

Exhibit 2: The EMA's Definitions of Interchangeability, Switch and Substitution



Source: European Medicines Agency. Biosimilars in the EU – Information guide for healthcare professionals. 2017[7].

European efforts to increase the reliability of, and public trust in, biosimilars in terms of quality and safety, are reflected in the EMA's attempts to increase the transparency of biosimilar approvals, as well as in the release of a document in collaboration with the European Commission aimed at providing reliable information for Health Care Practitioners (HCPs)[9]. This document provides a definition of biosimilars, a comparison of biosimilars to generics, reassurance of biosimilar safety and an in-depth overview of the biosimilar regulatory pathway. It further provides information and guidance for HCPs around communicating with patients on biosimilars.

Furthermore, the European Parliament adopted a resolution in March 2017 proposing measures to increase access to medicines within the European Union. In part, it calls for a more predictable and stable framework of drug patent protection and fewer delays hindering entry of biosimilars. It also calls for streamlining the assessment process, to accelerate patient access and lower administrative burdens for biosimilar companies[10]. The European Commission (EC) has also established a regular multi-stakeholder workshop aimed at bringing together all "concerned stakeholders (patients, physicians and other healthcare professionals, payers, the Member States' competent authorities and the pharmaceutical industry)" in an effort to establish further non-regulatory approaches to enhance access to and uptake of biosimilars in Europe[11].

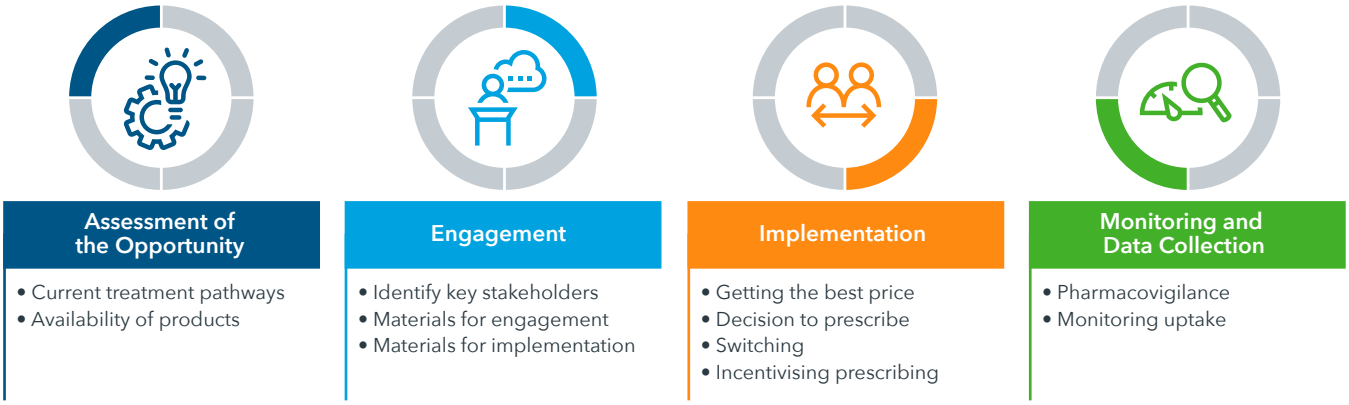
In addition to the biosimilar framework set by the European Medicines Agency and other European actions, countries have adopted different policies to manage biosimilars, particularly around pricing, purchasing and utilisation, although some of these policies may also apply to originator biologics:

1. **Biosimilar reference pricing:** Reference pricing rules, which set reimbursement based on the prices of the originator and other biosimilars for that molecule, function similarly to the reference pricing for generics, and exist in Spain, as well as Norway and Denmark. In addition, national payers in Italy and Spain expect biosimilars to have a 20–30% lower launch price versus originators. Originator price cuts are also expected by payers upon biosimilar entry in Germany, France and Italy in the hospital sector, as well as Denmark. Additional discounts on both biosimilar and originator list prices are also expected and are realised via tenders or negotiated through contracting arrangements, resulting in considerably lower net price levels.

2. **Biosimilar purchasing:** Hospital biosimilar purchasing is done via subnational or multiple tenders in France, Italy and Spain, while Norway and Denmark have national tenders in place. Hospital purchasing in Germany and the Netherlands is handled through contracts, while no specific purchasing mechanisms are used for biosimilars in the retail purchasing sector.

3. **Biosimilar utilisation:** Across the markets in scope, physician switching is allowed, while automatic pharmacy-level substitution is forbidden. Nevertheless, physicians may be encouraged to switch to a biosimilar product by hospital pharmacists informally across markets[8]. Incentives

Exhibit 3: U.K. Example of a National Framework for Biosimilar Commissioners



Source: National Health Service England. Commissioning framework for biological medicines (including biosimilar medicines), 2017 Sep[12].

for biosimilar use differ between the hospital and retail sectors. In the retail sector, incentives are implemented via prescription indicators or quotas that are usually softly enforced at the physician level, leading to slower biosimilar uptake. Meanwhile, in the hospital setting, incentives are usually applied at the practice or regional level by measuring them against performance indicators or internal benchmarks, as well as indirect financial incentives such as where funding is determined though diagnosis related groups (DRGs) and paid a fixed amount per-patient per-case.

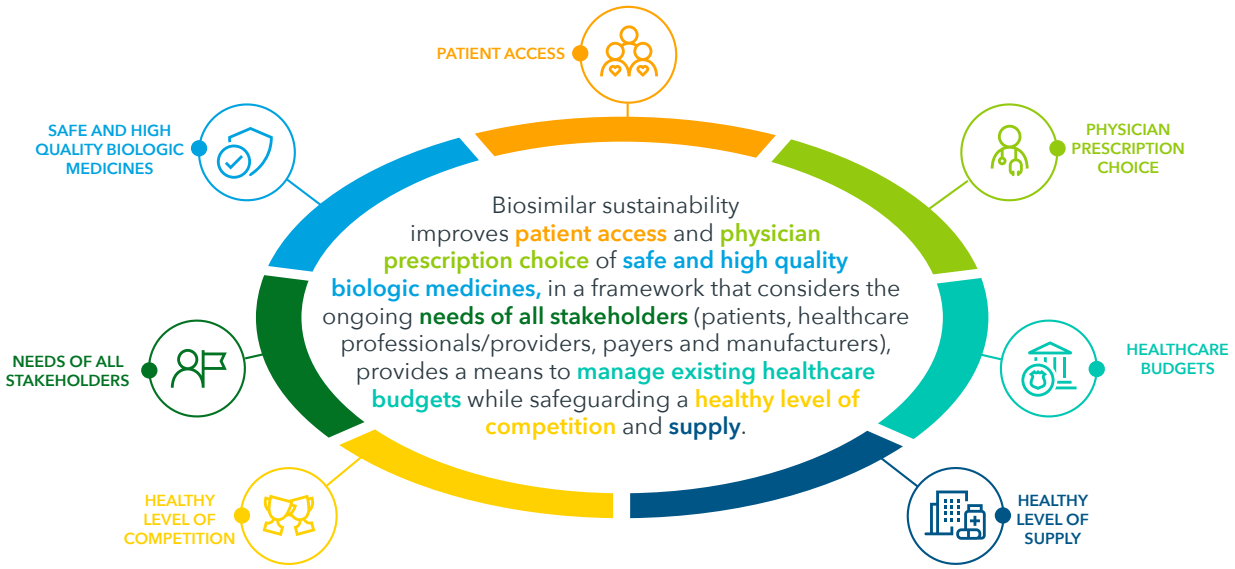
Biosimilar frameworks have further been created at the country level. For instance, the National Health Service (NHS) England developed a commissioning framework for biologics medicines[12] with an emphasis on the current and future use of biologics, highlighting potential savings of at least £200 million to £300 million per year by 2020 or 2021 through the use of biosimilars. The framework is aimed to support local commissioners, who are responsible for assessing, planning, prioritising, purchasing and monitoring the NHS health services in their respective regions. As such, it provides guidance on how best to utilise the opportunity presented by increased competition in the biologics market and to commission biosimilars, by guiding them to specific actions across four areas (see Exhibit 3). The NHS in England further highlights the need for collaboration and engagement with patients, prescribers and providers in these efforts. Commissioners are encouraged to promote switching where appropriate, incentivise prescribing and monitor biosimilar uptake via a dedicated database.

DEFINING SUSTAINABILITY FOR THE BIOSIMILARS MARKETPLACE

Biosimilars are seen as a key means to alleviate financial challenges faced by many stakeholders in the currently constrained European budgetary environment. With the potential to offer savings of more than €10 billion between 2016 and 2020 in the EU5 countries alone[5], payers could see increased biosimilar use resulting in a relief of budgetary constraints, or a reallocation of funds (for instance towards emerging innovative therapies), depending on the policy priorities of each country. Additionally, the availability of biosimilars promises to provide physicians with additional choices of biologics for prescribing, while improving patient access to such medicines and encouraging healthy competition between manufacturers. Simultaneously, maintenance of safety, quality and supply of all biologic medicines, including biosimilars, remains a key consideration for all stakeholders[7].

Sustaining the market for biosimilars is key in securing the long-term benefits of increased biosimilar use for

Exhibit 4: A Multi-Stakeholder Definition of Sustainability for the Biosimilars Marketplace

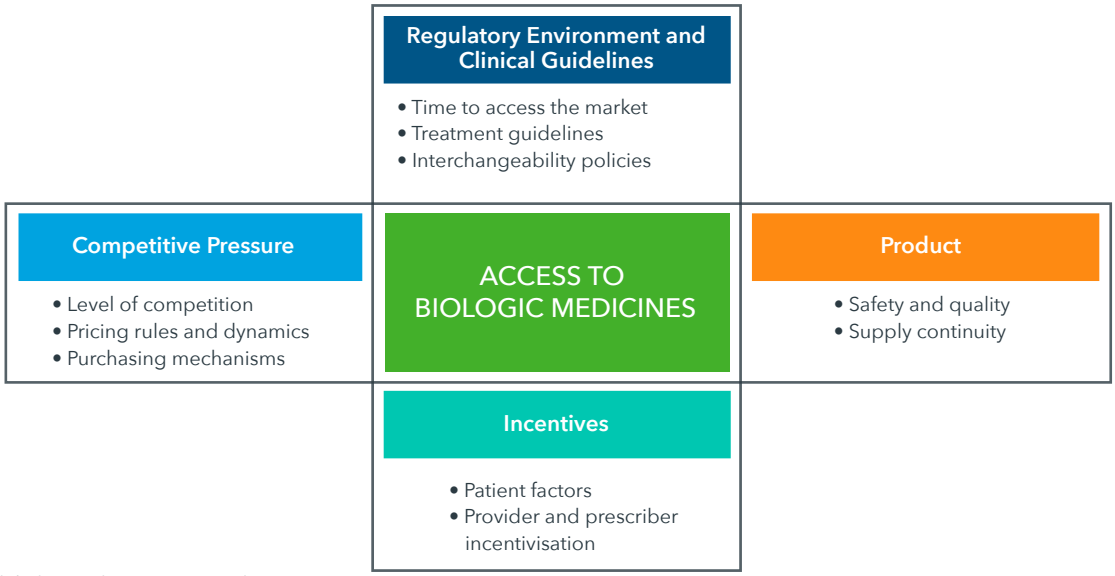


Source: IQVIA Global Consulting Services, Jul 2018

all stakeholders and supporting the development of further biosimilar molecules. A multi-faceted view of sustainability – one including elements affecting all key market stakeholders and influencing the uptake and utilisation of biosimilars – is therefore necessary to evaluate the current biosimilar policy landscape in Europe (see Exhibit 4). The elements included in this view therefore represent the needs of patients, physicians, payers and manufacturers and aligns with the healthy functioning of the marketplace for biologic medicines.

Policies can influence the achievement of these elements variably, and it is therefore valuable to explore which policies best secure a sustainable environment that supports these. Five key areas were identified that have significant influence on sustainability in the biosimilars marketplace, including the current regulatory environment and clinical guidelines for biosimilars, product and supply features, incentives for biosimilar use and competitive market pressures such as pricing, all of which influence overall patient access to biologic medicines (see Exhibit 5).

Exhibit 5: Biosimilar Sustainability Assessment Framework: Key Areas



Source: IQVIA Global Consulting Services, Jul 2018

These five key policy areas are:

1. **Access to biologic medicines:** Policies that support sustainability enable greater use of biosimilars, leading to increased patient access to biologic therapies.

2. **Regulatory environment and clinical guidelines:** Existing regulatory policies offer a bespoke pathway for biosimilars, granting them faster access to market, and hence support sustainability. Additionally, sustainable policies place biosimilars and originator biologics at the same level in clinical guidelines, allowing physicians to choose a treatment based on the patient's best interest and ensuring treatment continuity for previously treated patients, and have clear interchangeability policies not allowing for pharmacy-level substitution without physician consent.

3. **Product:** Policies that support sustainability guarantee safety, quality and supply standards for biosimilars. Procurement policies also minimise the risk of biosimilar and originator supply shortages, ensuring patient's product continuity.

4. **Incentives:** Policies that support sustainability ensure alignment between the direct incentives offered to different stakeholders by payers to influence product choice and indirect incentives tied to the financing and reimbursement mechanisms in place. Additionally, these policies should not encourage patient preference for a specific product.

5. **Competitive pressure:** Policies that support sustainability apply price pressure on biosimilar and originator biologics to enable reductions in the budget impact of biologic medicines, while safeguarding a healthy level of competition in the market. Sustainable policies avoid over-concentration, with no single product (either originator or one biosimilar) dominating the market or securing long-term contracts greater than 24 months. This helps to prevent supply challenges and keep the market attractive and competitive for manufacturers, as well as provide greater opportunity for manufacturers to obtain a return on their investment. Sustainable policies therefore ensure that more than one competitor continues to supply the market and periodicity is short for tenders (twelve months maximum). Finally, these policies aim to achieve a steady price erosion across competitors, and at the same time, guarantee that originators do not offer aggressive price discounts to sustain their market share.

> *"If the physician decides to switch a patient, that's fine. The economic value should not guide the medical decision... Now, even though there is more data present around biosimilarity, I would not subsume any clinical reasoning for economic reasoning."*
>
> *Expert, Italy*

Within these five policy areas, a set of qualitative and quantitative metrics were selected as the best means to assess impact on sustainability. These metrics were used within this study to examine the impact of current policies on long-term sustainability in the biosimilars marketplace, identify where sustainability may be at risk in the future based on the current landscape and determine how hypothetical changes in these (i.e., future scenarios) may impact these areas of risk (see Exhibit 6).

Exhibit 6: Biosimilar Sustainability Assessment Framework: Qualitative and Quantitative Metrics Examined

POLICY AREAS	AREA SUBTYPE	#	Metric	Measure
ACCESS	ACCESS TO BIOLOGIC MEDICINES	0.	Increased molecule use by biosimilar entry	Increase in DDD over the study time
REGULATORY ENVIRONMENT AND CLINICAL GUIDELINES	TIME TO ACCESS THE MARKET	1.	Time to first sales	Time from EMA approval to first sales of first biosimilar (months)
	TREATMENT GUIDELINES	2.	Treatment guidelines	Positive / neutral (molecule) / negative
	SWITCHING POLICIES	3.	Physician switching policies	(Not) enforced / allowed / other
	SUBSTITUTION POLICIES	4.	Pharmacist automatic substitution policies	(Not) enforced / allowed / other
PRODUCT	SAFETY AND QUALITY	5.	Safety and / or quality control alerts	Number of alerts
	SUPPLY CONTINUITY	6.	Presence / absence of supply shortages	Number of shortages
INCENTIVES	PATIENT FACTORS	7.	Patient incentives	Yes / No
	PROVIDER & PRESCRIBER INCENTIVISATION	8.	Existence of prescription quotas	Yes / No
		9.	Provider financial incentives	Yes / No; Specify incentives
		10.	Physicians quotas linked with financial incentives	Yes / No
COMPETITIVE PRESSURE	LEVEL OF COMPETITION	11.	Biosimilar penetration	% of biosimilars over total molecule
		12.	Biosimilar competitor concentration	# competitors taking 90% market
	PRICING RULES AND DYNAMICS	13.	Mandatory price cut policy for originator	Yes / No
		14.	Price reference policy at molecule level	Yes / No
		15.	Price erosion vs. originator	% vs. originator
		16.	Price evolution of biosimilars over time	% vs. originator
		17.	Price evolution of biosimilars over time	% price reduction
	PURCHASING MECHANISMS	18.	Length of contracts	Months
		19.	Number of winners	Single vs. multiple
		20.	Winner decision criteria beyond price	Positive / neutral / negative for biosimilars

Source: IQVIA Global Consulting Services, Jul 2018
Notes: DDD = Defined daily dose.

The various policy areas were assessed across multiple metrics, except for access to biologic molecules, which was measured by the impact of biosimilar introduction on overall molecule utilisation. The ecosystem created by the current regulatory environment and clinical guidelines was evaluated by estimating 'time to first sales', assessing the impact of guidelines discriminating biosimilar or originator products, as well as by identifying physician medicine switching policies and pharmacist substitution policies and their respective impact on biosimilar use and uptake. Product elements were assessed by examining the impact on biosimilar and originator supply shortages and their possible implications, looking at biosimilar safety alerts, supply shortages and contingency mechanisms. Further, patient, physician or care-institution incentives for increased biosimilar use were identified to determine their impact on sustainability. Finally, competitive pressure was assessed by determining biosimilars market penetration and competitor concentration, examining pricing policies for biosimilars and originator biologics, estimating their impact on price erosion and supply and finally the impact of existing purchasing practices (e.g., tendering).

The impact of each metric on sustainability in the biosimilars marketplace was assessed across a set of seven European markets with differing payer purchasing mechanisms – tendering-only markets, contracting-only markets and mixed markets that include either or both tendering and contracting – and across a set of seven biologic medicines that have faced recent biosimilar competition (see Exhibit 7). The biosimilars now available for the seven biologic medicines chosen were launched in the European market between 2013–2017, thus allowing for an analysis of relatively recent biosimilar competition, as well as investigation into historical trends. Further, these molecules have varied purchasing and use characteristics, and along with the countries selected, serve as a useful basis to study biosimilars in Europe.

Exhibit 7: Countries and Molecules Assessed

COUNTRY	MOLECULE	ACRONYM
Germany	Insulin lispro	INS-LP
Netherlands	Rituximab	RIT
France	Enoxaparin sodium	ENO
Italy	Etanercept	ETA
Spain	Insulin glargine	INS-G
Norway	Follitropin alfa	FOLα
Denmark	Infliximab	INF

Source: IQVIA Global Consulting Services, Jul 2018

Note: Erythropoietin (EPO) and granulocyte-colony stimulating factor (GCSF), the first biosimilars launched, were not included due to limited data availability.

Current dynamics of biosimilars in Europe

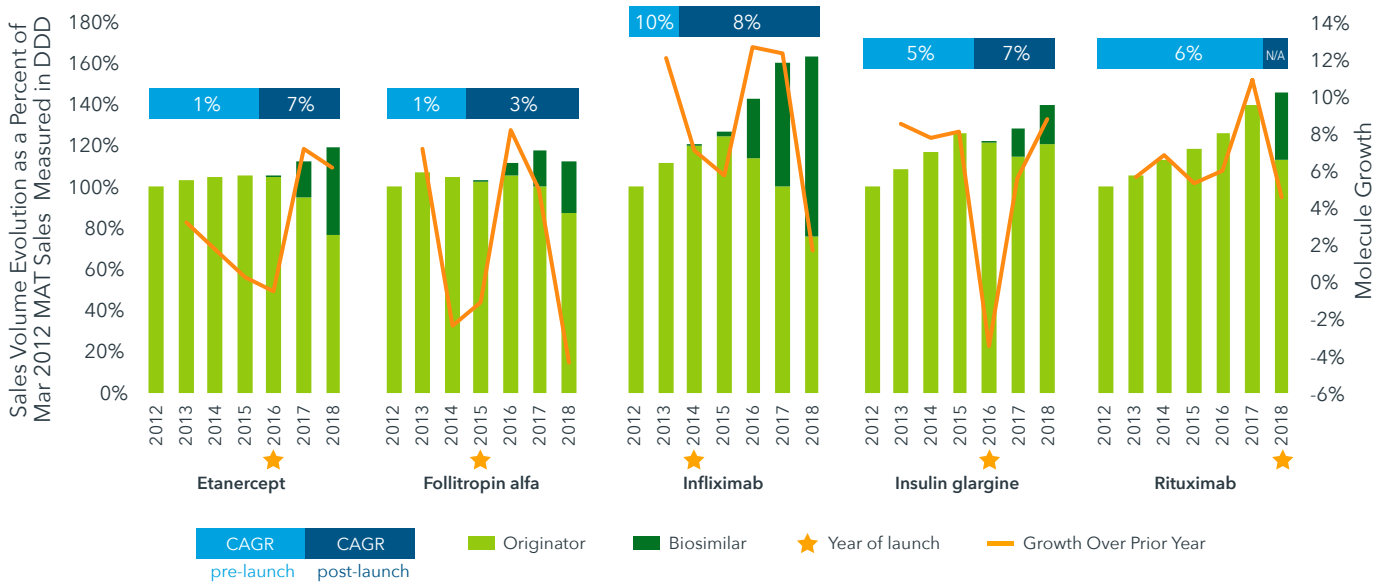
- Biosimilars have significantly contributed to increased patient access to biologic medicines.
- The European regulatory environment and clinical guidelines are generally positive toward sustainability by creating a neutral or positive environment for biosimilars relative to originator biologics.
- Biosimilars have proven to be safe, quality products and manufacturers have provided reliable supply to markets.
- Different payer purchasing mechanisms result in differential uptake, price erosion and concentration of biologics.
- In the retail setting, where physician switching incentives may formally exist but with lenient implementation, and patients may be familiar with or attached to specific products, biosimilar uptake is slower than in the hospital purchasing channel.
- In the hospital channel, different payer purchasing mechanisms, such as contracting and tendering, and different types of positive and negative incentives, provided by or enforced by payers result in different levels of uptake, price erosion and concentration.
- Price competition dynamics by manufacturers in response to different payer purchasing mechanisms result in different levels of price erosion, with single-winner tender markets resulting in the most significant short-term price reductions but jeopardising long-term sustainability.
- Recent dynamics in the biosimilars market pose threats to two key elements: payer-driven switch and tender systems, which award total molecule market volume to a single competitor.

PATIENT ACCESS TO BIOLOGICS

Among the countries and molecules reviewed, biosimilar launch brings with it an increase in patient access to biologic medicines by increasing overall biologic molecule utilisation (i.e., all variants of the same biologic medication, including the originator and biosimilar products). This can be seen for all molecules that have achieved a minimal level of adoption within a country (see Exhibit 8). The launch of biosimilar competitors increases molecule growth and utilisation in the years following launch. However, growth begins to slow to pre-launch levels within a few years, often reflecting the declining competitiveness of the molecule itself within a market that includes innovative therapies. In line with the recommendations of the European Society for Medical Oncology (ESMO)[13], prescribers prefer having some time to familiarise themselves with new agents, inform patients about possible treatment switch and monitor patients whose treatment has been switched more closely, before routinely prescribing a new biosimilar [8]. Faster biosimilar penetration rates are usually seen in specialties where physicians have previously been exposed to biosimilars and have more experience in using them[8].

Biosimilar use is also linked to fewer restrictions in the use of biologics with respect to treatment duration and dosing (e.g., using full loading doses in anti-TNF treatment) allowing, in most cases, for correct dosing and hence favouring better patient outcomes.

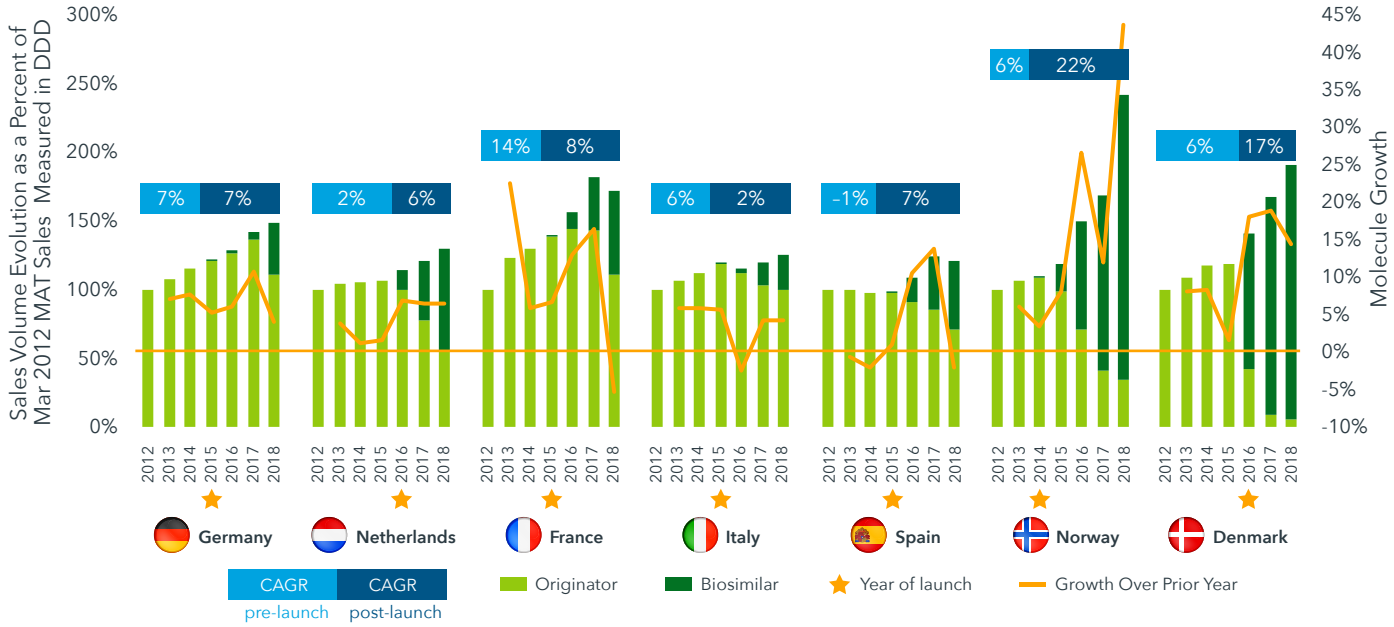
Exhibit 8: Growth in Molecule Utilisation Across Countries with Successfully Adopted Biosimilars, as a Percentage of 2012 Values



Source: IQVIA MIDAS, MAT Mar 2012 – Mar 2018.
Notes: DDD = Defined Daily Dose. Includes all countries and molecules where >6.6% country penetration of molecule was achieved by MAT 2018; Star indicates appearance of first sales within IQVIA data for countries included. All data shown is a full year moving annual total ending in March of that year. Drops in 2018 may reflect entry of alternative branded drugs or biosimilars with more convenient method of administration.

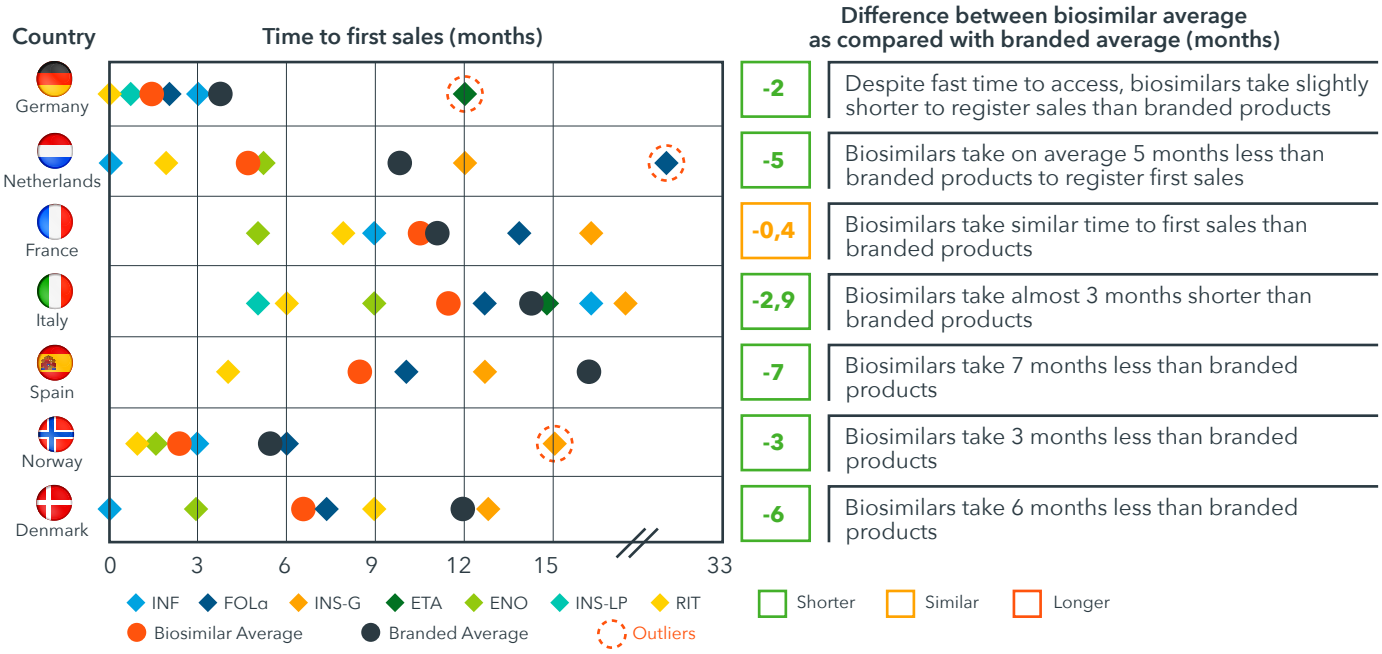
In line with public statements made by drug agencies, different uptake patterns have also been observed across countries. For example, in countries like Norway, where biosimilars are strongly promoted by health authorities, the uptake is usually fast, while in countries like Italy, where health authorities had a conservative perspective, the uptake has been slower (see Exhibit 9).

Exhibit 9: Growth in Utilisation by Country of All Molecules Exposed to Biosimilar Competition Where Biosimilars Were Successfully Adopted, as a Percentage of 2012 Values



Source: IQVIA MIDAS, MAT Mar 2012 – Mar 2018.
Notes: DDD = Defined Daily Dose. Includes all countries and molecules where >6.6% country penetration of molecule was achieved by MAT 2018; Star indicates appearance of first sales within IQVIA data for countries included. All data shown is a full year moving annual total ending in March of that year. Drops in 2018 may reflect entry of alternative branded drugs or biosimilars with more convenient method of administration.

Exhibit 10: Time to First Sales for Biosimilars versus Branded Products by Country



Source: IQVIA MIDAS, Mar 2018; IQVIA Global Consulting Services, Jul 2018
Notes: The average score does not take into account outliers. Time to first sales for infliximab in the Netherlands and Denmark is based on the extended patent expiry date. Clear outliers were excluded from country level analysis.

REGULATORY ENVIRONMENT AND CLINICAL GUIDELINES

Regulatory policies and clinical guidelines in the seven markets examined are generally neutral or positive towards sustainability in the biosimilars market, creating a favourable environment for biosimilars. As the European Commission reports, there is no single approach to ensure successful utilisation of biosimilars[11], as reflected in the variable uptake across markets and products.

Overall, the 'time to first sales' (defined as the time from market approval to first product sales) for biosimilars is lower than the time to first sales for branded products across all markets in scope (see Exhibit 10), reflecting a positive regulatory environment for biosimilars. Delays in product launches in some markets might be driven by the company's strategic decision and commercial opportunity or intellectual property issues, rather than by country health authorities. For instance, the manufacturer of the first rituximab biosimilar delayed launch in some countries to ensure supply continuity.

> *"[Italy] didn't experience as much uptake of biosimilars as expected. The OSMED database indicated some issues… that biosimilar uptake was good when more than four biosimilars of the same compound were available, but somehow the uptake was not as expected [since] it was only two products."*
>
> *Expert, Italy*

Overall, retail molecules tend to take longer to register first sales than hospital drugs, with significant time lag observed.

Finally, treatment guidelines are neutral or positive towards biosimilar products in most countries, placing

them all at the same level as the originator in terms of clinical efficacy. Decisions to switch treatments from originator biologic to biosimilar (or the other way around) remain at the physician's discretion across markets. An exception was in Italy, where Agenzia Italiana del Farmaco (AIFA) guidelines did not originally consider biosimilars as interchangeable with originator biologics, and physicians were required to justify the switch decision. However, updated guidelines were published recently and this requirement was removed[14]. Overall, guidelines discriminating between or against biosimilar or originator products, as well as physician switching and automatic pharmacy-level substitution policies, can have impact on biosimilar use and uptake.

BIOSIMILAR SAFETY, QUALITY AND SUPPLY

Authorised biosimilars have proven to be safe, high-quality products with manufacturers providing a reliable supply to markets. For this reason, the EMA states: "[…] biosimilars approved through the EMA can be used as safely and effectively in all their approved indications as other biological medicines"[7]. There have also been no supply shortages for biosimilar products reported to date by the EMA[15]. No safety or quality alerts have been identified, although this remains critical to the EMA and individual country health authorities as an issue to guard against. For instance, France is currently drafting a new law to create contingency mechanisms for possible supply chain shortages, and other countries like Norway or Germany include penalties for manufacturers if supply shortages occur.

> *"There are no shortages [of biosimilars], although it is difficult to manufacture them. We expected more of them…. It is not excluded that it won't happen though – prices are sharp and there are risks in the market. I would expect there to be more problems in the future as the prices will be lower and lower."*
>
> *Expert, Netherlands*

INCENTIVES

Incentives are used by payers across countries to influence physician and patient product choice. Patient, physician or care-institution incentives can influence biosimilar uptake as well as patient quality of care, by influencing treatment decisions based on price rather than on clinical criteria or patient needs. Incentives can be financial or non-financial (e.g., physician prescription quotas), positive or negative (e.g., financial bonuses or penalties, respectively), be applied as guidelines or targets, or be a combination of these[16]. Incentives within the hospital and retail sectors differ.

In the retail purchasing sector, physician switching incentives may formally exist, but often have lenient implementation. This is partly because prescribers are rarely the budget holders and are thus less focused on creating savings, combined with incentives that are not stringent and not always linked to consequences. Formal mechanisms in the retail sector set out by payers to incentivise biosimilar use include:

- Prescribing targets for biosimilars linked to financial or non-financial incentives, such as the prescribing-related performance bonuses for biosimilar insulin use enforced in France
- Federal prescribing targets, including minimum prescription volume targets for several biosimilars, currently in place in Germany

Existing provider incentives are not specifically designed to encourage biosimilars (at times stretching across a range of recommendations about care delivery) and not always linked directly to financial incentives. In the case of Germany, federal prescribing budget targets are employed as direct incentives to encourage overall biosimilar use, but since they are set on a regional level, it is up to the

Exhibit 11: Infliximab Biosimilar Prescribing Targets Set by KVs and KBV in Germany

SELECTED KVs	INFLIXIMAB BIOSIMILAR (AS A PERCENT OF TOTAL INFLIXIMAB VOLUME)					
	KV TARGETS			KBV TARGETS		
	2016	2017	2018*	2016	2017	2018*
Berlin	7.0%	n/a	n/a	2.2%	20.2%	35.0%
Saarland	9.6%	33%	n/a	9.6%	25.7%	47.6%
Sachsen	20%	20%	n/a	1.0%	11.6%	19.1%
Westfalen-Lippe	> 45%	> 75%	n/a	11.4%	44.8%	68.0%
Average (across KVs)	–	–	–	5.6%	24.6%	40.6%
Range (across KVs)	–	–	–	0.4-16%	11.5-45%	19-70%

Source: KVB national target recommendations 2017[17]; Saarland KV 2017 targets[18]; Westfalen-Lippe KV 2017 targets[19]; Sachsen 2017 targets[20]; Berlin KV 2016 targets[21]; Saarland KV 2016 targets[22]; Sachsen KV 2016 targets[23]; Westfalen-Lippe KV 2016 targets[24]; KVB national target recommendations 2016[25]; KVB national target recommendations 2018[26].

*Notes: Four selected Kassenärztliche Vereinigung (KVs) are presented in this table. Average and range estimated across all 17 KVs.

regions to implement them. At national level, federal prescribing targets for therapy areas are set between the GKV (Gesetzliche Krankenversicherung; German statutory health insurance) and KBV (Kassenärztliche Bundesvereinigung, or German national association of statutory health insurance physicians, that influences decisions on medical service provision by supervising and representing the interest of physicians at the federal level), including minimum prescription volume targets for several biosimilars which vary by region (see Exhibit 11). KBV targets[17] for the 2018 year have increased significantly versus 2017, with infliximab targets rising from 24.6% to 40.6%, and varying by region, ranging from 19.1% in Hamburg to 69.6% in Lower Saxony (average: 41%)[17-26]. Etanercept targets too range from 7.7% in Thüringen to 57% in Westfalen-Lippe (average: 25%). KVs (Kassenärztliche Vereinigung, or the 17 German associations of statutory health insurance physicians that are the members of the KBV) are not obliged to abide to the minimum prescribing targets set by KBV, such as in the case of Westfalen-Lippe and Sachsen, which have higher targets compared to the national quotas set by KBV for their respective regions, and can decide to make their own additional conditions or guidelines[17-26]. For instance, Westfalen-Lippe encourages physicians to prescribe biosimilar (e.g., Benepali) rather than the branded originator (Enbrel) for cost savings, describing them as therapeutically equivalent, while Bayern KV recommends only that naïve patients be started on biosimilar products.

Indirect patient incentives impacting retail biologics may also exist in the retail setting, such as when biosimilars are linked to lower co-payments or exemptions from co-payments. However, in cases when patients self-administer the product, they are familiar with and often more attached to the product or associated device used for their therapy, and therefore more resistant to being switched to a biosimilar. These factors, combined with lenient implementation of physician and care-institution incentives, results in slower biosimilar uptake compared to the hospital purchasing channel. Biosimilar uptake needs to be actively incentivised to ensure physician prescription and sustainability in the retail channel; learnings from the generics market also support the need for active incentives to promote switch from originators.

In the hospital purchasing sector, incentives for biosimilar use are less formal and indirect, but nonetheless have a stronger effect on uptake, as practice economics are directly impacted by the

"[For doctors] one of the biggest issues [discussed] in the past was losing their prescribing freedom. But they are also part of the health system and there are medical specialist groups that contract with the hospital, whose income depends on how well the hospital does…. If they prescribe less and the hospital does better, their income also becomes higher. The Ministry of Health accepts the freedom to prescribe, but they say, 'what you do for us, you do for yourself'. The doctors understand that the world is changing…. They understand that it is important to lower to the costs of healthcare. Prescribing freedom is big but they do think about costs."

Expert, Netherlands

physician's choice of biologic product. Depending on the purchasing and reimbursement mechanisms in place, care-institutions and physicians face different levels of pressure to promote switch to a biosimilar product. For instance, in hospitals funded based on diagnosis related groups (DRG) –where a hospital is paid a lump sum per patient per case based on diagnosis – such as in France, providers have an indirect incentive to increase use of biologic products with lower prices and retain the excess of the DRG tariff as profit. In addition, patients treated with products purchased in hospitals face no additional costs for their treatment and are usually less attached to the specific product used, and therefore do not express a preference between biosimilar and originator biologic products. Lower patient involvement in therapy decisions combined with stronger financial incentives for providers has contributed overall to stronger biosimilar uptake in the hospital sector as compared to the retail setting.

COMPETITIVE PRESSURE

The speed and level of biosimilar product penetration in each market varies substantially depending on market dynamics influenced by the payer purchasing mechanisms in place, as well as between the hospital and retail sectors.

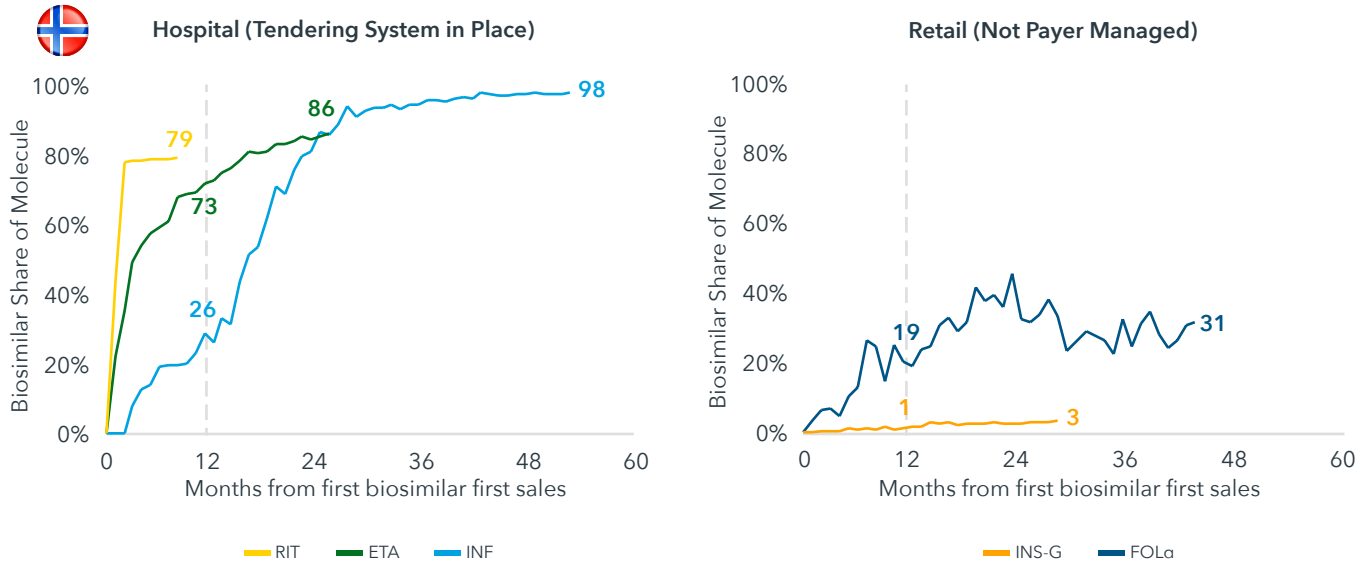
"When we are talking about biosimilars, we have to differentiate between biosimilars in the hospital versus the outpatient setting…. For retail treatments, the physician is totally free to make a decision between products on the market in France. The retail pharmacy is not allowed to switch the treatment. [For the hospital setting] at the beginning we decided to give the choice to the physician and all biologics were available on the formulary, but it won't go on like this anymore and it will only be one biosimilar… we will always have tenders with one winner."

Expert, France

Setting of care

Biosimilar uptake varies substantially between hospital-purchased and retail-purchased products, as the latter are not managed through stringent mechanisms, such as tenders. Use of single-winner tenders in the hospital setting can lead to rapid biosimilar uptake, with biosimilar volume shares

Exhibit 12: Biosimilar Penetration in Norway Over Time



Source: IQVIA MIDAS, Mar 2018; IQVIA Global Consulting Services, Jul 2018
Notes: Displays the additive share of all biosimilar products from the time of first biosimilar launch.

reaching 80% for biologic molecules in less than six months, such as in the case of rituximab in Norway (see Exhibit 12). In comparison, in the retail sector, where biosimilars are not actively managed and promoted, the uptake is significantly lower as in the case of drugs like insulin glargine.

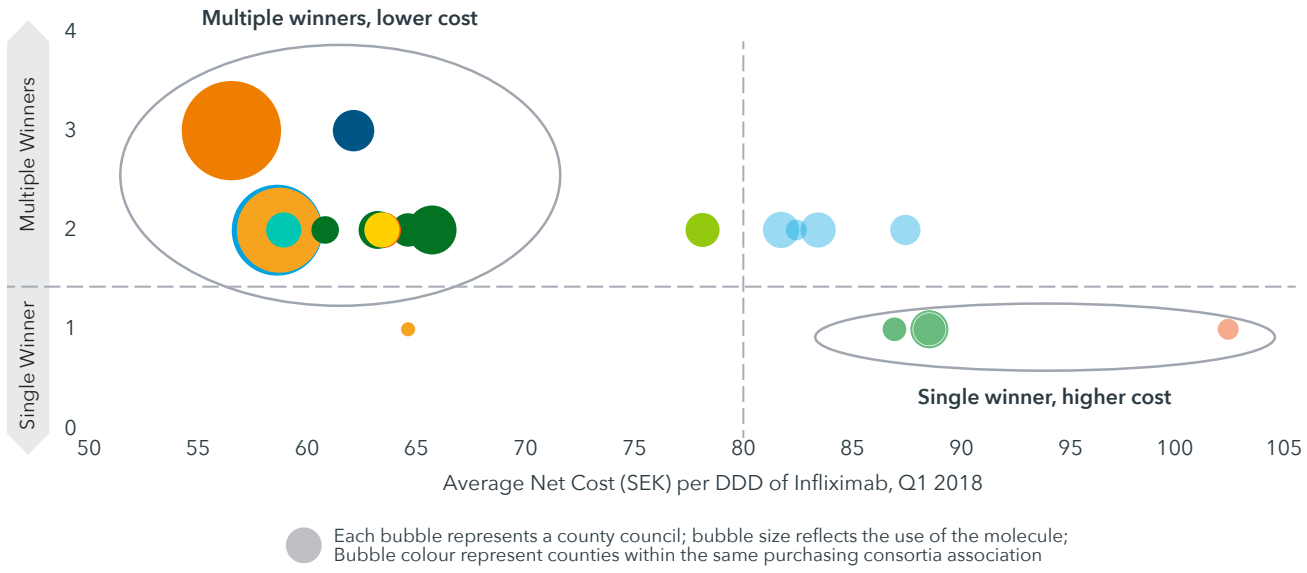
Additionally, markets vary in their payer purchasing mechanisms, from contracts – directly negotiated between insurers and manufacturers (as in Germany) or between hospitals and manufacturers – granting access to multiple biosimilars, to bidding processes where one or more manufacturers may be awarded entry to the market or region based on low price or other criteria. Such bidding processes include single (national) tenders or multiple tenders, with single or multiple winners, and many variations in between. In single-winner tenders, the winning product is primarily used to supply the market, but physicians may still request a different product for a patient as an exception, by providing justification for their choice. Conversely, contracts (e.g., German statutory health insurance) and tenders that are designed to have multiple winners with criteria beyond price alone keep multiple manufacturers actively engaged, commonly reduce the prices of all winning products, while providing multiple alternatives for prescribers to choose and may enable patient continuation on current biologic medicines as needed.

> *"We consider everything of course: safety, reliability, stability of the product, data, factors that might improve the chance for the product to be on the formulary, but we consider that if a product is on the French market, the product already got through several assessments so it means that we are able to use it safely. Which is why 85% of the decision is related to the price."*
>
> *Expert, France*

IMPACT OF TENDER TYPES

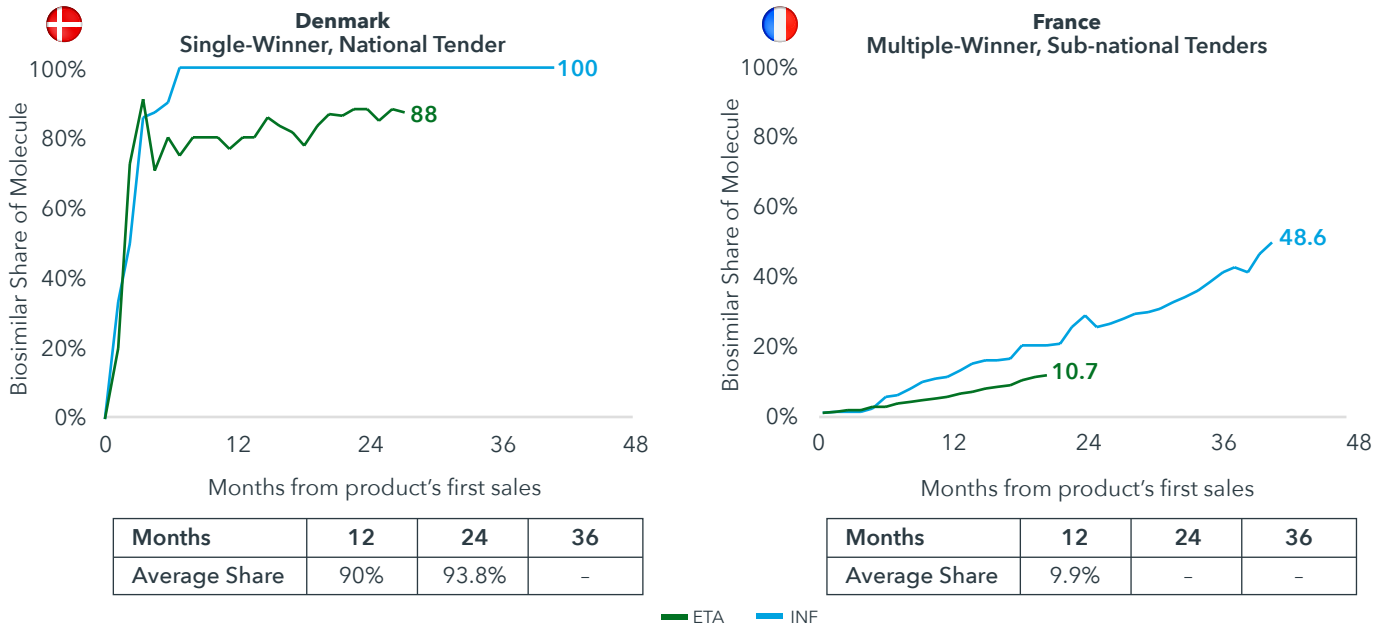
Although analysis in our report shows that single-winner tenders achieve greatest price reduction on biologic molecules when biosimilar competition exists, there is additional evidence from other data sources to show that multiple-winner tenders may result in lower average net molecule costs per defined daily dose (DDD) for a region overall (see Exhibit 13). This cost savings occurs since price reductions are obtained on all contracted products (often including the originator) in multiple-winner tenders rather than only on one product. In sustainable environments where physicians can choose between options to optimise patient care, and where they may gravitate towards higher list-price products, regions that achieve price-reductions on all available products see lower average costs. For instance, use of multiple-winner tenders in Sweden by individual, or groups of, county councils, led in some cases to lower average net cost for infliximab per DDD at the molecule level (reflecting all products and the product mix of originator and biosimilars) than single-winner tenders during the first quarter of 2018. The superior reductions seen here for multiple-winner tenders reflect the interplay of a number of factors including the price reductions achieved in tenders on any infliximab product (e.g., whether some products remain available at list- or high-price such as in single-tenders, or the influence of volume discounts in negotiations) and the increased use of less expensive forms in one area versus another. Examination of the data shows that regions with the highest net cost often have a high use of a non-preferred product at a high price. Since payers, similarly to healthcare providers, benefit from multiple-winner tenders, the fact that they at times realise greater overall molecule savings than single-winner scenarios is important to note. Finally, tenders with multiple winner offer the option of supply alternatives in case of distribution or stocking issues.

Exhibit 13: Infliximab Per DDD Product Costs by Swedish County in Relation to Use of Single - Versus Multiple-Winner Tenders, Q1 2018



Source: E-hälsomyndigheten (EHM) Hospital Data, Q1 2018
Notes: The difference in average net cost correlates with the negotiated price, and to a higher degree, the extent to which the lowest price product is used - i.e. the rate at which patients are switched to the lowest cost product.

Exhibit 14: Biosimilar Penetration in Denmark and France



Months	12	24	36
Average Share	90%	93.8%	–

Months	12	24	36
Average Share	9.9%	–	–

Source: IQVIA MIDAS, Mar 2018; IQVIA Global Consulting Services, Jul 2018

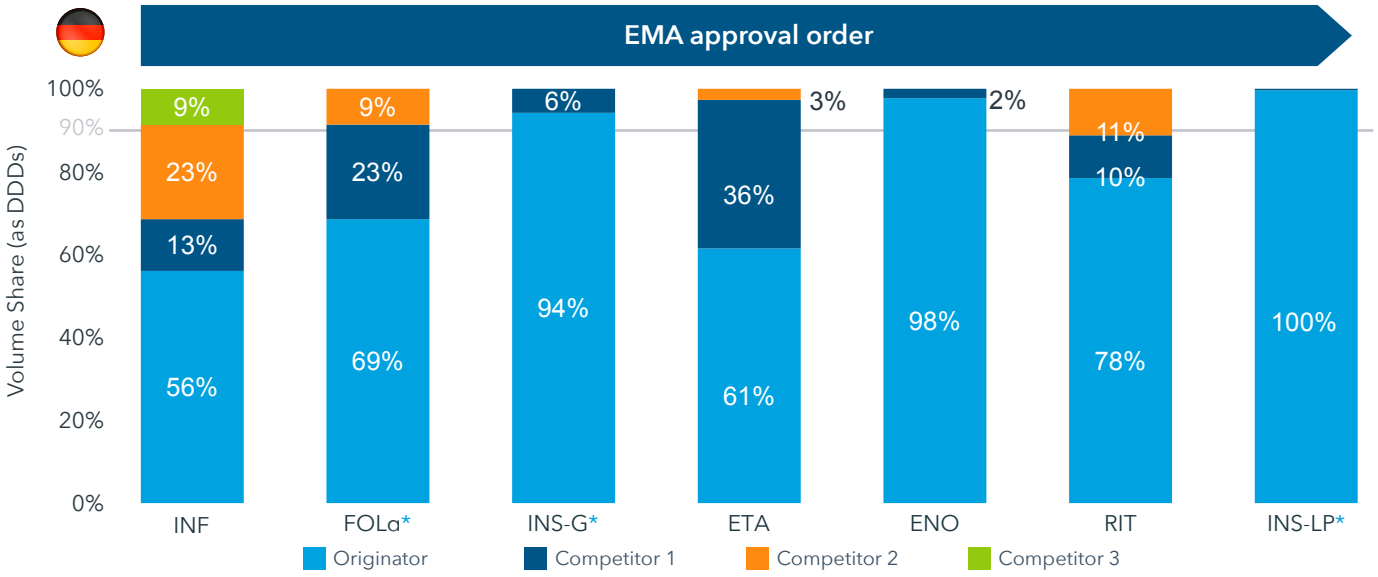
Moderate biosimilar uptake is recorded in markets where national tenders are not in place – including Germany, Netherlands, France, Italy and Spain – as physicians take more time to become familiar with the biosimilar products and start prescribing them routinely. In contrast, use of national tenders leads to faster and higher biosimilar penetration, particularly when run as single tenders with single winners, as in the case of Norway and Denmark (see Exhibit 14).

Competitor market concentration

Following the launch of the first biosimilar, the market for a biologic medicine is usually concentrated in a single product – either the originator biologic or the biosimilar. Due to the low number of existing competitors, the leading product may capture up to 90% of the market for the specific molecule (the level defined in this analysis as denoting a concentrated market). However, as new biosimilars become available over time, markets tend to become more fragmented, with new competitors starting to capture shares of a specific molecule (see Exhibit 15). In the retail purchasing sector, fewer biosimilar launches have led to originators retaining a higher market share over time, as demonstrated by the examples of insulin glargine, enoxaparin sodium and insulin lispro. It should be noted that in countries with single-winner tenders for a biologic molecule, market concentration remains high over time as the tender-winning product always captures the majority market share.

> *"The opportunity with biosimilars is to change between them and create more competition between companies. They give the opportunity to create release in budgets…. At the end of the day, the centralized council medicine took the decision to change patients to the cheapest option, and that why they have a fast and high uptake on biosimilars."*
>
> *Expert, Denmark*

Exhibit 15: Competition Concentration in Germany

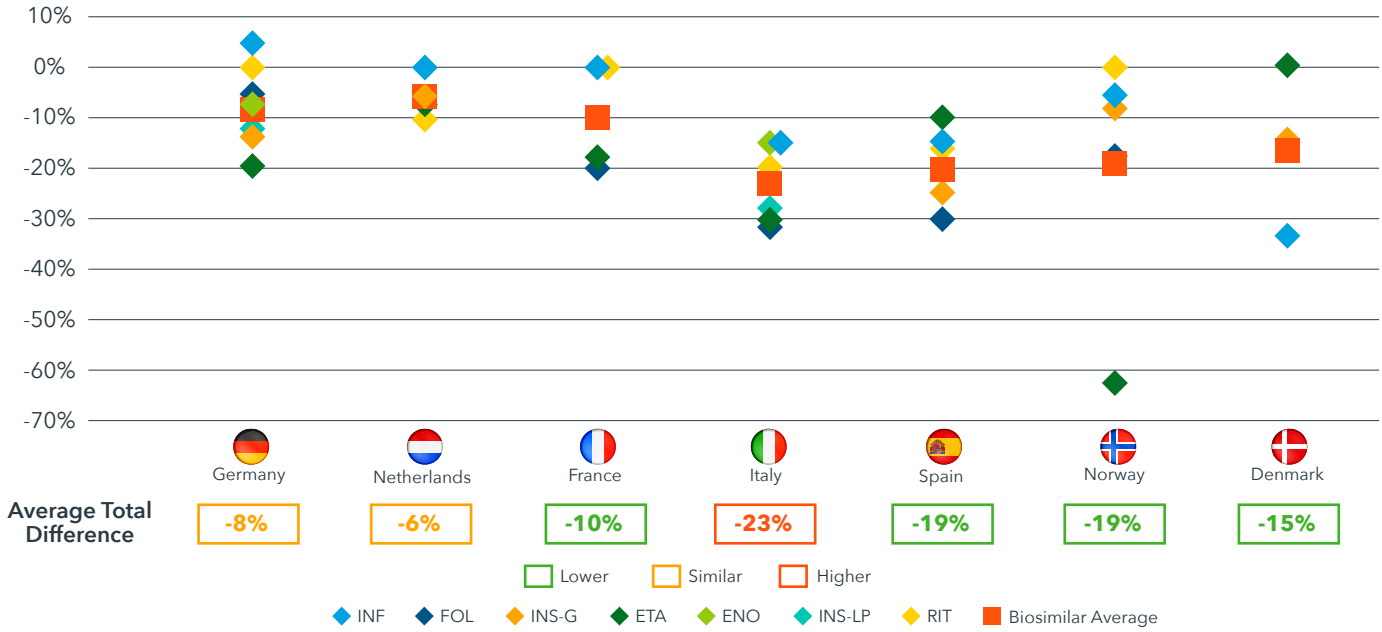


Source: IQVIA MIDAS, Mar 2018; IQVIA Global Consulting Services, Jul 2018
Notes: DDD = Defined Daily Dose. Depicts contracting markets in Germany as of 2018. Concentrated markets are defined as those with a single competitor capturing 90% or more of the market. * Denotes retail purchased products. INS-G presumed to have low penetration due to an aggressive originator product strategy and patient familiarity with the product device, etc. Totals may not add to 100% due to rounding

Pricing rules, at launch, for biosimilars and rules that impact the price of the originator when biosimilars enter the market (e.g., reference pricing) help payers manage budgets while limiting the impact on competition in the market. Payer control over pricing is enforced via price-regulation policies in the retail sector, and tenders or contracting arrangements in the hospital sector. Our analysis shows that across the retail and hospital segments, biosimilars launch at a 20% average discount, at list level, versus the originator (see Exhibit 16). In response to different payer purchasing mechanisms, originator and biosimilar manufacturer pricing behaviour differs, and results in varying levels of price erosion across markets and products; usually, single-winner tenders result in the fastest and most significant short-term price erosion, as in the case of Norway and Denmark.

> *"There is a policy [in Italy] about mandatory discounts for generics. [They are] at least 20% but normally much higher: 70%. This could not be applied for biosimilars… biosimilars would not be viable with such large discounts."*
>
> *Expert, Italy*

Exhibit 16: Percent Difference Between Biosimilar and Originator Price at Biosimilar Launch by Country



Source: IQVIA MIDAS, Mar 2018; IQVIA Global Consulting Services, Jul 2018
Notes: Displays biosimilar product average price vs. originator price at the date of the first biosimilar sales; Uses estimated simple average.

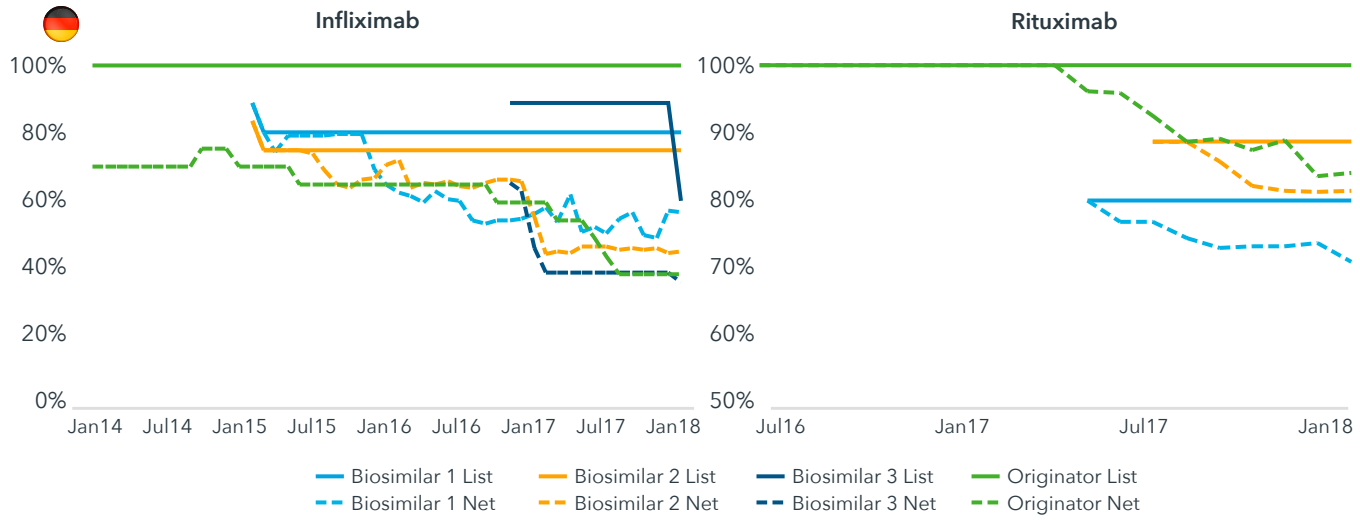
NOTE ON PRICING

This analysis of medicine spending is based on prices reported in IQVIA audits of pharmaceutical spending, which are in general reported as the invoice prices wholesalers charge to their customers including pharmacies and hospitals. In some countries, these prices are exclusive of discounts and rebates paid to governments, private insurers or specific purchasers. In other countries, off-invoice discounts are illegal and do not occur. The mix of true prices and opaque pre-discounted prices means the analyses in this report do not reflect the net revenues of pharmaceutical manufacturers or net cost to payers. The use of off-invoice discounts and rebates along with statutory price concessions required of manufacturers by governments or government programmes result in net prices and spending lower than invoice.

Originators are also subject to these discounts prior to the launch of biosimilars, and significant levels of off-invoice discounts and rebates are common for traditional branded medicines. However, discounts on originator specialty medicines (including biologics) are understood to be low, as payers' ability to negotiate lower net costs is often limited by the absence of direct competition with other branded originators or biosimilars.

The following example from Germany, selected based on net price data availability, demonstrates the greater and faster extent of price erosion at the net level: for infliximab, while the list price of the first biosimilar entering the market was 20% lower than the originator's list price, the net price was 44% lower than the originator list price (reflecting an additional 24% list-to-net discount) (see Exhibit 17).

Exhibit 17: List and Net Prices in Germany, as a Percent of Originator List Price



Product	Biosimilar 1	Biosimilar 2	Biosimilar 3	Originator
Product's Net vs. List Price Discount (Jan 2018)	24%	30%	24%	62%

Product	Biosimilar 1	Biosimilar 2	Originator
Product's Net vs. List Price Discount (Jan 2018)	9%	7%	16%

Source: IQVIA Pricing Insights, Apr 2018; MIDAS Mar 2018
Notes: Analysis is only feasible in Germany and Italy (not depicted) for hospital products, due to data availability. IQVIA Pricing Insights used for list prices. MIDAS prices used for hospital net prices.

RISKS TO SUSTAINABILITY

Reviewing the current biosimilar landscape across the individual metrics of the Biosimilar Sustainability Assessment Framework enables identification of areas that pose a potential risk to sustainability (see Exhibit 18).

Overall, the majority of metrics in our analysis were found to score positive for sustainability across the countries and biologic medicines in scope. Analysis shows that biosimilars have contributed to increased patient access to biologics by increasing the overall use of biologic medicines, in a regulatory environment that is positive towards biosimilar sustainability. No critical issues on biosimilar safety, quality and supply have been identified, while patient incentives (e.g. lower co-payments or exemptions from co-payments) are affected only indirectly by existing retail rules and are not applicable to hospital products.

However, two key elements in the current biosimilar policy framework can potentially pose threats to long-term sustainability in the biosimilars marketplace:

- Payer-driven switching incentives (metrics 8–10): Incentives to support biosimilar use are few and leniently implemented across markets, resulting in weak enforcement of a switch to a biosimilar product. However, potential enforcement of medicine switching policies by payers in the future, either via binding guidelines or negative incentives to physicians (e.g., financial penalties), remains an element of critical importance for the long-term outlook of sustainability in the biosimilars marketplace.

- Tendering process (metrics 18–20): Additionally, the results of this analysis reveal that biosimilars market concentration (metric 12) is currently high, and therefore suggests a high level of risk to supply, particularly due to the use of tendering in the hospital purchasing sector. Concentration has the potential to decrease over time as physicians gain experience and familiarity with biosimilar products. Biosimilar price evolution varies depending on the mechanism in place: single-winner tenders lead to accelerated

Exhibit 18: Biosimilar Sustainability Metrics Across Countries Based on Existing Policies

POLICY AREAS	AREA SUBTYPE	#	Metric	DE	NL	FR	IT	ES	NO	DK
ACCESS	ACCESS TO BIOLOGICS	0.	Increased molecule use by biosimilar entry	~	~	~	-	~	~	+
REGULATORY ENVIRONMENT AND CLINICAL GUIDELINES	TIME TO ACCESS THE MARKET	1.	Time to first sales	+	+	~	+	+	+	+
	TREATMENT GUIDELINES	2.	Treatment guidelines	~	+	~	-	~	~	+
	SWITCHING POLICIES	3.	Physician switching policies	+	+	+	+	+	+	+
	SUBSTITUTION POLICIES	4.	Pharmacist automatic substitution policies	+	~	~	+	+	+	~
PRODUCT	SAFETY AND QUALITY	5.	Safety and / or quality control alerts	+	+	+	+	+	+	+
	SUPPLY CONTINUITY	6.	Presence / absence of supply shortages	+	+	+	+	+	+	+
INCENTIVES	PATIENT FACTORS	7.	Patient incentives	-	-	+	~	~	-	-
	PROVIDER & PRESCRIBER INCENTIVISATION	8.	Existence of prescription quotas	-	~	~	~	~	-	~
		9.	Provider financial incentives	~	-	-	-	-	-	-
		10.	Physicians quotas linked with financial incentives	~	-	~	-	-	~	-
COMPETITIVE PRESSURE	LEVEL OF COMPETITION	11.	Biosimilar penetration	~	~	~	~	~	+	+
		12.	Biosimilar competitor concentration	-	-	-	-	-	-	-
	PRICING RULES AND DYNAMICS	13.	Mandatory price cut policy for originator	O-B+	+	+	O-B+	+	+	+
		14.	Price reference policy at molecule level	+	+	+	+	-	-	-
		15.	Price erosion vs. originator	~	~	+	-	+	+	+
		16.	Price evolution of biosimilars over time	~	+	+	-	-	~	~
		17.	Price evolution of originators over time	-	+	+	+	+	+	+
	PURCHASING MECHANISMS	18.	Length of contracts	+	+	+	+	+	+	+
		19.	Number of winners	+	+	~	+	+	-	~
		20.	Winner decision criteria beyond price	-	-	~	~	-	-	-

O: Originator B: Biosimilar + Positive for Sustainability ~ Neutral for Sustainability - Negative for Sustainability
Areas of Potential Sustainability Risk

Source: IQVIA Global Consulting Services, Jul 2018

price erosion and high savings for payers in the short term by creating highly concentrated situations, but raise concerns of sustainability risks. Multiple-winner tenders and contracting arrangements lead to less aggressive price erosion but offer the opportunity for physicians to gain experience with newly launched biosimilar products and maintain more choices when making prescribing decisions for patients. As a result, tendering was identified as a key element of current policies with the potential to substantially influence long-term sustainability in the biosimilars marketplace.

Changes in these policy elements were assessed as being able to restrict physician prescription choice, forcing patients to switch treatment as well as threatening supply and introducing instability for both originator biologic and biosimilar manufacturers. Pharmacy substitution was also reviewed as part of the current policy analysis (metric 4) and was found to pose threats to sustainability, but was not included in the hypothetical future scenario analysis as most countries are unlikely to introduce pharmacy substitution in the immediate future.

Areas of greater risk to long-term sustainability

- Payer-driven switch, especially if enforced though negative physician incentives, provides a means to manage healthcare budgets in the short term but jeopardises sustainability by reducing physician prescription choice, limiting or changing therapy for the patient, reducing patient involvement in treatment decisions, disrupting market forces and bringing uncertainty to manufacturers.
- Payer-driven switch potentially leads to loss of a therapy option currently working for patients, and the impact is estimated to be greater for patients whose disease requires chronic treatment.
- Single-winner tenders with price as the only selection criterion exert maximum pressure on price but jeopardise sustainability.
- By reducing physician prescription choice, limiting or changing therapy for the patient and minimising patient involvement in treatment decisions, single-winner tendering mechanisms with price as the only selection criterion fail to meet the needs of all stakeholders.
- Single-winner tendering mechanisms with price as the only selection criterion also disrupt market forces, thereby bringing uncertainty to manufacturers about continued market participation and investment profitability; jeopardising long-term competition and eliminating the incentive for manufacturers to innovate in areas to support patients and providers, hence putting long-term budget sustainability at risk.

IMPACT OF CHANGES IN PAYER-DRIVEN SWITCH

Payer-driven switch is defined as a payer's effort to increase the rate of physician use of biosimilars, possibly supported by incentives to elicit the desired prescribing behaviour. The impact on long-term sustainability in the biosimilars marketplace of payer-driven medicine switching policies, and associated implementation incentives put in place to drive switching, was evaluated as one of the key elements of the current biosimilar policy framework with the potential to influence sustainability in the future (see Methodology – Future Scenarios Design and Analysis). Three hypothetical future scenarios of payer-driven switch linked to different incentive structures were defined and subsequently analysed with respect to their impact on each of the elements encompassed under the sustainability definition (see Exhibit 19). The analysis also considered the influence of therapy duration on the outcome of each scenario, as switching was expected to have greater impact in the case of chronic patient treatment.

The results of this analysis indicate that payer-driven switch, despite providing a means to manage healthcare budgets in the short term with no adverse effect on patient access to biologic products, product quality and supply, jeopardises sustainability in a number of ways, especially if enforced though negative physician incentives. Firstly, payer-driven switch leads to reduced prescription choice for physicians, who are pressured to consider the payer's guidance on product options in addition to their clinical judgement. The impact of medicine switching policies is greater when linked to negative incentives, such as financial penalties, as physicians face greater pressure to achieve the specified quota, and may be influenced to act outside the patient's best interest. Negative incentives may further impact healthcare providers by adversely affecting the economics of their practice.

Similarly, payer-driven switch jeopardises patient continuity on the same product – as treatment

Exhibit 19: Payer-driven Switch Scenarios – Impact on Sustainability in the Biosimilars Marketplace

SCENARIO		I Payer driven switch with no financial incentives	II Payer driven switch with positive incentives*	III Payer driven switch with negative incentives
Patient Access		○	○	○
Physician Prescription Choice		=	✗	✗
Safe and High Quality Biologic Medicines		○	○	○
All Stakeholders	Patients	✗	✗	✗
	Providers	=	=	✗
	Payers	✓	✓	✓
	Originator Manufacturers	=	=	=
	Biosimilar Manufacturers	=	=	=
Healthcare Budgets		=	✓	✓
Healthy Level of Competition		=	✗	✗
Healthy Level of Supply		○	○	○

Scenarios that Best Support Sustainability

✓ Very Positive ✓ Positive = Neutral ✗ Negative ✗ Very Negative ○ No Impact

Source: IQVIA Global Consulting Services, Jul 2018
Notes: *Includes physician quota and margin gains from diagnosis related group (DRG) funding.

decisions become determined by price rather than clinical judgement – as well as a smooth transition from one product to another. The impact of payer-driven switch on patients is greater in the case of chronic conditions, such as diabetes, where patients receive lifelong treatment and are more attached to their therapy. Medicine switching policies thereby further reduce patient participation in treatment decisions.

Moreover, payer-driven switch has an overall negative impact on competition, as it disrupts the market, and forces physicians to use a specific biologic product, particularly when linked to positive or negative incentives. Enforcement of medicine switching policies by payers also brings uncertainty to both originator and biosimilar manufacturers who face the risk of being excluded from the preferred list of treatments.

IMPACT OF CHANGES IN PROCUREMENT POLICIES

The second part of the scenario analysis evaluated the impact of different procurement policies, with a focus on tender dynamics, since this area has an apparent effect on long-term sustainability in the biosimilars marketplace. Eight possible future scenarios of tendering arrangements were defined and analysed with respect to their impact on each of the elements encompassed under the sustainability definition (see Exhibit 20). Although not directly tested, contracting mechanisms are expected to have similar behaviour to multiple-winner tenders. Tendering arrangements were defined based on the number of tenders carried out per market (one vs. multiple), the number of tender winners (single vs. multiple) and the criteria used to award the tender (only price vs. price plus other criteria).

Exhibit 20: Tendering Scenarios – Impact on Sustainability in the Biosimilars Marketplace

SCENARIO		I	II	III	IV	V	VI	VII	VIII
Number of Winners Criteria Number of Tenders		One Price Multiple	One Price+ One	One Price+ One	One Price+ Multiple	Multiple Price Multiple	Multiple Price One	Multiple Price+ One	Multiple Price+ Multiple
Patient Access		✓	✓	✓	✓	✓	✓	✓	✓
Physician Prescription Choice		✗	✗	✗	✗	✗	✗	✗	✗
Safe and High Quality Biologic Medicines		○	○	○	○	○	○	○	○
All Stakeholders	Patients	✗	✗	✗	✗	✗	✗	✗	✗
	Providers	✗	✗	✗	✗	✗	✗	✗	✗
	Payers	✓	✓	✓	✓	✓	✓	✓	✓
	Originator Manufacturers	✗	✗	=	=	✗	✗	✓	✓
	Biosimilar Manufacturers	✗	✗	=	=	✗	✗	✓	✓
Healthcare Budgets		✓	✓	✓	✓	✓	✓	✓	✓
Healthy Level of Competition		✗	✗	✗	✗	=	✗	✗	=
Healthy Level of Supply		=	=	=	=	✓	✓	✓	✓

Scenarios that Best Support Sustainability

✓ Very Positive | ✓ Positive | = Neutral | ✗ Negative | ✗ Very Negative | ○ No Impact

Source: IQVIA Global Consulting Services, Jul 2018

The analysis of current dynamics indicate that tenders overall improve access to biologic treatments as products become available at lower prices and do not adversely affect safety, quality and supply stability.

While single-winner, national-level tendering with price as the only selection criterion was identified as the tendering arrangement with the potential to exert the maximum pressure on price, this jeopardises long-term sustainability. This tendering arrangement results in substantially reduced prescription freedom for physicians, who are required to provide justification for choosing to treat a patient with a different product. In addition, single-winner tenders negatively impact patients and the healthcare systems that serve them by disrupting their continuity on specific products and forcing them to switch treatment at the end of each tender contracting period based on non-clinical criteria (i.e., tender price). Furthermore, single-winner tendering disrupts market forces as manufacturers can get excluded from the market for variable periods of time, depending on tender-contract duration. Single-winner tenders are therefore negative for both originator and biosimilar manufacturers, particularly when a single tender is conducted at national level rather than multiple individual tenders at subnational levels. Exclusion of manufacturers from a market or region is expected to jeopardise healthy competition in the long-term; while price as the only assessment criteria is expected to eliminate manufacturers' incentives to innovate in areas of added value (e.g., administration route, device design, patient support programs) providing further support to patients and providers.

AREAS OF GREATER RISK TO LONG-TERM SUSTAINABILITY

Conversely, contracts (such as with the German Krankenkassen, or health insurers) and tenders that are designed to have multiple winners with criteria beyond price are expected overall to have a more positive impact on sustainability in the marketplace and better serve the needs of all key stakeholders. In this scenario, physicians and patients are still presented with multiple prescription and treatment choices respectively, while the risk of supply shortages is reduced. Finally, manufacturers have better chances of securing part of the market volume, thus increasing the likelihood that their investment in biosimilars yield positive returns and further increases the likelihood that they will invest in the development of biosimilars in the future. Moreover, having tender criteria broader than price allows manufacturers to better address patient needs and compete more meaningfully. For instance, additional criteria may include value-added services, device design, considerations around inactive ingredients or excipients, traceability and supply stability, that help to adequately cover the needs of patient, physician and care-institution and thus lead to better biosimilar sustainability. This is because more manufacturers secure a place in the market and receive fair gains, encouraging them to continue development of both biosimilar and new biologic medicines.

> *"We see where the lower price limits are of a manufacturer, and we try to find a price that is in that lower range but that is still acceptable for more manufacturers to ensure multiple products on the market"*
>
> *Expert, Germany*

The path to strengthen sustainability

Policies for the biosimilars marketplace that are designed to ensure they meet the needs of all key stakeholders have a positive influence on sustainability overall. Such approaches enable countries not only to improve patient access and manage healthcare budgets, but to also encourage competition, provide healthcare that meets the needs of individual patients and support manufacturers in developing biosimilars that offer additional value. Many of the best-practice approaches that support sustainability (see Exhibit 21) are already present in Europe, though not in every market, and the value of various policies continue to be debated.

Exhibit 21: Best Practices to Achieve Sustainability for All Stakeholders in the Biosimilars Market

SUSTAINABILITY ELEMENTS	
Patient Access	• Continue to maintain a regulatory environment and clinical guidelines favourable to biosimilar approval and uptake, to increase patient access to biologic treatment • Ensure guidelines and policies support a smooth transition for patients from one therapy to another when patient is guided to switch by the treating physician
Physician Prescription Choice	• Maintain prescription freedom for physicians, enabling them to select therapy for patients • Ensure multiple products are available on the market, enabling physicians to have choice of approved therapies • Create well-designed incentives that foster biosimilar uptake, while safeguarding physician choice and patient input into treatment decisions, such as treatment switch
Safe and High Quality Biologic Medicines	• Incentivise both originator biologic and biosimilar manufacturers to continue innovating in differentiation areas for their products to better support the needs of patients, physicians and care-institutions • Implement payer purchasing mechanisms that include criteria other than price, thus encouraging the provision of additional value – e.g., patient services, design elements, formulations, etc.
All Stakeholders	• Maintain involvement of all relevant stakeholders in discussions and decision-making regarding biologic and biosimilar medicines in Europe • Balance the price pressures exerted by tenders or other payer purchasing mechanisms with the requirements for long-term market sustainability e.g., by implementing procurement policies in the biologics market that simultaneously addresses the needs of all key market stakeholders
Healthcare Budgets	• Continue to incentivise the uptake of biosimilars to facilitate budget release in the short term, while considering the long-term sustainability of the market • Design incentives considering the needs of target physicians and care-institutions
Healthy Level of Competition	• Sustain healthier levels of competition with multiple-winner tenders as compared with single-winner tenders • Make purchasing decisions based on additional criteria beyond price, thus incentivising biosimilar manufacturers to innovate in areas to support patients and providers
Healthy Level of Supply	• Sustain a healthy supply of biologics to the market, by enabling access of both originator and biosimilar products • Encourage multiple manufacturers to function within a market through multiple-winner tenders/contracts reducing the potential risk of shortages

Source: IQVIA Global Consulting Services, Jul 2018

THE PATH TO STRENGTHEN SUSTAINABILITY

In order for payers and policy makers to help strengthen sustainability in the long-term and set a path to ensure biosimilars continue to improve access to safe and high-quality biologic treatments, increased focus on a number of areas is necessary.

Patient interest and prescriber choice: Safeguarding the interest of patients and serving their needs in the best way possible remains a critical consideration for health authorities and will become even more so as a greater number of new biosimilars coming to market are able to be self-administered and patient familiarity with product and device is likely to exert greater influence on physician product choice and patient compliance[27]. Ensuring physicians retain prescription freedom, along with the ability to choose and access approved therapies to offer product selection for patients, is therefore necessary, along with the creation of incentives that promote biosimilar uptake and take into account patient clinical considerations.

Use of incentives: In addition to the policy frameworks currently in place, European countries can create further incentives to promote biosimilar uptake – to boost savings to the healthcare system and support the sustainability of the market – without adversely affecting the quality of care offered to patients. Medicine switching policies that avoid incentives limiting patient input and physician choice – predominantly negative incentives – are best able to balance system savings with patient needs. Incentives linked to treatment switch also need to be carefully designed to avoid eliciting unfavourable prescribing behaviours by physicians – such as prescribing a particular biologic without due regard for individual patient factors due to an offered financial reward. Further, effective demand-side incentives are designed considering the behaviour and needs of physicians and care-institutions that will be the ultimate target of those incentives. Incentives that encourage switching according to the physician's discretion, and allow for some time from launch of a biosimilar to when it is subject to the existing incentive structure, are the most sustainable.

Use of purchasing mechanisms: Careful design of the purchasing system is needed to balance the effectiveness of tenders and contracts with the requirements for long-term market sustainability. Tendering and contracting in the biologics market can, if properly balanced, facilitate the generation of healthy market competition while allowing payers to adequately manage healthcare budgets over time, as well as addressing the needs of other key market stakeholders (e.g., patients, physicians, care-institutions, biosimilar and originator manufacturers).

Awarding multiple winners: Tenders and contracts better support sustainability when they are designed to have multiple winners and include criteria other than price. These purchasing mechanisms allow greater prescription and product choice for physicians and patients respectively, as well as sustain healthier levels of competition as compared with single-winner tenders. This is because more manufacturers secure a place in the market and receive fair gains, encouraging them to continue development of both biosimilar and new biologic medicines. All of these are increasingly important in both the hospital purchasing and retail sector. Moreover, having tender criteria broader than price allows manufacturers to better address patient needs and compete more meaningfully. For instance, additional criteria may include value-added services, device design, inactive ingredients, traceability and supply stability, that help to adequately cover the needs of patients, physicians and care-institutions and thus lead to better biosimilar sustainability.

Pricing control policies: Price control policies in the form of molecule reference pricing, direct price cuts, or other forms, facilitate budget release in the short term while granting access to the biologics markets for all biosimilar and originator players. In parallel, physician prescription freedom is maintained and patient product continuity is guaranteed to a higher extent. Price control should however be implemented to the extent that market forces are not significantly disrupted and manufacturers remain able to freely

compete based on multiple product criteria and services beyond price.

Promote innovation: In an environment that fosters sustainability, both originator biologic and biosimilar manufacturers are incentivised and encouraged to continue innovating in differentiation areas for their products outside price, and to continue the development of new products, further supporting the sustainability of the market and finding new ways to support the needs of all other key stakeholders.

Overall, a number of policies currently in place in Europe can be leveraged to ensure and support long-term sustainability of the biosimilars market, while additionally fulfilling the needs of all stakeholders. By simultaneously securing aspects of sustainability, including physician prescription choice, a means to manage healthcare budgets, and healthy levels of competition, supply, and product safety and quality, the biosimilars marketplace offers to bring with it lower costs and increased patient access to valuable biologic medicines, with benefits likely to increase over time.

Notes on sources

This report is based on the IQVIA services detailed below.

IQVIA MIDAS™ is a unique platform for assessing worldwide healthcare markets. It integrates IQVIA's national audits into a globally consistent view of the pharmaceutical market, tracking virtually every product in hundreds of therapeutic classes and provides estimated product volumes, trends and market share through retail and non-retail channels.

IQVIA Pricing Insights offers a series of solutions combining core pricing and reimbursement data. IQVIA Pricing Insights provides regulated pricing information and price points for in-line brands and future products to help mitigate against price changes across multiple markets. In addition, the service provides access to integrated customised databases, dashboards and reports as well as pricing and reimbursement applications to address each client's specific needs – by country, competitive climate and therapy area.

Biosimilars Landscape Tracker offers summaries of biosimilar regulatory, policy, pricing and market access landscape and biosimilar sales across multiple developed and emerging markets.

Biosimilar Knowledge Connect centralises news, information and resources pertaining to biosimilars.

e-hälsomyndigheten – the Swedish eHealth Agency (e-hälsomyndigheten or eHm) provides aggregated sales data for drugs in Sweden and includes medicines sold in pharmacies and hospitals.

Methodology

BIOSIMILAR SUSTAINABILITY ASSESSMENT FRAMEWORK

Research into this topic included both qualitative and quantitative analyses of relevant IQVIA data sources, secondary research, as well as consolidation of insights from discussions with IQVIA biosimilar experts, relevant Pfizer affiliates and external policy experts.

Secondary research using external and IQVIA publications was performed to obtain a preliminary view on the current biosimilar landscape in each market, and to inform the relevant qualitative metrics included in the framework. IQVIA MIDAS sales data and data from other public sources (e.g., EMA) were used to estimate the remaining quantitative metrics included in the framework (see Exhibit 22). All price-related metrics are based on list prices, which can be robustly gathered and referenced across the markets in scope.

IQVIA BIOSIMILAR SUSTAINABILITY PRIMARY MARKET RESEARCH PROGRAM

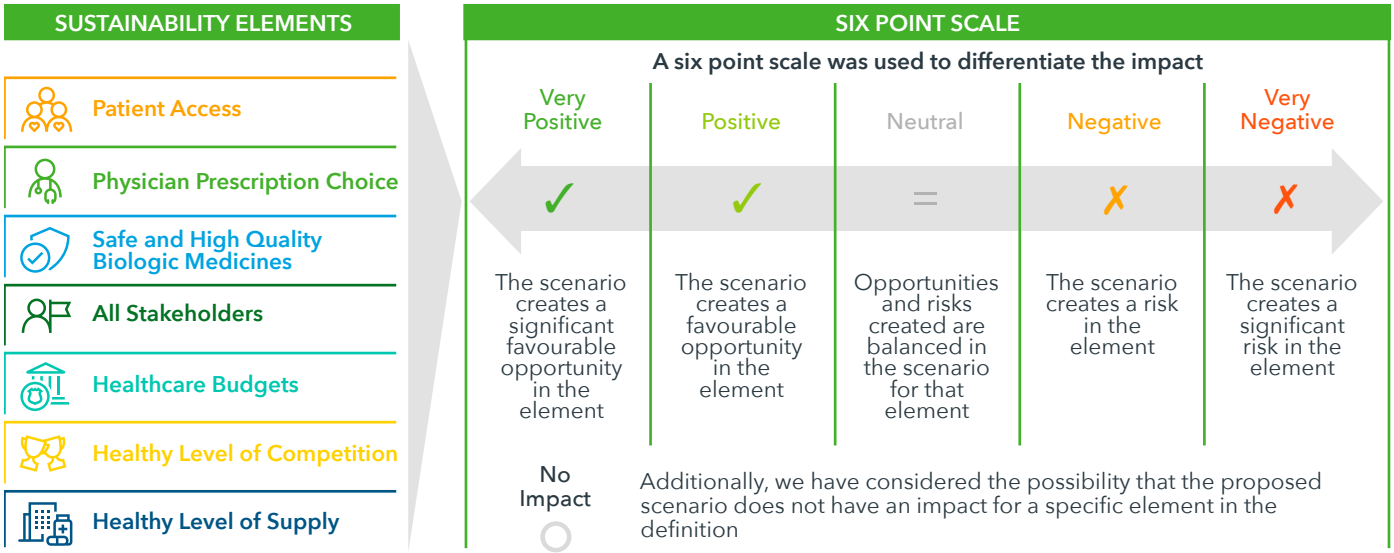
A primary market research study was performed from June to July 2018 and included discussions with 26 stakeholders from countries in Europe (including payers, policymakers, thought-leaders from IQVIA and Pfizer employees) in order to validate analytic findings on the current biosimilar landscape in each market and to obtain insights on future policy developments likely to have an impact on sustainability in the biosimilars marketplace. Eight of these interviews were conducted with external policy experts across the countries profiled in this report to specifically validate the results of the current policy landscape analysis and to pressure test the future scenario analysis. Perspectives of the external policy experts provided insight into both current and future policy trends and potential threats to sustainability across Europe and within individual markets.

Exhibit 22: Metrics to Evaluate

#	CATEGORY	METRIC	MEASURE		SOURCE
Access					
0.	**Access to biologic medicines**	Increased molecule utilization	Increased molecule use (measured in DDD) with biosimilar entry	Quantitative	MIDAS
Regulatory Environment and Clinical Guidelines					
1.	**Regulatory and P&MA pathway**	Time to biosimilar access*	Time from EMA approval to first sales of first biosimilar (months)	Quantitative	EMA, MIDAS
2.	**Treatment guidelines**	Differentiation between policies for biosimilars and originator	Positive / neutral (molecule) / negative	Qualitative	National guidelines
3.	**Substitution policy**	Physician switching policies	(Not) enforced / allowed / other	Qualitative	Public sources
4.		Automatic substitution policies at pharmacy level	(Not) enforced / allowed / other	Qualitative	
Product					
5.	**Safety and quality**	Safety and / or quality control alerts	Yes / No; number of alerts	Qualitative	National Drug Agency websites
6.	**Supply continuity**	Presence / absence of supply shortages	Yes / No	Quantitative	
Incentives					
7.	**Patient factors**	Patient incentives	Yes / No; Specify incentives	Qualitative	Public sources
8.	**Provider and prescriber incentivization**	Existence of prescription quotas	Yes / No; Specify quotas	Qualitative	Public sources
9.		Physician Rx and financial incentives	Mandatory quotas vs. recommended	Qualitative	Public sources
10.		Physicians quotas linked with financial incentives	Yes / No; Specify incentives	Qualitative	Public sources
Competitive Pressure					
11.	**Level of competition**	Biosimilar penetration	% of biosimilar over total molecule	Quantitative	MIDAS
12.		Biosimilar competitor concentration	Number of competitors equaling 90% of the market	Quantitative	
13.	**Pricing rules and dynamics**	Mandatory price cut policy for originator	Yes /no	Quantitative	Public sources
14.		Price reference policy at molecule level	Yes/no	Quantitative	
15.		Price erosion vs. originator	Percent biosimilar vs. originator	Quantitative	MIDAS
16.		Price evolution of biosimilars over time	Percent biosimilar vs. originator	Quantitative	
17.		Price evolution of originators over time	Percent price reduction	Quantitative	
18.	**Tendering process**	Length of contracts	Months	Quantitative	Public sources
19.		Number of winners	Single vs. multiple	Qualitative	
20.		Winer decision criteria beyond price	Positive / neutral / negative for biosimilars	Qualitative	

Source: IQVIA Global Consulting Services, Jul 2018
Notes: DDD = Defined daily dose

Exhibit 23: Multi-Stakeholder Assessment



FUTURE SCENARIOS DESIGN AND ANALYSIS

A three-step process was followed to analyse the impact of the two key policies – payer-driven switch and tendering – that were assessed to potentially pose threats to long-term sustainability in the biosimilars marketplace. All possible scenario options were first outlined for each, based on the key variables with potential impact on sustainability. The impact of each scenario was then assessed separately for its impact on sustainability across all the key elements encompassed under the Multi-Stakeholder Definition of Sustainability.

The impact of each scenario was evaluated across each of the sustainability definition elements, and mapped to a six-point scale based on IQVIA expertise, leveraging on existing understanding on the market and supported by analysis of current landscape (see Exhibit 23).

Further review of this assessment was then conducted to pressure test assumptions and conclusions of the analysis.

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Manuel Vázquez is manager within the IQVIA Global Consulting Services. He has over eight years of consulting experience with a focus on global pricing and market access (PMA) projects and health economics and outcomes research (HEOR) strategy to support the PMA decision making process. Prior to IQVIA, he worked for six years as a retail pharmacist manager in the United Kingdom. Manuel holds a PharmD from Universidad de Salamanca in Spain and an MBA from Manchester Business School in the U.K.

About the IQVIA Institute

The IQVIA Institute for Human Data Science contributes to the advancement of human health globally through timely research, insightful analysis and scientific expertise applied to granular non-identified patient-level data.

Fulfilling an essential need within healthcare, the Institute delivers objective, relevant insights and research that accelerate understanding and innovation critical to sound decision making and improved human outcomes. With access to IQVIA's institutional knowledge, advanced analytics, technology and unparalleled data the Institute works in tandem with a broad set of healthcare stakeholders to drive a research agenda focused on Human Data Science including, including government agencies, academic institutions, the life sciences industry and payers.

Research Agenda

The research agenda for the Institute centers on 5 areas considered vital to contributing to the advancement of human health globally:

- Improving decision-making across health systems through the effective use of advanced analytics and methodologies applied to timely, relevant data.
- Addressing opportunities to improve clinical development productivity focused on innovative treatments that advance healthcare globally.
- Optimizing the performance of health systems by focusing on patient centricity, precision medicine and better understanding disease causes, treatment consequences and measures to improve quality and cost of healthcare delivered to patients.
- Understanding the future role for biopharmaceuticals in human health, market dynamics, and implications for manufacturers, public and private payers, providers, patients, pharmacists and distributors.
- Researching the role of technology in health system products, processes and delivery systems and the business and policy systems that drive innovation.

Guiding Principles

The Institute operates from a set of Guiding Principles:

- Healthcare solutions of the future require fact based scientific evidence, expert analysis of information, technology, ingenuity and a focus on individuals.
- Rigorous analysis must be applied to vast amounts of timely, high quality and relevant data to provide value and move healthcare forward.
- Collaboration across all stakeholders in the public and private sectors is critical to advancing healthcare solutions.
- Insights gained from information and analysis should be made widely available to healthcare stakeholders.
- Protecting individual privacy is essential, so research will be based on the use of non-identified patient information and provider information will be aggregated.
- Information will be used responsibly to advance research, inform discourse, achieve better healthcare and improve the health of all people.

The IMS Institute is now the IQVIA™ INSTITUTE for Human Data Science

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