



INNOVATION



# Towards a sustainable European market for off-patent biologics

Pugatch Consilium

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# List of abbreviations and terminology

ADR	Adverse Drug Reaction
ATC	Anatomical Therapeutic Chemical classification
CAGR	Compounded Annual Growth Rate
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
ERP	External Reference Pricing
EU	European Union
EUR	Euro
FDA	United States' Food and Drug Administration
INN	International Non-proprietary Name
PPP	Purchasing Power Parity
IRP	International Reference Pricing
R&D	Research and Development
UK	United Kingdom
USD	United States Dollars
VBP	Value Based Pricing

## **Definitions:**

Biologic medicine: a medicinal product or a vaccine that consists of, or has been produced by the use of living organisms. Examples include therapeutic proteins such as antibodies, insulins or interleukins, and also vaccines, tissues and cells.

Biosimilar medicine: Within the EU a biosimilar is defined as a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product) in the EU. Similarity to the

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reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise needs to be established.

Off patent biologics: This refers to both an original biologic reference product after loss of market exclusivity and corresponding biosimilar(s).

Substitution: The practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber.

Switching: A decision by the treating physician to exchange one medicine for another medicine with the same therapeutic intent in patients who are undergoing treatment.

Note: All definitions are adapted from European Commission's Consensus Information Paper of 2017: 'What you need to know about biosimilar medicinal products' created separately for patients and healthcare professionals,<sup>1</sup> and are only applicable to European markets. There are cases, particularly with reference to the US, where the use and definition of these terms may differ.

# Executive Summary

Biologic medicines have revolutionized the treatment of many life-threatening illnesses such as cancer and autoimmune diseases as well as many rare diseases. Many biologic products can actually slow the progress of or even prevent disease, leaving healthy cells unaffected and generally causing fewer side effects.

As technology advances and major biologic products are no longer under exclusivity, follow-on products have begun expanding the biologics market considerably. Yet because of their intricate molecular structure and complex manufacturing process in living cells, unlike generic follow-on products to traditional chemical entities, the production and manufacturing process of biosimilars cannot guarantee that the follow-on product's properties are identical to those of the reference product. For this reason, follow-on products of innovative biologic medicines are referred to as *biosimilars*.

Europe and the EU have historically been pioneers with regards to the regulatory approval and use of biosimilars – being the first to develop a biosimilar pathway in 2003 and the first to approve a biosimilar for marketing in 2006 – and is now reaping the economic benefits, with increased availability of biological treatments at lower prices. At the same time, Europe maintains its lead role in fostering innovation, with more than 12,000 clinical trials on biologic medicines conducted in Europe to date, and a steady growth of biologic clinical trials activity at an average Compounded Annual Growth Rate (CAGR) of 7% between 2010 and 2015 within the EU-5 countries.

With increased patient access and healthcare system efficiencies generated through competition on the one hand and continued innovation on the other, the biologics segment represents a rapidly-growing segment of the European biopharmaceutical market, whose health, social and economic impact on the European economy is significant. Securing a sustainable future for the European biologics and biosimilars market is a top priority for European countries and for the European economy as a whole.

Driven by increasing demand for healthcare and its associated costs, many European countries are increasingly focusing on maximising short-term savings rather than ensuring the long-term sustainability of this market. The lack of a unified approach and the high diversity of policies governing the daily practice of off-patent biologics may eventually undermine the goal of creating a sustainable European market for off-patent biologics.

In this respect, this study aims to answer the following question:

*How should policy and governance frameworks be designed and implemented to ensure long-term sustainability of off-patent biologic markets while taking into account health system financing and efficiency, in addition to commercial and patient access perspectives?*

To answer this, the study combines a ‘top-down’ analysis of the current policy ecosystem for off-patent biologics with a ‘bottom-up’ analysis of relevant stakeholders’ perceptions of which policies are key in creating a sustainable European market for off-patent biologics.

## Key findings

**Key finding 1: The policy environment across Europe is diversified and lacks a coherent long-term vision of a sustainable European off-patent biologics market**

The analysis of the policy ecosystem for off-patent biologics examines the types of policies in place across a sample of 15 European countries within three core themes of a sustainable market for off-patent biologics:

- 1) the pricing environment;
- 2) procurement practices, and
- 3) physician autonomy and patient choice.

The analysis reveals a highly-diversified European market for off-patent biologics, with unfavourable – at times even discouraging – policies for a sustainable off-patent biologics market in place in at least one of the three core themes in most European countries sampled. While some countries maintain a policy framework that is based on



the principle of genuine competition and a level playing field within all three themes, other countries show a relatively intense preference for maximising short-term savings that in some cases limits physicians' prescribing freedom and patient choice.

**Key finding 2: There is broad agreement amongst all key stakeholders on what a sustainable market for off-patent biologics should look like**

The Expert Opinion survey – encompassing healthcare professionals, patients and representatives of patient groups, medical organizations, government institutions and innovative biologic and biosimilar medicines manufacturers – provides six key insights on which policies are the most important and conducive for achieving market sustainability for off-patent biologics:

1. Physician autonomy, wide access to treatments and availability of reliable, up-to-date information are key characteristics of a sustainable market.
2. Lack of information, of patient-physician dialogue and of wide access are viewed as most critical barriers to prescribe the optimal treatment.
3. Maintaining prescribing freedom is essential.
4. Reimbursement frameworks should strive to account for patients' medical needs and long-term economic benefits.
5. Procurement of off-patent biologics should ensure the consistent supply of a wide range of high-quality products.
6. Better communication and understanding of good pharmacovigilance practices for off-patent biologics is required.

**Key finding 3: The findings of the policy environment analysis and Expert Opinion survey reveal that there is a clear roadmap and 'Gold Standard' on what a sustainable European market for off-patent biologics should look like**

**A Gold Standard for a sustainable European market for off-patent biologics**

<b>1. Rewarding innovation</b>	<ul style="list-style-type: none"><li>• At its core a sustainable market for off-patent biologics should be built on incentivizing biopharmaceutical R&amp;D</li><li>• Strong and clear incentives must be in place for continuous and sustained investment in innovative biologics as well as in off-patent biologics and biosimilars both from a R&amp;D perspective as well as with regards to manufacturing</li></ul>
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<b>2. Healthcare financing</b>	<ul style="list-style-type: none"> <li>• Health care sustainability should be viewed from a holistic perspective recognizing the long-term societal benefits and cost savings that sustainable competition and access to medicines provides European health systems</li> <li>• Pricing and reimbursement policies for all biologic products, including biosimilars, should be tailored to and reflect the unique characteristics of these medicines, including the substantial resources, risk and technical capacity required for developing and manufacturing a large molecule biologic medicine</li> </ul>
<b>3. Procurement practices</b>	<ul style="list-style-type: none"> <li>• Within a sustainable European market for off-patent biologics, procurement practices should:             <ol style="list-style-type: none"> <li>a) be performed solely at a molecule level;</li> <li>b) include the possibility of a wide variety of products from multiple suppliers (as opposed to a ‘winner takes all’ tender);</li> <li>c) ensure an effective supply term that ranges between a minimum of 12 months and a maximum of 24 months; and</li> <li>d) include an option for physicians to opt-out individual patients based on their medical needs at the physician’s discretion.</li> </ol> </li> </ul>
<b>4. Physician autonomy &amp; patient choice</b>	<ul style="list-style-type: none"> <li>• Physicians should have autonomy to prescribe what they consider to be the most appropriate medicine for their patients.</li> <li>• The substitution of a biologic medicine with another biologic medicine should not happen automatically; it may only take place in cases where it is:             <ol style="list-style-type: none"> <li>a) recommended by the physician; and</li> <li>b) consented to by the patient.</li> </ol> </li> <li>• Patients undergoing treatment should only be switched between biologic medicines if the following conditions are met:             <ol style="list-style-type: none"> <li>a) The physician and the patient have both consented to the switch;</li> <li>b) The patient is closely monitored following the switch.</li> </ol> </li> <li>• Reliable and up-to-date information about the availability, cost-effectiveness and comparative assessment of off-patent biologics and biosimilars should be fully transparent and accessible to physicians</li> </ul>
<b>5. Pharmacovigilance and traceability frameworks</b>	<ul style="list-style-type: none"> <li>• A robust pharmacovigilance system for reporting and analysis of ADRs should be in place and healthcare professionals should be aware of the importance of reporting ADRs by brand name and batch number.</li> <li>• All biologic products should be prescribed by the product’s brand name in order to avoid unintended switching of treatments and ensure effective traceability of ADRs</li> </ul>

A sixth component of the Gold Standard details the policies and measures the countries should refrain from in order to secure the sustainability of the off-patent biologics market:

<b>6. Policies with a potential to undermine sustainability of the market</b>	<ul style="list-style-type: none"> <li>• Treating off-patent biologics as ‘bio-generics’ by adopting policies or measures aimed at generating savings or inducing uptake that may be in place for generic medicines that do not require an extensive R&amp;D phase and that are significantly less complex to produce compared to biosimilars.</li> <li>• Adopting extreme discriminatory measures and/or preferential treatment (including within the pricing and reimbursement, procurement and clinical practice aspects) that impede competition and may limit physician autonomy and patient choice.</li> </ul>
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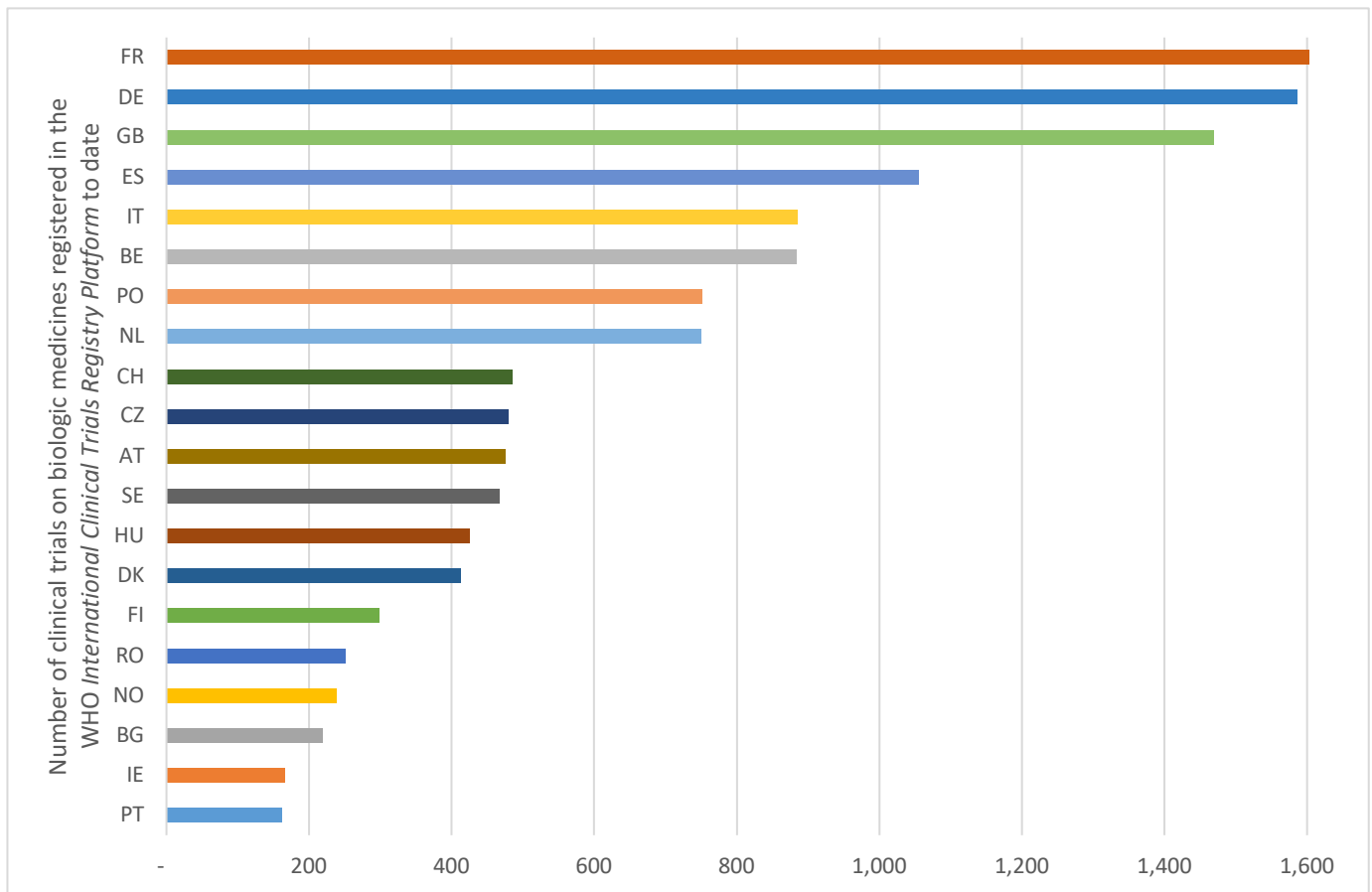
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|  | <ul style="list-style-type: none"><li>• Placing physicians and patients under unwarranted restrictions or limitations with regards to their freedom to choose the most suitable treatment for their needs.</li><li>• Using policies such as INN prescribing and/or pharmacy-level substitution that greatly complicate product traceability in cases of adverse drug reactions.</li></ul> |
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# Introduction

Europe is among the world's largest pharmaceutical markets, with an aggregate population of over 500 million and an average pharmaceutical spending of ~USD500 per capita per annum at PPP.<sup>2</sup> Pharmaceutical sales in Europe are currently estimated at EUR180 billion, and projected to increase to EUR220 billion by 2022.<sup>3</sup> Biologic medicines – medicinal products developed and manufactured from living cells using biotechnology methods – are estimated to account for up to 25% of that spending.<sup>4</sup> In 2013 the biologic medicines R&D pipeline consisted of over 900 promising candidates – nearly three times more than in 2001 – with investments of over USD100 billion from biopharmaceutical companies alone.<sup>5</sup> Indeed, biologics have revolutionized the treatment of many life-threatening illnesses such as cancer and autoimmune diseases as well as many rare diseases by moving beyond merely treating the symptoms of illnesses to instead slow the progress of or even prevent disease, leaving healthy cells unaffected and generally causing fewer side effects. Their continued evolution using state-of-the-art biotechnology could also revolutionize biologics delivery platforms.<sup>6</sup>

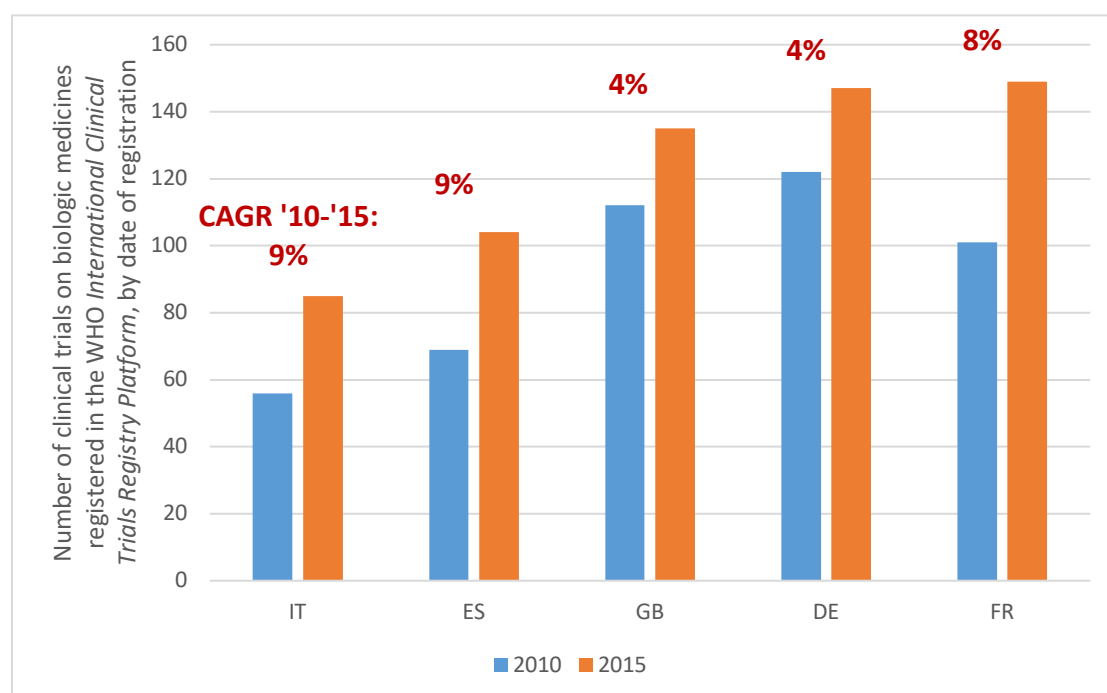
The European market has a leading role in fostering biopharmaceutical innovation. Biopharmaceutical companies invested EUR33.5 billion in R&D across Europe in 2016 alone, directly employing over 112,000 people in R&D activities.<sup>7</sup> This investment is also evident in the intensity of clinical research on biologics – the cornerstone of innovative biologic and biosimilar medicines development. European countries are global leaders in terms of clinical research on biologics, with more than 12,000 clinical trials on biologic medicines conducted to date, as is evident in the below Figure 1. Between 2010 and 2015 the EU-5 countries maintained steady growth at an average CAGR of 7% in terms of the intensity of clinical research on biologics, hosting on average some 120 clinical trials on biologics a year, as is seen in the below Figure 2.

Figure 1: Clinical trials on biologic medicines registered to date, selected European countries<sup>8</sup>



Source: World Health Organization, International Clinical Trials Registry portal, 2019; analysis: Pugatch Consilium. Legend: AT – Austria; BE – Belgium; BG – Bulgaria; CH – Switzerland; CZ – Czech Republic; DE – Germany; DK – Denmark; ES – Spain; FI – Finland; FR – France; GB – United Kingdom; HU – Hungary; IE – Ireland; IT – Italy; NL – Netherlands; NO – Norway; PO – Poland; PT – Portugal; SE – Sweden.

Figure 2: Clinical trials on biologic medicines in 2010 and in 2015, EU-5 countries<sup>9</sup>



Source: World Health Organization, International Clinical Trials Registry portal, 2019; analysis: Pugatch Consilium. Legend: DE – Germany; ES – Spain; FR – France; GB – United Kingdom; IT – Italy.

### Off-patent biologics and biosimilars: A growing market

With many major biologic products no longer under exclusivity and more coming off-patent in the near future, follow-on products are a growing part of the overall market. Yet because of their intricate molecular structure and complex manufacturing process in living cells - unlike generic follow-on products to traditional chemical entities - the production and manufacturing process of biosimilars cannot guarantee that the follow-on product's properties are identical to those of the reference product. For this reason, follow-on products of innovative biologic medicines are referred to as *biosimilars*.<sup>10</sup>

The EU has historically been a pioneer with regards to biosimilars – being the first to develop a biosimilar pathway in 2003 and the first to approve a biosimilar for marketing in 2006.<sup>11</sup> To date, 51 biosimilars have been approved for marketing by EMA with more applications under review at the beginning of 2019.<sup>12</sup>

## Building a sustainable market for off-patent biologics

The biologics market represents a rapidly-growing segment of the European biopharmaceutical market, whose health, social and economic impact is significant. Securing a sustainable future for the European biologics market – including innovative biologics, off-patent biologic medicines and biosimilars – is a top priority for European countries and for the European economy as a whole.

Yet looking at the current state of the market and policy environment there are a number of key challenges. While the EMA is the final arbiter on biosimilars being approved for market in the EEA, member states' competent authorities are responsible for setting the policies that govern access (through individual pricing and reimbursement policies) and the clinical practice, including decisions on interchangeability, switching and substitution.<sup>13</sup> This results in a state-of-affairs where the policy environments for off-patent biologics and biosimilars varies greatly between European countries.

In this respect this study aims to answer the following question:

*How should policy and governance frameworks be designed and implemented to ensure long-term sustainability of off-patent biologic markets while taking into account health system financing and efficiency, in addition to commercial and patient access perspectives?*

To answer this, the study combines two approaches:

First, a 'top-down' comprehensive analysis of the current policy ecosystem for off-patent biologics is conducted, examining the types of policies in place across a sample of 15 European countries within three core themes of a sustainable market for off-patent biologics: 1) the pricing environment; 2) procurement practices and 3) physician autonomy and patient choice.

Second, this policy analysis is complemented by an Expert Opinion survey of relevant stakeholders who provide useful insights from practical experience on which policies are most conducive to a sustainable market for off-patent biologics.

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Finally, by fusing the insights from both analyses, the study establishes a definition of market sustainability for off-patent biologics and creates a ‘Gold Standard’ and roadmap for achieving a sustainable European market for off-patent biologics.





# 1. Mapping the current policy ecosystem for off-patent biologics across Europe

Over the last decade nearly all European countries have introduced new or intensified existing cost cutting measures targeting pharmaceutical spending. These measures range from price cuts, reductions to reimbursement rates, imposition of compulsory rebates, claw-backs, INN prescribing, substitution policies and a host of other measures aimed at reducing overall pharmaceutical expenditure. In some cases these policies have also applied to biosimilars.

However, as discussed above, the process of bringing a biosimilar medicine to market is considerably longer and more expensive than for a chemically synthesised generic medicine. While the production of generic medicines is estimated to take 3 to 5 years and cost about USD1-5 million, developing a biosimilar medicine takes 8 to 10 years at an estimated cost of USD100-200 million.<sup>14</sup> In this respect, pricing systems and cost-containment measures that are widely used for encouraging generic uptake are not suitable for biologics and biosimilars. At present, most regulatory authorities in Europe and outside it exclude biologics (and biosimilars) from switching and substitution policies such as INN prescribing and pharmacy-level substitution.<sup>15</sup>

## Mapping the current policy ecosystem for off-patent biologics across Europe

Within this context, this section provides an in-depth analysis of the policy environment for off-patent biologics in a sample of 15 European countries, as listed in the below Table 1. The sample contains a mix of Western-European and Eastern-European countries that vary in population size and macro-economic indicators; all, except Norway, are currently EU-member states.<sup>16</sup> The purpose is to examine the current policy ecosystem for off-patent biologics in Europe, and identify which policies promote and which policies discourage a sustainable European market for off-patent biologics.

**Table 1: The 15 European countries sampled for the analysis of their policy ecosystems for off-patent biologics**

	<b>Population (2017)</b>	<b>GDP per capita, PPP (2017)</b>	<b>Health expenditure per capita, PPP (2016)</b>
<b>Belgium</b>	11,372,068	\$47,840.2	\$4,391.6
<b>Czech Republic</b>	10,591,323	\$36,327.3	\$2,146.3
<b>France</b>	67,118,648	\$42,850.4	\$4,508.1
<b>Germany</b>	82,695,000	\$50,638.9	\$5,182.1
<b>Greece</b>	10,760,421	\$27,601.9	\$2,098.1
<b>Hungary</b>	9,781,127	\$28,107.9	\$1,826.7
<b>Italy</b>	60,551,416	\$39,426.9	\$3,283.9
<b>Netherlands</b>	17,132,854	\$52,503.3	\$5,201.7
<b>Norway</b>	5,282,223	\$61,414.3	\$6,346.6
<b>Poland</b>	37,975,841	\$29,122.1	\$1,570.4
<b>Romania</b>	19,586,539	\$26,656.8	\$1,079.3
<b>Slovakia</b>	5,439,892	\$31,616.5	\$2,179.1
<b>Spain</b>	46,572,028	\$37,997.9	\$2,965.8
<b>Sweden</b>	10,067,744	\$50,208.2	\$5,218.9
<b>UK</b>	66,022,273	\$43,268.8	\$3,376.9

Source: The World bank, 2019.

The analysis examines the types of policies in place (as of March 2019) in each of the 15 sampled European countries within three core themes of a sustainable market for off-patent biologics:

1. The pricing environment;
2. Procurement practices; and,
3. Physician autonomy and patient choice.

### **The pricing environment**

Pricing systems are a key component in creating a sustainable market that combines the generation of savings while increasing patient access and incentivizing future innovation. A stable and predictable pricing environment that acknowledges the costs and risks associated with the development of innovative biologics and biosimilars and incentivises continued investment in both is essential to long-term market sustainability.

The analysis of the pricing environment theme examines the following four indicators:

1. Type of pricing system in place;
2. Calculation method;
3. ‘Generic’ price link for biosimilars (price setting in relation to the originator’s price); and,
4. Mandatory price reduction upon market entry.

**Table 2: Mapping the off-patent biologics policy ecosystem across Europe: 1. the pricing environment theme (four indicators)**

	Type of pricing system for biosimilars	Calculation method	‘Generic’ price link for biosimilars (price setting in relation to the originator’s price)	Mandatory price reduction
<b>Belgium</b>	Negotiations	The biosimilar product’s price cannot exceed the price of the originator, following mandatory price reduction	Yes	At biosimilar market entry, the originator’s price is reduced by up to 38% (depending on volume of sales)
<b>Czech Republic</b>	ERP	Average of the lowest 3 in a basket of 18 countries	Yes	1 <sup>st</sup> biosimilar at 70% of the originator’s price, reimbursement level is adjusted per the price of the biosimilar product
<b>France</b>	Application of the conventional rule	Hospital setting: The biosimilar product’s price cannot exceed the price of the originator, following mandatory price reduction of 30%	Yes	Hospital setting: Additional price reductions applied at 24 months and 48 months to biosimilar market entry (between -10% and -30% for both the originator and biosimilar products, according to hospital commercial discounts offered)
		Retail setting: The maximum price for the biosimilar product is 40% below the originator’s price (prior to mandatory price reduction)		Retail setting: Additional price reductions applied at 24 months and 48 months to biosimilar market entry (between -5% and -15% for both the originator and biosimilar products, according to market shares)

	Type of pricing system for biosimilars	Calculation method	'Generic' price link for biosimilars (price setting in relation to the originator's price)	Mandatory price reduction
Germany	Free pricing <sup>1</sup>	None	No	General discounts apply to all products upon biosimilar market entry
Greece	ERP	Average of the lowest 2 prices within a basket of 19 Eurozone countries <sup>2</sup>	No	No
Hungary	ERP	Lowest price in a basket of 31 EEA countries	Yes	1 <sup>st</sup> biosimilar at 30% of the originator's price, additional 10% reduction applies for the 2 <sup>nd</sup> and 3 <sup>rd</sup> products
	IRP	Lowest price within a therapeutic group		
Italy	Negotiations (with indirect reliance on ERP)	ERP: Average of 27 countries	Yes	20%
Netherlands	ERP	Average of 4 EU countries	No <sup>3</sup>	No
Norway	ERP	Average of the lowest 3 in a basket of 9 countries	Yes <sup>4</sup>	No <sup>5</sup>
Poland	Negotiations (with indirect reliance on ERP)	Lowest price in a basket of 31 EEA countries	Yes	1 <sup>st</sup> biosimilar at 75% of the originator's price
Romania	ERP	Lowest price in a basket of 12 countries	Yes	1 <sup>st</sup> biosimilar at 80% of the originator's price
Slovakia	ERP	Average of the 3 lowest prices within all EU countries	Yes	1 <sup>st</sup> biosimilar at 75% of the originator's price; the price of each subsequent product is capped at 95% of the lowest priced product

<sup>1</sup> Some restrictions apply.

<sup>2</sup> In cases where the lowest two prices are identical, the 3<sup>rd</sup> lowest price is included in order to calculate the average price applicable.

<sup>3</sup> The ERP method is applied to all products, based on the product's INN.

<sup>4</sup> The reference product's price is the maximum price applicable.

<sup>5</sup> Evidence suggest aggressive discounts for biosimilars over the originator achieved through national tenders.

	Type of pricing system for biosimilars	Calculation method	'Generic' price link for biosimilars (price setting in relation to the originator's price)	Mandatory price reduction
Spain	Negotiations (with reliance on ERP and IRP)	Determined on a case-by-case basis, usually at 20%-30% below the originator's price	Yes	No <sup>6</sup>
Sweden	VBP	-	No	No
UK	Tenders	-	No	No

As is evident from Table 2, European countries differ greatly in the pricing methods applied for biologics. For example, of the 15 European countries sampled, only 2 countries are utilising the External Reference Pricing (ERP) method in a manner aimed at achieving a consistent price (by taking the average price from a small basket of similar countries), while 7 countries use it as a measure of achieving the lowest possible price (by taking the lowest price from a large basket of countries). In another example, of the 15 European countries sampled 8 countries condition the market entry of a biosimilar medicine with a mandatory price reduction at a pre-defined percentage from the reference product's price, regardless of any additional discounts required by, for example, regional and/or institutional tenders. In 6 countries these mandatory reductions exceed 25% of the originator's price.

### Procurement practices

Public procurement is an important tool for public payers to incentivise innovation and address societal needs through genuine competition. The governing EU framework for public procurement provided by Directive 2014/24/EU seeks to maintain patient access to a wide range of treatments and maintain physician autonomy while ensuring the sustainability of healthcare systems through security of supply and continued investment in innovation.<sup>17</sup>

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<sup>6</sup> Though no mandatory price reductions exist in Spain's legislative framework, in order to maintain inclusion in national / regional formularies, the originator must meet the biosimilar product's price; an annual update to the reference price list and daily treatment costs apply additional downward pressure on prices.

Within the context of a procurement framework that promotes patient access and choice and physician autonomy while ensuring a level playing field for genuine competition, the analysis evaluates the procurement practices for off-patent biologics within the 15 sampled European countries based on the following seven indicators:

1. Availability of biologics;
2. Type of tender;
3. Scope of tender;
4. Average frequency of tender (in months);
5. Does the decision-making process always involve medical advice?;
6. Could tenders result in switching of treatment for existing patients?; and,
7. Can physicians opt-out individual patients?

**Table 3: Mapping the off-patent biologics policy ecosystem across Europe: 2. Procurement practices theme (seven indicators)**

	Availability of biologics	Type of tender	Scope of tender	Average frequency of tender (in months)	Does the decision-making process always involve medical advice?	Could tenders result in switching of treatment for existing patients?	Can physicians opt-out individual patients?
<b>Belgium</b>	Reimbursement lists + tenders	Single winner + multiple winners	Same substance (ATC-5 level)	NA	Yes	Yes, in single winner tenders	Yes
<b>Czech Republic</b>	Reimbursement lists + tenders	Multiple winners	Same substance (ATC-5 level)	6-12	Yes	No	Yes
<b>France</b>	Reimbursement lists + tenders	Multiple winners	Same substance (ATC-5 level)	18	Yes	Yes	Yes
<b>Germany</b>	General reimbursement + tenders	Multiple winners	Therapeutic area (ATC-4 level)	NA	No	Yes	Yes
		Single winner	Same substance (ATC-5 level)				
<b>Greece</b>	Reimbursement lists only	NA	NA	NA	NA	NA	NA

	Availability of biologics	Type of tender	Scope of tender	Average frequency of tender (in months)	Does the decision-making process always involve medical advice?	Could tenders result in switching of treatment for existing patients?	Can physicians opt-out individual patients?
<b>Hungary</b>	Reimbursement lists + tenders	Single winner	Same substance (ATC-5 level)	12-24	Yes	No	No
<b>Italy</b>	Institutional tenders only	Single winner + multiple winners	Same substance (ATC-5 level)	12-48	No	Yes	Yes
<b>Netherlands</b>	Reimbursement lists + tenders	Single winner + multiple winners	Same substance (ATC-5 level)	12-24	No	Yes	Yes
<b>Norway</b>	Reimbursement lists + tenders	Multiple winners	Therapeutic area (ATC-4 level) and same substance (ATC-5 level)	12	Yes	Yes	Yes
<b>Poland</b>	Reimbursement lists + tenders	Single winner	Therapeutic area (ATC-4 level) and same substance (ATC-5 level)	6-12	Yes	Yes	No
<b>Romania</b>	Reimbursement lists + tenders	Single winner (lowest price)	Same substance (ATC-5 level)	12-24	NA	Yes	NA
<b>Slovakia</b>	Reimbursement lists + tenders	Single winners	Same substance (ATC-5 level)	12	No	Yes	Yes
<b>Spain</b>	Reimbursement lists + tenders	Single winner + multiple winners	Same substance (ATC-5 level)	24-36	Yes	Yes	Yes
<b>Sweden</b>	Reimbursement lists + tenders	Single winner +	Therapeutic area (ATC-4 level) and same	12-24	Yes	Yes	Yes

		multiple winners	substance (ATC-5 level)				
UK	Tenders	Multiple winners	Same substance (ATC-5 level)	12-24	No	Yes	Yes

Looking at the actual biopharmaceutical procurement practices in many countries it is clear that more often than not the focus is mainly on price.<sup>18</sup> For example, two recent analyses of public procurement frameworks in Europe found that many tender contracts for biologics limit choice by utilizing a ‘winner-takes-all’ form that is primarily focused on the ‘lowest bid’.<sup>19</sup> For example, tenders in Norway allow products from the entire therapeutic range (ATC-4 level) and entail switching of treatment for patients undergoing treatment, and evidence suggests that tenders are used to achieve substantial discounts.<sup>20</sup> In another example, tenders in Poland allow for a single winner, for a short duration of between 6 to 12 months, and also allow products from the entire therapeutic range (ATC-4 level) without enabling physicians to opt-out specific patients. Indeed, a recent study surveying the policy environment for biologics finds that a tender frequency of 12 months or less is evident in 11 of 25 European countries sampled.<sup>21</sup>

At the same time, some countries have reformed their public procurement frameworks to try and ensure their market’s sustainability. For example, inconsistent clinical guidelines and procurement decisions for biosimilars between regions in Italy were recently reformed under the new biosimilars law of 2016, which includes multiple-winners tenders for both originators and biosimilars. Automatic substitution is prohibited, and physician autonomy and treatment continuity are maintained even if the product of choice has not won the contract.<sup>22</sup>

### Physician autonomy and patient choice

Physicians’ freedom to prescribe what they consider the most appropriate medicine for their patients, and patients’ ability to choose from a wide range of treatments – based on accurate and up to date information about the availability, cost, safety and efficacy profile of biologic and biosimilar medicines – are at the core of clinical practice within the off-patent biologics market.



In the third theme the analysis examines the policies in place that govern the clinical practice with regards to off-patent biologics, looking at the following five indicators:

1. Is INN prescribing allowed for biologics?
2. Is automatic substitution enabled for biosimilars?
3. Is there an official position / guideline in place on interchangeability of biologics?
4. Are there any measures in place that limit or restrict prescribing practices?
5. If they exist, do these measures differentiate between naïve and existing patients?

**Table 4: Mapping the off-patent biologics policy ecosystem across Europe: 3. Physician autonomy and patient choice theme (five indicators)**

	Is INN prescribing allowed for biologics?	Is automatic substitution enabled for biosimilars?	Is there an official position / guideline in place on interchangeability of biologics?	Are there any measures in place that limit / restrict prescribing practices?	Do these measures differentiate between naïve and existing patients?
<b>Belgium</b>	Yes <sup>7</sup>	No	Yes	Prescription audits, recommendation to prescribe biosimilars, financial incentives under a pilot project for specific products	No
<b>Czech Republic</b>	Yes <sup>8</sup>	Yes	No	No	NA
<b>France</b>	No	Yes <sup>9</sup>	Yes	Financial incentives	No
<b>Germany</b>	Yes <sup>10</sup>	No <sup>11</sup>	Yes	Prescription quotas	Partial
<b>Greece</b>	Yes	No <sup>12</sup>	Yes	e-prescribing; Prescription audits; financial restrictions; therapeutic protocols	Yes

<sup>7</sup> INN prescribing allowed with no legal text excluding biologics, yet INN prescribing not applied in practice to biologics under guidance of the Federal Agency for Medicines and Health Products (FAMHP).

<sup>8</sup> INN prescribing allowed with no specific guideline or policy in place excluding biologics, yet INN prescribing not applied in practice to biologics

<sup>9</sup> For naïve patients only, pending the promulgation of new regulations

<sup>10</sup> Prescribing is at the discretion of the prescribing physician.

<sup>11</sup> Substitution at retail level is only allowed for biosimilar medicines coming from the same cell line and production site

<sup>12</sup> Biosimilars are classified as ‘high-cost medicines’ which are not eligible for automatic substitution

	Is INN prescribing allowed for biologics?	Is automatic substitution enabled for biosimilars?	Is there an official position / guideline in place on interchangeability of biologics?	Are there any measures in place that limit / restrict prescribing practices?	Do these measures differentiate between naïve and existing patients?
<b>Hungary</b>	No	No	No	Recommendation to prescribe biosimilars	No
<b>Italy</b>	No	No	Yes	Prescription quotas and audits	No
<b>Netherlands</b>	Yes	No <sup>13</sup>	Yes	Recommendation to prescribe biosimilars	Yes <sup>14</sup>
<b>Norway</b>	Yes <sup>15</sup>	No	No <sup>16</sup>	e-prescribing; recommendation to prescribe biosimilars	No
<b>Poland</b>	Yes	Yes	No	Financial incentives, correcting factors	No
<b>Romania</b>	Yes <sup>17</sup>	No	No	e-prescribing; prescription protocols	Partial
<b>Slovakia</b>	No	No	No	No	No
<b>Spain</b>	No	No	No	Recommendation to prescribe biosimilars	Yes; naïve only
<b>Sweden</b>	No	No	Yes	Recommendation to prescribe biosimilars	No
<b>UK</b>	No	No	No	Financial incentives	Yes

During recent years, some European countries began, or are considering to apply various cost-containment measures aimed at increasing the uptake of biosimilars, such as prescription guidelines, audits and quotas, and financial incentives / restrictions.<sup>23</sup> For example, in Greece direct financial restrictions on physicians are considered the most effective way of increasing the uptake of biosimilars,<sup>24</sup> while in the UK NHS England requires a written explanation from Clinical Commissioning Groups where a target of placing 90% of new patients under a treatment of the ‘best value biological

<sup>13</sup> The Medicines Evaluation Board permits prescribing of a biosimilar product to naïve patients, as well as switching between an originator biologic and a biosimilar product and between two biosimilar products, conditioned by approval from the General Physician / specialist and the patient, and adequate clinical monitoring; automatic substitution at the pharmacy level is prohibited.

<sup>14</sup> The Medicines Evaluation Board permits prescribing of a biosimilar product to naïve patients, under approval from the General Physician / specialist and the patient, and adequate clinical monitoring.

<sup>15</sup> The Pharmaceutical Division within the Norwegian Hospital Procurement Trust applies ranking to prescribed products within the hospital sector, based mainly on a product’s price; physicians must prescribe based on products’ rankings, except where clinical reasons apply.

<sup>16</sup> Pending developments related to the final results from the NOR-SWITCH clinical study.

<sup>17</sup> INN prescribing for biologics is allowed and applied in the hospital sector, yet is restricted in the retail sector.

medicine' within 3 months of product launch and 80% of existing patients within 12 months, was not met.<sup>25</sup> Physicians are offered incentives for prescribing biosimilars in at least 13 European countries.<sup>26</sup>

However, in some cases the measures utilised include INN prescribing and pharmacy-level substitution, which may pose challenges from a traceability and pharmacovigilance perspective.<sup>27</sup> Though a recent survey finds that pharmacy-level substitution for biologic products is not allowed in 22 European countries, it is allowed (to varying extent) in 8 European countries, including Belarus, Estonia, Finland, France, Latvia, Poland and Serbia.<sup>28</sup>

These measures divert from, rather than contribute to a sustainable market for off-patent biologics, due to their influence on – and in the case of INN prescribing and pharmacy-level substitution, the circumvention of – physicians' autonomy and prescribing freedom, and on patients' choice.

### **Mapping the off-patent biologics policy ecosystem across Europe: Summary**

This section provided an analysis of the types of policies that govern the off-patent biologics market in a sample of 15 European countries within three core themes: The pricing environment; procurement practices; and physician autonomy and patient choice. The policies in these themes are assessed vis-à-vis a set of policy measures and guiding principles that are considered as appropriate strategies for governments to create sustainable competition as well as those considered inappropriate when reflecting on the specificities of biological medicines.<sup>29</sup>

The analysis reveals a high variance in the policies governing the off-patent biologics, ranging from policies that contribute to a sustainable market to policies that discourage it. These differences are not only between countries, but also in-between themes. Some countries maintain a policy framework that is based on the principle of a genuine competition and a level playing field within all three themes, while other countries show a relatively intense preference for maximising short-term savings that in some cases limits physicians' prescribing freedom and patient choice. The analysis also shows that

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discriminatory policies that divert from a level playing field are utilised regardless of their geographic location or performance in macro-economic indicators. For example, a mandatory price reduction of over 20% of the originator biologic product's price is applied for the first biosimilar to enter the market in the Czech Republic, France, Hungary, Poland, and Slovakia, while automatic substitution is allowed in the Czech Republic, France (for in-patients) and Poland.

**In sum, what stands out most prominently from this analysis is that the European market for off-patent biologics is highly diverse, with unfavourable – at times even discouraging – policies for a sustainable off-patent biologics market in place in at least one of the three core themes in most European countries sampled.**

What is the impact of these policies ‘on-the-ground’? How do various stakeholders perceive the current policy environment for off-patent biologics in their countries? Which policies, in their view, are key in creating a sustainable European market for off-patent biologics?

The next section presents the key insights drawn from a survey covering various stakeholders within the off-patent biologics market: physicians, patients, representatives of the biopharmaceutical industry and of government institutions from the 15 European countries sampled in this section.

The policy analysis in this section relies on publicly available official sources and the academic literature, using the following sources (in alphabetical order):

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- Rémuzat C. et al. (2017). “Supply-side and demand-side policies for biosimilars: an overview in 10 European member states”, *Journal of Market Access & Health Policy*, Vol. 5, <https://pdfs.semanticscholar.org/4f1f/1b687db6b879ccb6f48ab4ea4f06badf2203.pdf>.
- Roediger A., Freischem B., Reiland JB. (2017). “What pricing and reimbursement policies to use for off-patent biologicals in Europe? – results from the second EBE biological medicines policy survey”, *GaBI Journal*, Vol. 6, Issue 2, pp. 61-78.
- Statens Legemiddelverk, Guidelines for price setting in Norway, <https://legemiddelverket.no/Documents/English/Price%20and%20reimbursement/Maximum%20price/Guidelines%20for%20price%20setting%20in%20Norway%20oppdatert.pdf>.
- Toumi M. et al. (2013). External reference pricing of medicinal products: simulation-based considerations for cross-country coordination, European Commission.
- Vogler S., Schneider P. (2017). “Do pricing and usage-enhancing policies differ between biosimilars and generics? Findings from an international survey”, *GaBI Journal*, Vol. 6, Issue 2, pp. 79-88.

## 2. Ensuring the sustainability for off-patent biologics: Stakeholders' perception

The 'top-down' analysis of the off-patent biologics' policy ecosystem in the preceding section is complemented by a 'bottom-up' analysis of stakeholders' perceptions carried through an Expert Opinion survey with the purpose of understanding how these stakeholders perceive the current policy environment for off-patent biologics and which policies, in their view, are key in creating a sustainable European market for off-patent biologics.

### Survey methodology and limitations

The survey was conducted between November 2017 and January 2018 among stakeholders within the 15 sampled European countries: Belgium, Czech Republic, France, Germany, Greece, Hungary, Italy, Greece, Netherlands, Norway, Poland, Romania, Slovakia, Spain, Sweden and the UK. The questionnaire was developed by Pugatch Consilium together with EFPIA and consisted of 17 closed- and open-ended questions grouped under seven policy themes:

1. Top priorities for market sustainability;
2. Patient-centricity;
3. Prescribing and dispensing;
4. Pricing and reimbursement;
5. Procurement;
6. Pharmacovigilance; and
7. Transparency and Information.

A total of 76 responses were received from stakeholders in all 15 countries sampled, and were divided into four stakeholder groups, based on respondents' profile and affiliation:

- Healthcare professionals,

- Patients / patient group representatives,
- Government institution representatives, and
- Industry / trade association representatives.<sup>18</sup>

Participation in the survey was voluntary and did not incur any reimbursement or payments for participation. Data collection is compliant with EFPIA's data collection guidelines. The questionnaire was available in English only and is provided in the Annex of this study, along with the definitions used in the survey and in this study.

## Results

The responses from the four distinct stakeholder groups offer six key insights on which policies are imperative in creating a sustainable European market for off-patent biologics, as well as to where these groups differ in their view of the gaps and challenges of the current policy environment for off-patent biologics. However, these insights are extrapolated from a relatively limited number of responses and uneven distribution in respondents' affiliations and therefore do not purport to reflect the general or common views held by these stakeholder groups within the sampled countries.

### Key insight #.1: Stakeholders are in wide agreement on key characteristics of a sustainable market

Respondents were asked the following question:

*If you had to sum up the three (3) most important requirements for market sustainability of off-patent biologic medicines in your country and rank them in priority from 1-3, what would they be?*

Provided with six options as well as free text, the overwhelming majority of respondents across all stakeholder groups prioritized the key characteristics of a sustainable market for off-patent biologics as follows:

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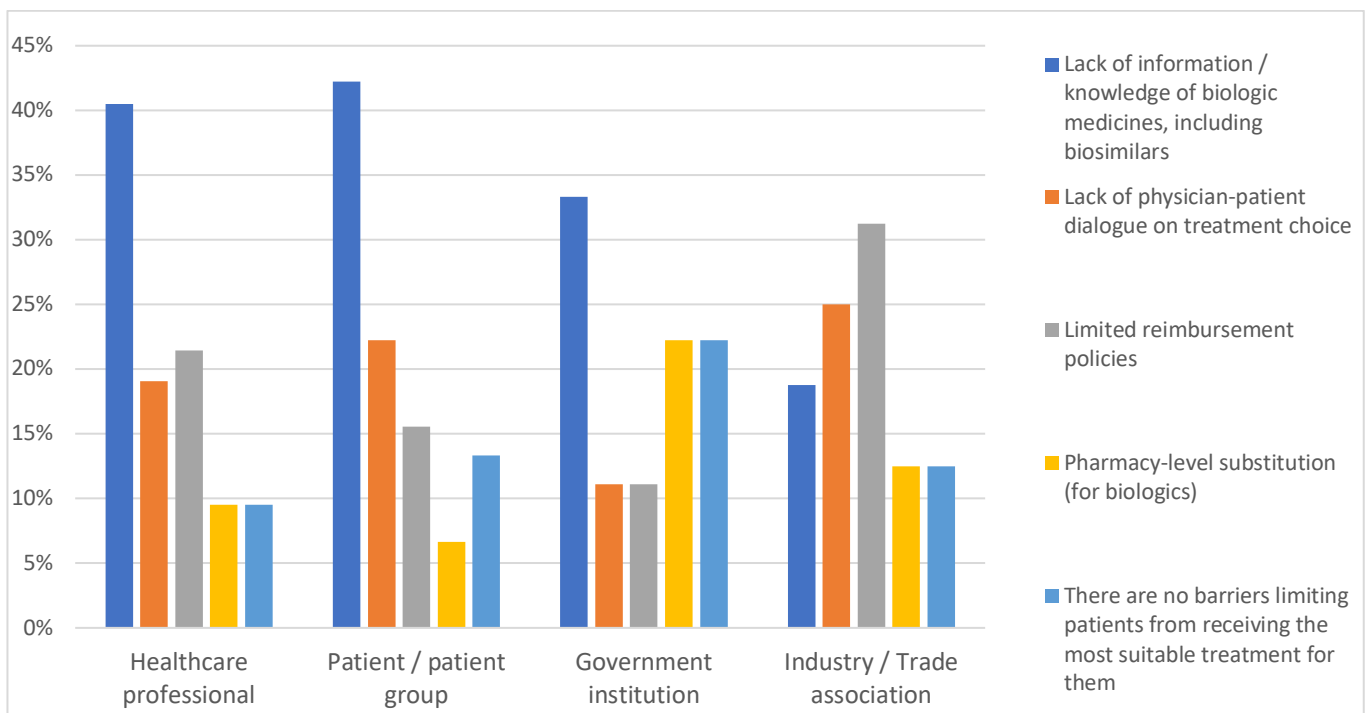
<sup>18</sup> The 'industry' stakeholder group includes responses from respondents from both the innovative and biosimilar medicines manufacturers. Responses from respondents from medical organizations were included within the 'healthcare professionals' stakeholder group.

1. Physician autonomy to prescribe the most appropriate treatment based on the individual patient’s needs
2. Access to a range of available treatments through wide and flexible coverage of biologic medicines
3. Access to reliable and up-to-date information about available treatments and their appropriate uses for different conditions

**Key insight #.2: Lack of information, of patient-physician dialogue and of wide access are viewed as the most critical barriers to prescribing the optimal treatment**

Respondents were asked to select from five statements the two statements that represent the key barriers limiting patients from receiving the most suitable treatment for them from available off-patent biologic medicines in their country. As is evident in Figure 3 below, **“lack of information / knowledge of biologic medicines, including biosimilars”** is perceived as the most prominent barrier, followed by the **“lack of physician-patient dialogue on treatment choice and limited reimbursement policies”**.

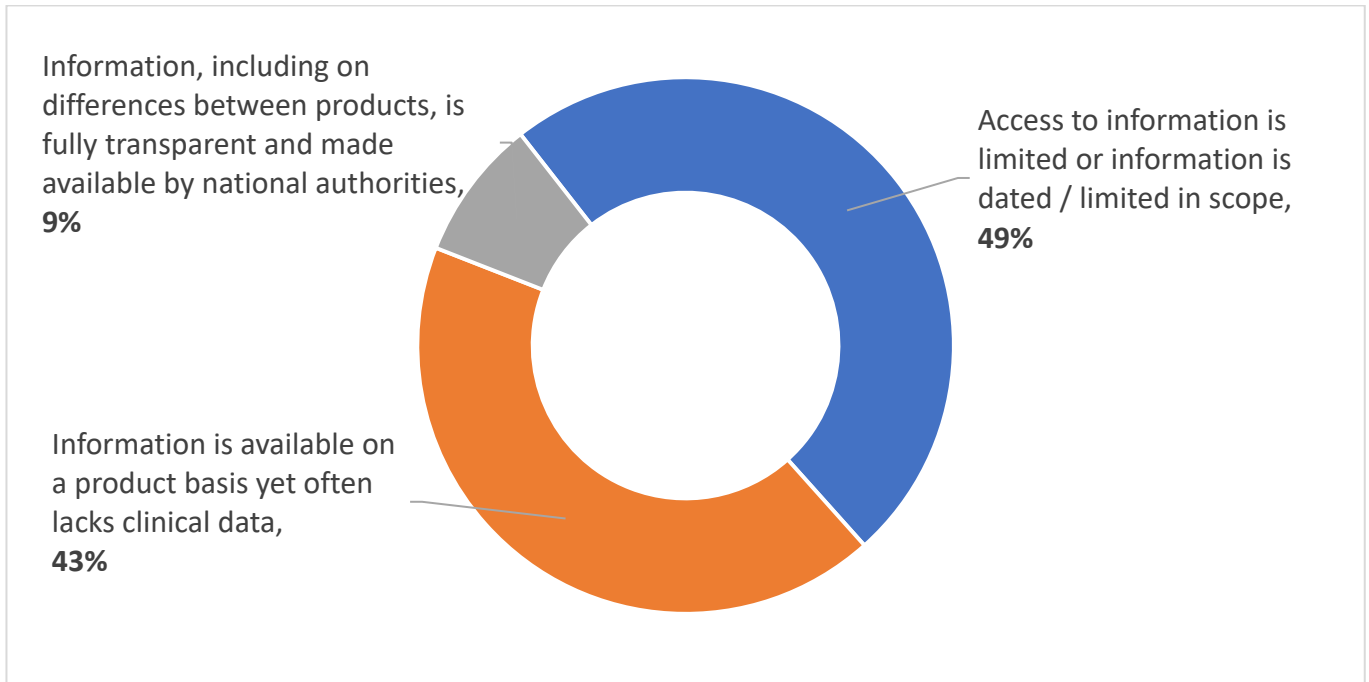
**Figure 3: Key barriers to receiving the most suitable treatment**





Furthermore, as depicted in Figure 4, the majority of respondents emphasized the lack of reliable and up-to-date information, with 49% of respondents citing limited access to information or that the data is dated or limited in scope, with an additional 43% stating that information is available yet is often incomplete or insufficient.

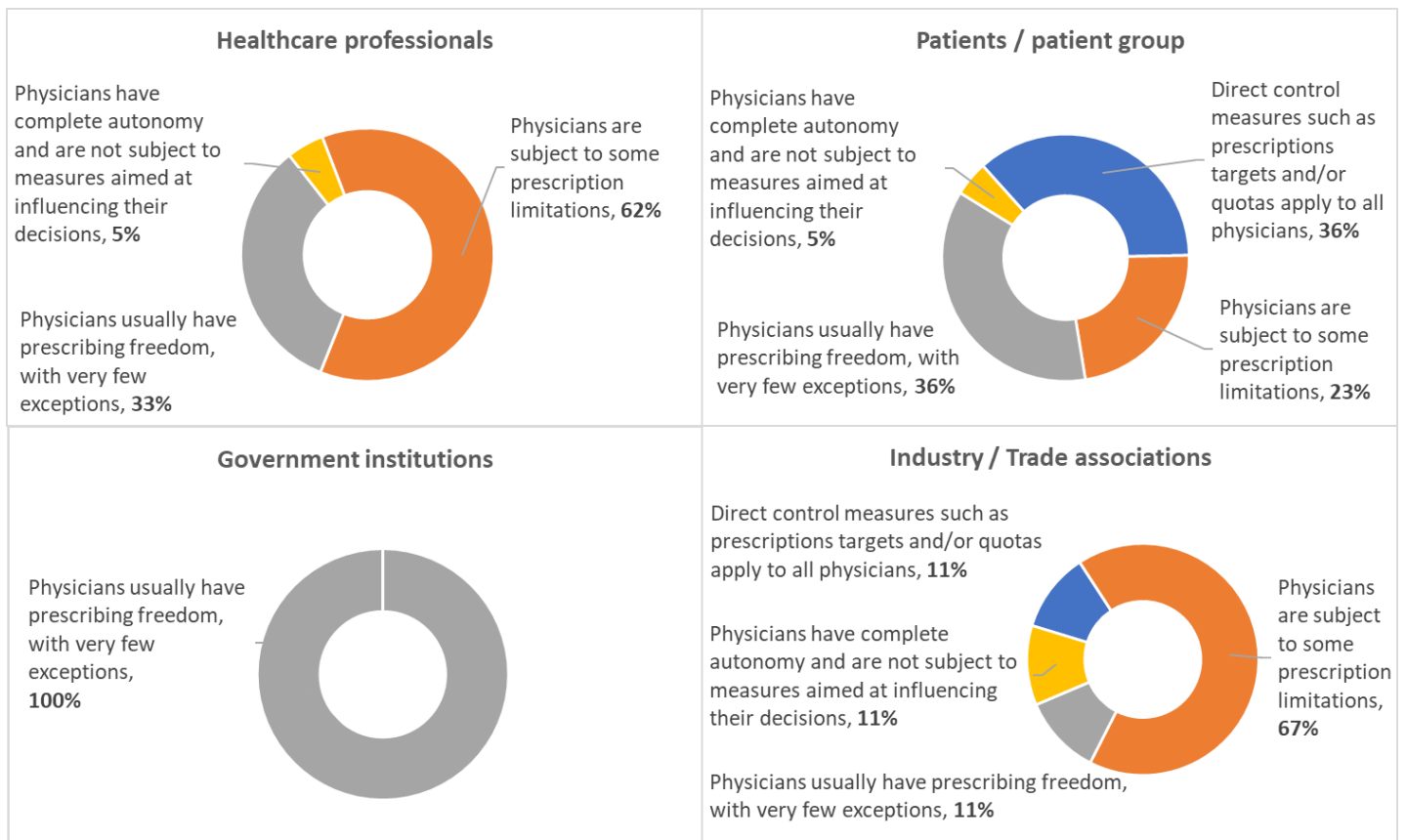
**Figure 4: Stakeholders' view on availability of reliable and up-to-date information on off-patent biologics in their countries**



**Key insight #.3: Maintaining prescribing freedom is essential**

Only 5% of respondents feel that physicians in their country are able to prescribe the off-patent biologic medicinal product they think is most appropriate for their patients. The remaining 95% cite some limitations in place, with nearly two-thirds of respondents across the 'patients / patient group', 'healthcare professionals' and 'industry / trade associations' stakeholders groups citing measures such as prescription targets and quotas that restrict physicians' prescribing freedom in their countries.

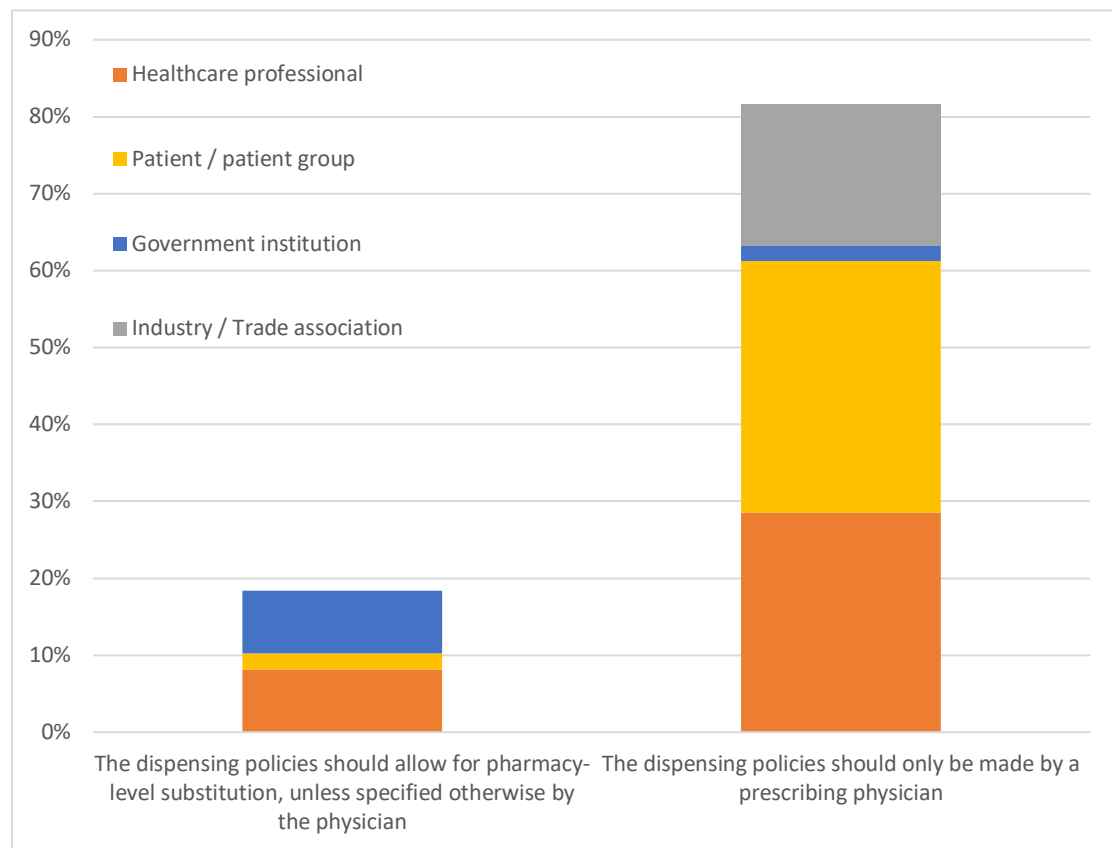
Figure 5: Stakeholders' perceptions of policy measures in place that limit physicians' prescribing freedom



In addition, nearly half of the respondents expressed their opposition to measures that aim to affect the prescribing choices of physicians, while 30% expressed their support for such restricting measures, with the remaining 20% opting for a neutral view.

Furthermore, 82% of respondents believed that dispensing decisions (choosing which off-patent biologic medicine a patient receives) should only be made by the prescribing physician, while the remaining 18% of respondents felt that dispensing policies for off-patent biologics should allow for pharmacy-level substitution, unless specified otherwise by the physician.

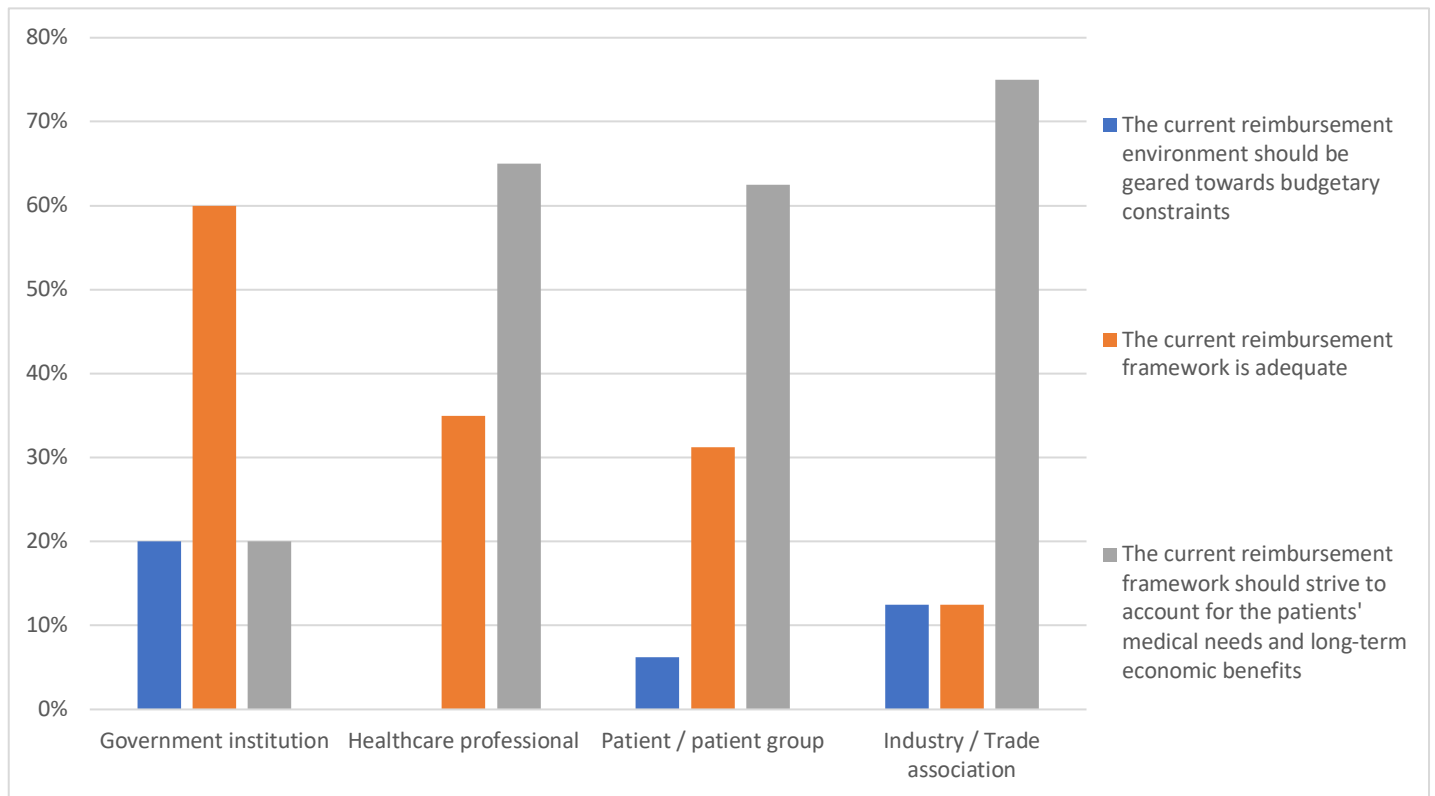
Figure 6: Stakeholders' opinion on the decision-making within dispensation policies



**Key insight #.4: Reimbursement frameworks should strive to account for patients' medical needs and long-term economic benefits**

When asked for their opinion on the reimbursement frameworks with respect to off-patent biologics, 56% of respondents answered that reimbursement of off-patent biologics in their country is mainly focused on short-term budgetary constraints. Subsequently, when asked for their opinion of what factors should guide the considerations on reimbursement for off-patent biologics in their country, 60% of respondents highlighted the patients' medical needs and long-term economic benefits.

Figure 7: Stakeholders' perceptions of the current reimbursement frameworks for off-patent biologics in their countries

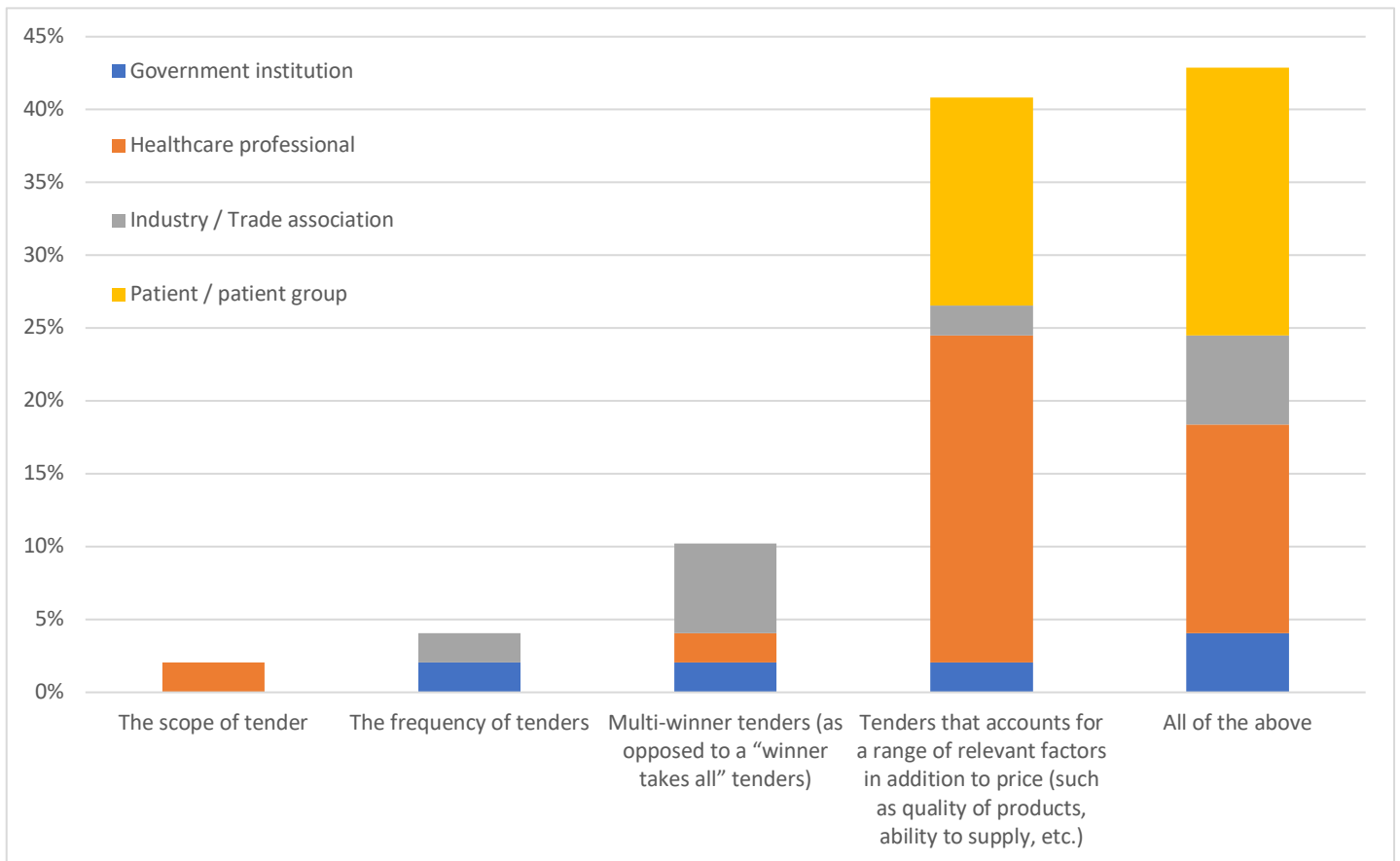


**Key insight #.5: Procurement of off-patent biologics should ensure the consistent supply of a wide range of high-quality products**

When asked for their opinion on what factors contribute to the sustainable tendering of off-patent biologics, 41% of respondents highlighted that tenders should account for factors such as the quality of the products and the provider's ability to secure the supply. An additional 45% of respondents included, in addition to the above, factors such as multiple winners, as well as the scope and frequency of the tenders.



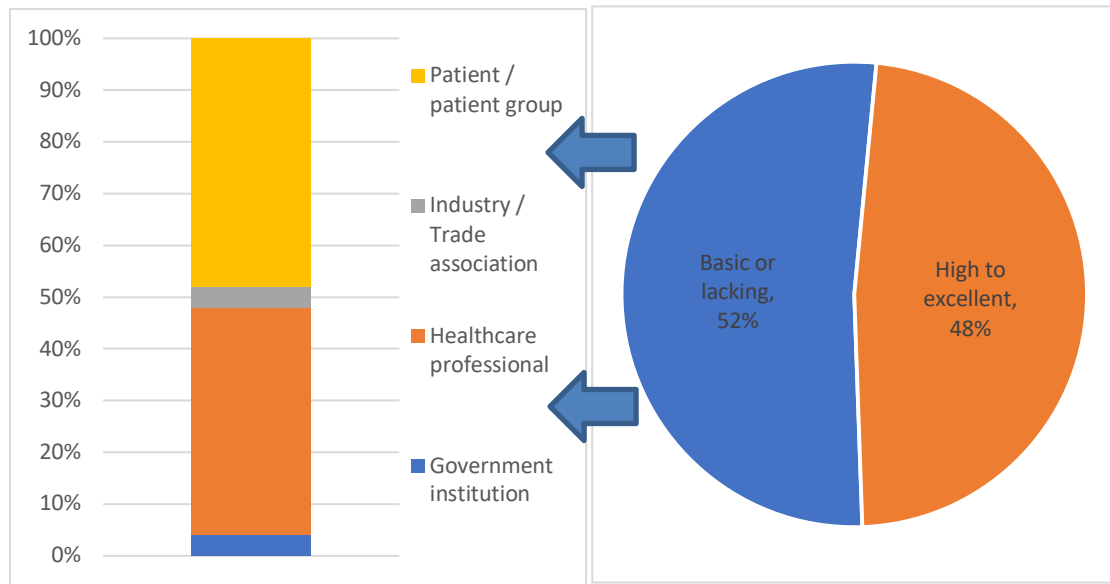
Figure 8: Factors that make up a sustainable procurement environment for off-patent biologics



**Key insight #.6: Better communication and understanding of good pharmacovigilance practices for off-patent biologics is required**

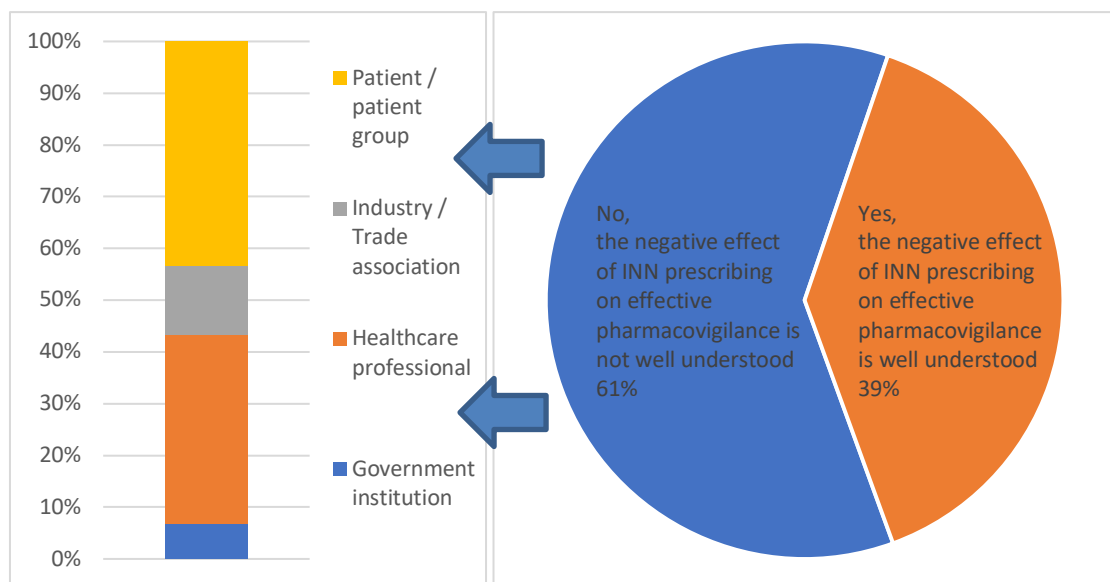
Pharmacovigilance systems are used to monitor and evaluate ADRs from the use of all medicines, including biologics and biosimilars. An effective pharmacovigilance system will have a direct and clear process in which healthcare professionals are aware of the importance of monitoring for and reporting ADRs and the relevant structures are in place that encourage and allow such reporting to take place.<sup>30</sup> In this respect, 52% of the respondents, comprised mostly of respondents from the healthcare professionals and patients stakeholder groups feel that the need for a robust pharmacovigilance system is not effectively communicated and is not well understood, as is displayed below in Figure 9.

Figure 9: How effectively is the need for robust pharmacovigilance system communicated and understood by stakeholders?



Additionally, 61% of the respondents felt that the negative impact that INN prescribing for biologics may have on good pharmacovigilance practice is not well understood in their country / stakeholder group, as is seen in the below Figure 10:

Figure 10: The understanding of the negative impact that INN prescribing for biologics may have on good pharmacovigilance practice



# 3. Building a sustainable future: A ‘Gold Standard’ for creating a sustainable European market for off-patent biologics

The purpose of this study has been to answer the following question:

*How should policy and governance frameworks be designed and implemented to ensure long-term sustainability of off-patent biologic markets while taking into account health system financing and efficiency, in addition to commercial and patient access perspectives?*

To answer this, the study has combined a ‘top-down’ analysis of the current policy ecosystem for off-patent biologics with a ‘bottom-up’ analysis of relevant stakeholders’ perceptions of which policies are key in creating a sustainable European market for off-patent biologics.

What conclusions can be drawn from this exercise?

**The findings of the ‘top-down’ policy analysis and Expert Opinion survey reveal that there is a clear roadmap and ‘Gold Standard’ on what a sustainable European market for off-patent biologics should look like.**

Sustainability requires a predictable, balanced and supportive policy environment that provides for a level playing field and accounts for all the components of the off-patent biologics market. This entails the need to incentivise both biosimilar development and

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continued biopharmaceutical innovation through the research and development of new medicines.

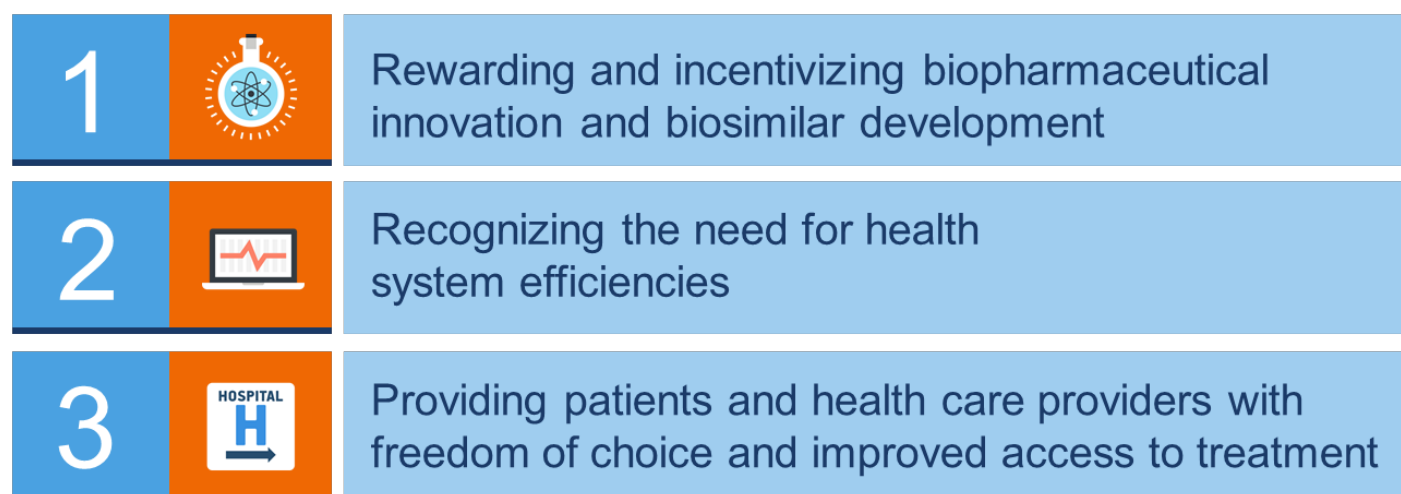
Sustainability also relies on the efficiency of healthcare systems. Inefficient healthcare systems have a detrimental impact on national budgets, economies and society. That said, governments and payers should recognize that biopharmaceuticals generate efficiencies to healthcare systems by providing both short- and long-term benefits through their therapeutic and economic value. Procurement and reimbursement frameworks that identify this value result in healthcare systems that provide wider access to a range of treatments while also generating savings to the health system and socio-economic benefits.

Finally, sustainability also rests on the core principle to which all stakeholders – patients, healthcare professionals, payers and manufacturers – agree: that the physicians’ freedom to prescribe what they evaluate as the most appropriate treatment to their patients, and a patients’ ability to choose from a wide array of treatments should be secured. Efforts should be directed to the generation and provision of wide access to accurate and up to date information about the availability, cost, safety and efficacy profile of biologic and biosimilar medicines, in order to supply physicians and patients with the best information to make their treatment decisions.

These three findings represent the pillars of a sustainable European market for off-patent biologics.



Figure 11: The three pillars of a sustainable European market for off-patent biologics



Building on these three pillars and on the insights from the policy analysis and the Expert Opinion survey, a set of core principles can be established under six components, comprising a ‘Gold Standard’ for a sustainable European market for off-patent biologics:

Table 5: A Gold Standard for a sustainable European market for off-patent biologics

<b>1. Rewarding innovation</b>	<ul style="list-style-type: none"> <li>At its core a sustainable market for off-patent biologics should be built on incentivizing biopharmaceutical R&amp;D</li> <li>Strong and clear incentives must be in place for continuous and sustained investment in innovative biologics as well as in off-patent biologics and biosimilars both from a R&amp;D perspective as well as with regards to manufacturing</li> </ul>
<b>2. Healthcare financing</b>	<ul style="list-style-type: none"> <li>Health care sustainability should be viewed from a holistic perspective recognizing the long-term societal benefits and cost savings that sustainable competition and access to medicines provides European health systems</li> <li>Pricing and reimbursement policies for all biologic products, including biosimilars, should be tailored to and reflect the unique characteristics of these medicines, including the substantial resources, risk and technical capacity required for developing and manufacturing a large molecule biologic medicine</li> </ul>
<b>3. Procurement practices</b>	<ul style="list-style-type: none"> <li>Within a sustainable European market for off-patent biologics, procurement practices should:                             <ol style="list-style-type: none"> <li>be performed solely at a molecule level;</li> <li>include the possibility of a wide variety of products from multiple suppliers (as opposed to a ‘winner takes all’ tender);</li> <li>ensure an effective supply term that ranges between a minimum of 12 months and a maximum of 24 months; and</li> </ol> </li> </ul>

	<p>d) Include an option for physicians to opt-out individual patients based on their medical needs at the physician’s discretion.</p>
<b>4. Physician autonomy &amp; patient choice</b>	<ul style="list-style-type: none"> <li>Physicians should have autonomy to prescribe what they consider to be the most appropriate medicine for their patients.</li> <li>The substitution of a biologic medicine with another biologic medicine should not happen automatically; it may only take place in cases where it is: <ul style="list-style-type: none"> <li>a) recommended by the physician; and</li> <li>b) consented to by the patient.</li> </ul> </li> <li>Patients undergoing treatment should only be switched between biologic medicines if the following conditions are met: <ul style="list-style-type: none"> <li>a) The physician and the patient have both consented to the switch;</li> <li>b) The patient is closely monitored following the switch.</li> </ul> </li> <li>Reliable and up-to-date information about the availability, cost-effectiveness and comparative assessment of off-patent biologics and biosimilars should be fully transparent and accessible to physicians</li> </ul>
<b>5. Pharmacovigilance and traceability frameworks</b>	<ul style="list-style-type: none"> <li>A robust pharmacovigilance system for reporting and analysis of ADRs should be in place and healthcare professionals should be aware of the importance of reporting ADRs by brand name and batch number.</li> <li>All biologic products should be prescribed by the product’s brand name in order to avoid unintended switching of treatments and ensure effective traceability of ADRs</li> </ul>

A sixth component of the Gold Standard details the policies and measures the countries should refrain from in order to secure the sustainability of the off-patent biologics market:

<b>6. Policies with a potential to undermine sustainability of the market</b>	<ul style="list-style-type: none"> <li>Treating off-patent biologics as ‘bio-generics’ by adopting policies or measures aimed at generating savings or inducing uptake that may be in place for generic medicines that do not require an extensive R&amp;D phase and that are significantly less complex to produce compared to biosimilars.</li> <li>Adopting extreme discriminatory measures and/or preferential treatment (including within the pricing and reimbursement, procurement and clinical practice aspects) that impede competition and may limit physician autonomy and patient choice.</li> <li>Placing physicians and patients under unwarranted restrictions or limitations with regards to their freedom to choose the most suitable treatment for their needs.</li> <li>Using policies such as INN prescribing and/or pharmacy-level substitution that greatly complicate product traceability in cases of adverse drug reactions.</li> </ul>
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# Appendix: EFPIA's “Establishing a sustainable European market for off-patent biologics” survey questionnaire

The following Appendix presents the survey questions submitted to respondents and analysed in the above report.

## **Creating sustainable competition**

1. If you had to sum up the three (3) most important requirements for market sustainability of off-patent biologic medicines in your country and rank them in priority from 1-3, what would they be?

You may answer by providing free text or by choosing from the below options, or both.

- 1.
- 2.
- 3.

Options:

- Physician autonomy to prescribe the most appropriate treatment based on the individual patient's needs
- Access to reliable and up-to-date information about available treatments and their appropriate uses for different conditions
- Policy environment that accommodates both budgetary constraints as well as long-term benefits from enhanced access to treatments and cures (such as increased longevity and productivity, reduced hospitalization and overall savings to the healthcare system)
- A competitive environment that allows players and products to compete on the basis of an equal setting
- Access to a range of available treatments through wide and flexible coverage of biologic medicines
- Stable and predictable pricing environment that reflects the product's value to the healthcare system

**Patient-centricity**

2. In your country / region, what are the key barriers limiting patients from receiving the most suitable treatment for them from available off-patent biologic medicines?

Please select from the five statements provided below the two statements that you feel are most representative your view:

- Lack of information / knowledge of biologic medicines, including biosimilars
- Lack of physician-patient dialogue on treatment choice
- Limited reimbursement policies
- Pharmacy-level substitution (for biologics)
- There are no barriers limiting patients from receiving the most suitable treatment for them from available off-patent biologic medicines
- Comments:

**Prescribing and dispensing**

3. In your view, are physicians in your country / region able to prescribe the off-patent

biologic medicinal product they think is most appropriate for their patients?

1. Not at all  
(direct control measures such as prescriptions targets and/or quotas apply to all physicians)
  2. To a limited extent  
(physicians are subject to some prescription limitations)
  3. To a reasonable extent  
(physicians usually have prescribing freedom, with very few exceptions)
  4. To a great extent  
(physicians have complete autonomy and are not subject to measures aimed at influencing their decisions)
- Comments:

4. What is your opinion on measures that aim to affect the prescribing choices of physicians (such as prescriptions targets, quotas and financial incentives) with respect to off-patent biologics?

Please elaborate on/explain your answer in the comments section below.

- Strongly oppose
- Oppose
- Neutral view
- Support with conditions
- Fully support
- Comments:

5. In your opinion, to what extent should a physician be involved in circumstances where a tender or a change in formulary/new prescribing guidelines results in the potential switch of a stable patient's treatment?

- None at all  
(physicians should always adhere to formularies / prescribing guidelines)
- To a limited extent  
(physicians can opt-out for individual patients so that they will continue to receive their existing medication)
- To a reasonable extent

(in most cases patients that are stable under a given treatment with a biologic medicine will continue to receive it)

- To a great extent

(as a rule, patients that are stable under a given treatment will continue to receive it, regardless of any changes to the formulary / prescription guidelines)

- Comments:

6. In your opinion, the dispensing decisions (choosing which off-patent biologic medicine a patient receives) should:

- only be made by a prescribing physician
- allow for pharmacy-level substitution, unless specified otherwise by the physician
- not require physician involvement
- more evidence is required in this field
- comments:

### **Pricing and reimbursement**

7. How comprehensive is the public reimbursement framework in your country / region with regards to coverage of off-patent biologics? Please provide additional comments beyond the suggested response options below in the Comments box.

- Non-existent

(there is no national or public reimbursement of off-patent biologics)

- Lacking

(reimbursement is usually provided to less costly products)

- Partial

(most off-patent biologic medicines are reimbursed, but limitations are imposed on products which are considered more costly)

- Comprehensive

(reimbursement is provided across the board, including the possibility of reimbursing costlier medicines)

- Comments:

8. In your view, which of the below statements is most representative of reimbursement considerations for off-patent biologics in your country / region? Please provide

additional comments in the box below if your view is not represented in the options below.

In my country / region, reimbursement of off-patent biologics:

- is based predominantly on short-term budgetary constraints
- is mainly focused on short-term budgetary constraints while aiming to accommodate the individual patient's medical needs
- takes a more holistic perspective by accounting for long-term economic benefits (including overall savings to the healthcare system generated by e.g. reduced hospitalization)
- is based predominantly on the individual patient's medical needs
- strives to accommodate all three: The individual patient's medical needs, short-term budgetary constraints and long-term economic benefits
- Comments:

9. Considering your response to the last question, which of the below statements should guide the considerations on reimbursement of off-patent biologics in your country / region? Again, please provide additional comments in the box below if your view is not represented in the following options.

In my opinion, reimbursement of off-patent biologics should:

- be based predominantly on short-term budgetary constraints
- be focused mainly on short-term budgetary constraints while aiming to accommodate the individual patient's medical needs
- take a more holistic perspective by accounting for long-term economic benefits (including overall savings to the healthcare system generated by e.g. reduced hospitalization)
- be based predominantly on the individual patient's medical needs
- strive to accommodate all three: The individual patient's medical needs, short-term budgetary constraints and long-term economic benefits
- Comments:

10. The high overall costs of bringing a biologic or a biosimilar medicine to market - compared to generics - render the pricing policies applied for generics (and the following price erosion) unrealistic or unsustainable and do not lead to competitive off-patent

biologics market. In your country / region, how effective is the pricing environment in providing a sustainable environment for off-patent biologics? Please provide additional comments in the box below

- Entirely ineffective  
(there is no difference at the national level between off-patent biologics compared to generic chemical entities in terms of pricing policies)
- Little effectiveness  
(off-patent biologics are subjected to restrictive pricing policies, such as price caps, yet these are higher compared to generic medicines)
- Partially effective  
(off-patent biologics are subjected to significantly less restrictive pricing policies compared to generic chemical entities)
- Highly effective  
(prices of off-patent biologics are set at a level that stimulates competition)
- Comments:

11. In your country / region, does the pricing environment distinguish between off-patent biologics and innovative (on-patent) biologic products? Please provide any comments you may have on the result of this in the comments box below

- No  
(prices of innovative biologic products are set by comparison to biosimilars (e.g. therapeutic group reference pricing))
- Yes  
(price setting for innovative biologic products is *not* influenced by the prices and price setting of off-patent biologics)
- Don't know
- Comments:

12. In your opinion, do the pricing policies for both new, innovative medicines and off-patent biologic medicines in your country / region have a negative effect on the sustainability of the European market (including the biopharmaceutical industry and availability of innovative biologic medicines)?

- Yes (please describe the impact in the comments box below)
- No (please explain why not in the comments box below)



- Comments:

### **Procurement**

13. In your opinion, do any of the factors described below contribute to sustainable tendering of off-patent biologics?

- multi-winner tenders (as opposed to a “winner takes all” tenders)
- tenders that accounts for a range of relevant factors in addition to price (such as quality of products, ability to supply, etc.)
- the frequency of tenders
- the scope of tender (i.e. by limiting the scope of tender to off-patent products within the same ATC-4/3 class)
- all of the above
- other (please specify):

### **Pharmacovigilance**

14. Pharmacovigilance systems are used to monitor and evaluate Adverse Drug Reactions (ADRs) from the use of all biologic medicines. How effectively is the need for such systems communicated and understood by your stakeholder group/in your country / region? Please provide additional detail in the comments box below if the options below do not fully reflect your views

- Lacking (limited access to information)
- Basic (information provided is limited in scope and/or often too technical and/or difficult to access)
- High (information is provided but often too technical)
- Excellent (high level of information that is easy to access and easy for non-technical experts to understand)

Comments:

15. International Non-proprietary Name (INN) prescribing for biologic medicines may potentially hinder good pharmacovigilance practice if products share the same INN and the trade name is not given in the ADR report. In your view, are the reasons for this well understood in your country / region / stakeholder peer group?

- No, this is not well understood
- Yes, this is well understood

- Comments:

### **Transparency and Information**

16. How would you describe the scope and level of access to reliable, up-to-date information for healthcare professionals and patients in your country / region about off-patent biologics? Please provide additional views in the comments section below.

- Lacking  
(healthcare professionals have very limited access to information and only for some medicines)
- Basic  
(information provided by national authorities is dated and/or limited in scope)
- High  
(information is available on a product basis yet often lacks comparative data)
- Excellent  
(information, including on differences between products, is fully transparent and made available by national authorities)

Comments:

17. Are there any topics that have been raised in the course of this survey that you believe could warrant further work in terms of producing information guides for stakeholders?

- No
- Yes (please specify):

# Endnotes

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- <sup>1</sup> See: <http://ec.europa.eu/DocsRoom/documents/26643>;  
<http://ec.europa.eu/DocsRoom/documents/22924>.
- <sup>2</sup> OECDstat, Total pharmaceutical sales per capita / US\$ purchasing power parity, 2015 or latest available year; Pugatch Consilium analysis.
- <sup>3</sup> EvaluatePharma, European Pharma Market Outlook to 2022, October 2017,  
<http://info.evaluategroup.com/rs/607-YGS-364/images/Evaluate-European-Drug-Forecasts-Infographic-IG.pdf>.
- <sup>4</sup> See for example : Deloitte, Winning with biosimilars : Opportunities in global markets, p. 1 ; QuintilesIMS Institute, Outlook for Global Medicines through 2021 : Balancing Cost and Value, December 2016, p. 38.
- <sup>5</sup> PhRMA, Medicines in Development: Biologics, 2013 Report, <http://phrma-docs.phrma.org/sites/default/files/pdf/biologics2013.pdf>; Caroll, J. “Tufts: Big Pharma bets its future on a swelling pipeline of biologics”, 18/11/2013, Fierce Biotech, <https://www.fiercebiotech.com/r-d/tufts-big-pharma-bets-its-future-on-a-swelling-pipeline-of-biologics>.
- <sup>6</sup> In-Pharma Technologist, Novartis to assess biologics with micro-sugar-needle delivery tech, 27.5.2015, <http://www.in-pharmatechnologist.com/Drug-Delivery/Novartis-to-assess-biologics-with-micro-sugar-needle-delivery-tech>.
- <sup>7</sup> EFPIA (2018). The Pharmaceutical Industry in Figures: Key Data, p. 3.
- <sup>8</sup> All clinical trials with ‘biologic’ within the intervention rubric registered by March 2019. Source: World Health Organization, International Clinical Trials Registry portal; analysis: Pugatch Consilium.
- <sup>9</sup> All clinical trials with ‘biologic’ within the intervention rubric, based on date of registration, from January 1<sup>st</sup> to December 31<sup>st</sup> of 2010 and of 2015. Source: World Health Organization, International Clinical Trials Registry portal (accessed March 2019); analysis: Pugatch Consilium.
- <sup>10</sup> Biosimilars is the most common reference to follow-on products for biologic medicines, yet some countries/organizations use different definitions. For example, biosimilars are referred to as “Subsequent Entry Biologics” in Canada, and as “Similar Biotherapeutic Products” by the World Health Organization.
- <sup>11</sup> IMS (2017). The Impact of Biosimilar Competition in Europe.
- <sup>12</sup> EMA, Applications for new human medicines under evaluation by the Committee for Medicinal Products for Human Use, February 2019, EMA/115443/2019-corr, 12 February 2019; IMS (2017). The Impact of Biosimilar Competition in Europe, p.28
- <sup>13</sup> European Medicines Agency, European Commission, Biosimilars in the EU: Information guide for healthcare professionals, April 2017, p. 29,  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Leaflet/2017/05/WC500226648.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdf).
- <sup>14</sup> Belloni, A., Morgan D. and Paris V. (2016). “Pharmaceutical Expenditure And Policies: Past Trends And Future Challenges”, p.38, OECD Health Working Papers, No. 87, OECD Publishing, Paris.
- <sup>15</sup> In 2014 the NOR-SWITCH clinical trial was initiated (with funding from the Norwegian Ministry of Health and Care Services) with the purpose of evaluating the clinical impact of switching stable patients from the treatment with the innovative biologic infliximab to its biosimilar product, across the six inflammatory diseases for which infliximab is approved. The study results, published in May 2017, showed that switching to the biosimilar did not result in inferior treatment compared to the originator, on an aggregate basis. The NOR-SWITCH study provides important new information for physicians and patients in the use of biosimilars. Yet it is worth noting the study’s limitations from a policy perspective. Most importantly, the study only examined the clinical implications of switching from the originator biologic to a specific biosimilar product. Thus, the study’s conclusions cannot be applied to multiple switches, for instance where a given hospital tender switches the originator biologic with a biosimilar, and a later tender switches from the first biosimilar to a second biosimilar. Furthermore, the measured risks from switching in specific disease groups, such as Crohn’s disease, were considerably higher compared to other disease groups at 14.3%, yet the aggregate results were not affected by these differences, due to a

- relatively high margin of 15%. See Jørgensen, K. K. et al. (2017). “Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial”, *The Lancet*, Vol. 389, No. 10086, pp. 2304-2316; Husereau, D., Feagan, B. and Selya-Hammer, C. (2018). “Policy Options for Infliximab Biosimilars in Inflammatory Bowel Disease Given Emerging Evidence for Switching”, *Applied Health Economics and Health Policy*, First Online: 06 February 2018; and AR Welch (2016) “The Norwegian Biosimilar Phenomenon: From Biosimilar To "Biogeneric"”, *Biosimilar Development*, July 26 2016.
- 16 Correct as of March 2019.
- 17 European Commission, Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs, Multi-stakeholder Workshop on Biosimilar Medicinal Products, Brussels, 5 May 2017, [http://ec.europa.eu/growth/content/third-stakeholder-conference-biosimilar-medicines-0\\_en](http://ec.europa.eu/growth/content/third-stakeholder-conference-biosimilar-medicines-0_en).
- 18 See for example a comprehensive analysis of the public procurement frameworks in a sample of 14 European countries: Bird & Bird, Public procurement of medicinal products, Common legislation but diverging implementation approaches throughout the EU – While Paper, Martens M. & Carbonnelle N. (Eds.), <https://www.twobirds.com/~media/pdfs/white-papers/public-procurement-of-medicinal-products.pdf>.
- 19 See: EuropaBio, White Paper on Public Procurement of Biological Medicines, June 2015, [https://www.europabio.org/sites/default/files/europabio\\_white\\_paper\\_on\\_public\\_procurement\\_of\\_biological\\_medicines\\_final.pdf](https://www.europabio.org/sites/default/files/europabio_white_paper_on_public_procurement_of_biological_medicines_final.pdf); Bird & Bird, Public procurement of medicinal products...
- 20 AR Welch (2016) “The Norwegian Biosimilar Phenomenon: From Biosimilar To "Biogeneric"”, *Biosimilar Development*, July 26 2016; GaBI Journal, Biosimilar etanercept offered at 47% discount in Norway (Editorial), 5.2.2016, <http://www.gabionline.net/Biosimilars/General/Biosimilar-etanercept-offered-at-47-discount-in-Norway>.
- 21 Roediger A., Freischem B., Reiland JB. (2017). “What pricing and reimbursement policies to use for off-patent biologicals in Europe? – results from the second EBE biological medicines policy survey”, *GaBI Journal*, Vol. 6, Issue 2, pp. 61-78.
- 22 European Commission, Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs, Multi-stakeholder Workshop on Biosimilar Medicinal Products, Brussels, 5 May 2017, [http://ec.europa.eu/growth/content/third-stakeholder-conference-biosimilar-medicines-0\\_en](http://ec.europa.eu/growth/content/third-stakeholder-conference-biosimilar-medicines-0_en).
- 23 See for example: Medicines for Europe – Biosimilar Medicines Group, Market Review – European Biosimilar Medicines Markets 2017, <http://www.medicinesforeurope.com/wp-content/uploads/2017/09/Market-Review-biosimilar-medicines-market-2017.pdf>; Roediger A., Freischem B., Reiland JB. (2017). “What pricing and reimbursement policies to use for off-patent biologicals in Europe? – results from the second EBE biological medicines policy survey”, *GaBI Journal*, Vol. 6, Issue 2, pp. 61-78. See also: Ireland Department of Health, National Biosimilar Medicines Policy, Public Consultation Paper, August 2017, <https://health.gov.ie/wp-content/uploads/2017/08/National-Biosimilar-Medicines-Policy-Consultation-Paper-2017.pdf>.
- 24 Rémuzat C. et al. (2017). “Supply-side and demand-side policies for biosimilars: an overview in 10 European member states”, *Journal of Market Access & Health Policy*, Vol. 5, <https://pdfs.semanticscholar.org/4f1f/1b687db6b879ccb6f48ab4ea4f06badf2203.pdf>.
- 25 NHS England, Commissioning framework for biological medicines (including biosimilar medicines), 12.9.2017, <https://www.england.nhs.uk/wp-content/uploads/2017/09/biosimilar-medicines-commissioning-framework.pdf>
- 26 Moorkens, E. et al. (2017). “Policies for biosimilar uptake in Europe: An overview”, *PLOS one*, Vol. 12, Issue 12.
- 27 See: EFPIA Policy Principles for Off-Patent Biologic Medicines in Europe, 28.9.2015, <https://www.efpia.eu/media/25877/efpia-principles-for-off-patent-biologic-medicines-in-europe-30092015.pdf>.
- 28 See: Larkin, H. et al. (2017). “Pharmacy-mediated substitution of biosimilars – a global survey benchmarking country substitution policies”, *Generics and Biosimilars Initiative Journal*, Vol. 6, Issue 4.
- 29 The principles guiding the assessment of the policy environment in the analysis were created by the LoE Biologics Working Group within the European Federation of Pharmaceutical Industries and Associations (EFPIA), which can be found here: <https://www.efpia.eu/media/25877/efpia-principles-for-off-patent-biologic-medicines-in-europe-30092015.pdf>.

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<sup>30</sup> Pugatch Consilium (2014). Developing a Culture of pharmacovigilance: Towards International Best Practices, p. 26.