Biosimilars: A global roadmap for policy sustainability

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Abbreviations

AAM	Association for Accessible Medicines
AE	adverse event
ANVISA	Agência Nacional de Vigilância Sanitária [*Brazilian regulatory agency*]
ASMR	amélioration du service médical rendu [*improvement of medical benefit*]
AU / AUS	Australia
BE / BEL	Belgium
BPD	Biosimilar Product Development
BR / BRA	Brazil
CA / CAN	Canada
CADTH	Canadian Agency for Drugs and Technologies in Health
CCG	Clinical Commissioning Groups
CEIS	Centre for Economic and International Studies
CEO	Chief Executive Officer
CH / CHE	Switzerland
CHF	Swiss francs
CINVESTAV	Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional [*centre of research and advanced studies from the National Polytechnic Institute*]
COFEPRIS	Comisión Federal para la Protección contra Riesgos Sanitarios (Federal Committee for Protection From Sanitary Risks)
COVID	COVID-19, Coronavirus
pCPA	pan-Canadian Pharmaceutical Alliance
CRA	Charles River Associates
CT	Commission de la Transparence (Transparency Committee)
DE / DEU	Germany
DNA	deoxyribonucleic acid
DPC	Diagnostic Procedure Combination
EEHTA	Economic Evaluation and HTA
EMA	European Medicines Agency
ES / ESP	Spain
EU	European Union
FDA	Food and Drug Administration
FR / FRA	France
FTA	free-trade agreements
GB/GBR	Great Britain

GDPR	General Data Protection Regulation
GEK	Gmuender Ersatzkasse [*statutory sick fund*]
GKV	Gesetzliche Krankenversicherung-Spitzenverband [*statutory health insurance*]
GSAV	Gesetz für mehr Sicherheit in der Arzneimittelversorgung [*law for more safety in the supply of medicines*]
HAS	Haute Autorité de Santé [*high authority of health*]
HCP	healthcare professional
HPV	Human papillomavirus
HSA	health sciences authorities
HTA	health technology assessment
ICS	integrated care systems
IGBA	International Generic and Biosimilar Medicines Association
INESSS	Institut national d'excellence en santé et en services sociaux [*national institute of health and social services excellence*]
INN	international non-proprietary name
IP	intellectual property
IT / ITA	Italy
IV	intravenous
JP / JPN	Japan
KBV	Kassenärztlichen Bundesvereinigung [*association of statutory health insurance physicians*]
KSA / SAU	Kingdom of Saudi Arabia
KU	Katholieke Universiteit [*Catholic university*]
KV	Krankenversicherung [*statutory health insurance system*]
LoE	loss of exclusivity
LMI	Legemiddelindustrien [*pharmaceutical industry association*]
MEX / MX	Mexico
MHRA	Medicines and Healthcare products Regulatory Agency
MNGHA	Saudi Ministry of National Guard Health Affairs
MOHAP	Ministry of Health and Prevention
NICE	National Institute for Health and Care Excellence
NL / NLD	Netherlands
NMS	non-medical switching
NO / NOR	Norway
PAG	patient advocacy group
PBAC	Pharmaceutical Benefits Advisory Committee

PDP	product development partnership
PUCRS	Pontifícia Universidade Católica do Rio Grande do Sul [Pontifical Catholic University of Rio Grande do Sul]
Q4	fourth quarter
R&D	research and development
RD	rare disease
RWE	real world evidence
SAU	Saudi Arabia
SC	subcutaneous
SL	specialities list
SPC	supplementary protection certificate
TA	therapeutic area
TGA	Therapeutic Goods Administration
UAE	United Arab Emirates
UDIBI	Unidad de Desarrollo e Investigación de Bioterapéuticos [*biotherapeutic research and development unit*]
UDIMEB	Unidad de Investigación, Desarrollo e Innovación Meédica y Biotecnológica [*medical and biotechnological research, development and innovation unit*]
UFMG	Universidade federal Minas Gerais [*Federal University of Minas Gerais*]
UN	United Nations
US / USA	United States of America
USPTO	US Patent and Trademark Office
USTR	US Trade Representative
VR	verification route
WHO	World Health Organization

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Executive summary

Introduction

A biosimilar is a biological medicine which has been shown not to have any clinically meaningful differences from the originator medicine in terms of quality, safety and efficacy. The manufacture of biologics from living organisms subjects them to various modifications intrinsic to biology and nature. The first regulatory pathway for biosimilars to be commercialised was established in 2005 in Europe and the first European biosimilar approved in 2006.[1] Since then, the European Medicines Agency (EMA) has approved 55 biosimilars (with 65 marketing authorisation decisions) for 16 different reference products. In the US, a biosimilars pathway was created in 2010, and the first US biosimilar was approved in 2015. As of April 2022, the US Food and Drug Administration (FDA) has approved 30 biosimilars for 10 reference products.[2] Canada has 46 biosimilars approved for 14 different reference products.[3] Other countries also have official biosimilar guidelines, including Japan[4] and Saudi Arabia.[5] The biosimilar pipeline in different countries will continue to evolve as biologics in new therapeutic areas approach patent expiry. Biologics expected to lose exclusivity in the EU and the US in the next five years include golimumab for musculoskeletal disorders in 2024 and belimumab for musculoskeletal and haematological disorders in 2026. Although the number of biologics facing loss of exclusivity (LoE) is continuing to grow, it cannot be expected that there will necessarily be biosimilars manufactured for all of these biologic products (especially within orphan indications).[6] Furthermore, not all biosimilars approved by the EMA are available in the majority of European countries, reflecting potential sustainability limitations across existing policy frameworks. It will be important that adaptations to existing policy frameworks are managed such that they create a sustainable environment for newer biosimilar products in the long term.

Given the potential of biosimilars to help control healthcare expenses, it is not surprising that there is a growing literature on the long-term sustainability of markets for biosimilars. A number of existing studies have sought consensus on how to define sustainability.[7,8] We have chosen to use the definition developed by Vulto et al. (2020),[9] which defines a sustainable biosimilar market as an environment where *"all stakeholders, including patients, benefit from appropriate and reliable access to biological therapies. Competition leads to a long-term predictable price level, without compromising quality, while delivering savings that may be reinvested."*

The need to understand how policy can improve sustainability of the biosimilar market is clear:

- **Variation in biosimilar uptake:** As of 2021, biosimilars capture 10% of the total biologic pool in Europe, 7% of this share having been achieved in the last five years, demonstrating their growth.[10] Biosimilar uptake in countries such as Japan and the US has been significantly slower, although this can vary widely across products. This suggests that the potential for biosimilars has not been completely realised.

- **The issue of market confidence persists:** Misconceptions around the safety of biosimilars as non-identical molecular entities result in mistrust among physicians and even patients that can affect usage.[11]

- **The effectiveness of biosimilar practices and policy is questioned:** Policies in some markets have led to debates between payers/governments and manufacturers. For example, the lack of specific pricing mechanisms accounting for biosimilar differences in Brazil can result in biosimilars being priced similarly to generics, attracting industry criticism. As a result, there are ongoing negotiations with governments focused on introducing biosimilar pricing reforms with biosimilar-specific considerations.[12]

- **Policymakers continue to apply policy designed for generic small molecules inappropriately to biosimilars:** Many biosimilar policies draw on the experience of the small molecule generic market. Moreover, many markets do not differentiate between these two very different products. There is a concern that applying small molecule policies to the biosimilar market is unsustainable; for example, when markets are overly dependent on a small number of suppliers, this may increase the risk of supply shortages.

This paper addresses three key questions:

(1) Can we define an 'ideal' biosimilar policy toolkit that will ensure long-term sustainability that is applicable across different market circumstances, across different types of biosimilars?

(2) To what extent does existing biosimilar policy across a global selection of countries promote a long-term sustainable environment benefitting all stakeholders?

(3) Can we provide countries with tangible and actionable recommendations for meaningful improvements to the biosimilar sector applicable to different types of biosimilars?

To tackle these three questions, we undertook a literature review, which was followed by external consultation with country experts. A long list of biosimilar policies across nine key biosimilar policy areas (**Table 1**), developed on a basis of secondary research, was validated by experts. Two international advisory board meetings, made up of these experts, were held in order to develop actionable policy recommendations regarding the most appropriate policies to ensure a sustainable biosimilar environment in the long term. This evaluated the pros and cons of each of the policies regarding their contribution to long-term sustainability for biosimilars, drawing on real-life experience. We then were able to assign 'sustainability ratings' for each policy area for 17 countries: Australia, Belgium, Brazil, Canada, France, Germany, Italy, Japan, Mexico, Netherlands, Norway, Saudi Arabia, Spain, Switzerland, United Arab Emirates, the UK and the US.

Table 1: Biosimilar policies evaluated across nine key policy areas

	**Manufacturing and R&D**	• Local manufacturing incentives • Manufacturing exemption waivers
	**Regulatory approval**	• Streamlined evidence requirements • Simplified regulatory approval through international collaboration • Regulatory support for biosimilar submission
	**Health technology assessment**	• Exemption from HTA requirements • Simplified assessments
	**Pricing and reimbursement**	• Automatic reimbursement following regulatory approval • Full coverage or partial coverage • Exclusionary contracts • Mandatory discounts for biosimilars and/or originators • Tiered price discounts for subsequent biosimilar products • Progressive price discounts, applied over time • Reference pricing (both internally and internationally)
	**Contracting**	• Direct contracting with providers • Tendering procedures
	**Biosimilar education and understanding**	• Healthcare professional (HCP) and pharmacist educational programs • Patient educational programs
	**Prescribing**	• Clinical recommendations for prescriber-initiated prescription of biosimilars • Mandated switching • Prescription quotas for volume of biosimilar prescription • Financial incentives linked to volume of biosimilar prescription • Financial penalties linked to volume of biosimilar prescription • International non-proprietary name (INN) prescribing
	**Dispensing**	• Automatic substitution • Regressive retailer markups • Reduced patient co-payments
	**Monitoring**	• Post-commercialisation pharmacovigilance measures • Transparency in usage reporting • Monitoring of product ability to supply

Source: CRA

1 – Can we define an 'ideal' biosimilar policy toolkit that will ensure long-term sustainability?

Based on secondary research, there are some areas where there is a clear consensus on 'ideal' sustainable biosimilar policies. For example, policies ensuring safe and high-quality biosimilars are consistently considered sustainable (e.g. post-commercialisation pharmacovigilance measures – although, even here, countries recognised that this went beyond biosimilars and would take years to fully implement in some markets). Similarly, policies supporting mitigation of frequently held biosimilar misconceptions were also considered prerequisites for sustainability (e.g. multi-stakeholder educational programs led by patient advocacy groups and/or governmental organisations). However, there are also many instances where seemingly similar policies are being applied in different markets, but they are seen as sustainable in some and unsustainable in others. For example, use of healthcare professional

(HCP) incentives in the UK to drive initial uptake of biosimilars is seen as a means of improving sustainability. However, such measures have been highlighted as unsustainable in Latin America countries like Mexico, given the lack of transparency around them and the perception that this inappropriately influences physician behaviour. In other markets, incentives are seen as a temporary policy to boost biosimilar initial adoption that should slowly be removed as the community gains knowledge and experience with biosimilars. Similarly, the sustainability of a given policy can vary depending on the type of biologic used for treatment. For example, incentivising switching to best alternative treatments can be seen as a positive regulation to increase biosimilar uptake in areas like oncology, where the focus is on initiation of new patients, as treatment is of a shorter duration. However, there are different concerns for chronic diseases where patients will be on treatment for an extended duration and patients and physicians may have preferences for a particular manufacturer and hence, there are different considerations regarding any proposal to switch.

More generally, the sustainability of many policies depends on the nature of the healthcare system, the way that the biosimilar is prescribed or dispensed and the history and experience with biosimilar use. A clear example of the latter are policies promoting the use of 'best value biologics', which are unlikely to result in a sustainable environment if the relevant stakeholders (e.g. physicians, pharmacists and patients) have different views on how to define biosimilar value. Some argue that the concept of best value biologics places biosimilars and their innovative counterparts on the same level and allows for a fair competitive baseline. Furthermore, it promotes the use of biologics (either biosimilar or originator) from the perspective of their specific added value in a given situation, without establishing policies to restrict the use of one or the other. However, it also has implication beyond a biologic and its biosimilar, so can be perceived as excessively complicated. This indicates that while there are some general 'biosimilar policy sustainability principles', the ultimate 'ideal policy environment' will vary from country to country and with the type of biologic losing protection. This is particularly the case for biosimilar policies relating to 'pricing and reimbursement', 'contracting' and 'dispensing'. Therefore, this study has instead defined a set of 'ideal policy sustainability elements' that should underpin biosimilar policy development over time, as biosimilars become more established (**Figure 1**).

Key findings

- Biosimilar policy environments cannot be considered in isolation, and therefore the 'ideal biosimilar policies' vary across countries depending on:
    - The country's level of experience with current biosimilars
    - The country's existing pharmaceutical policies, including pricing and reimbursement processes, contracting approaches
    - The type of product under consideration
- Across the nine areas, we find that policies which do not differentiate between biosimilars and generics are generally more likely to be unsustainable. There is a need for a specific set of biosimilar policies.
- Although the sustainability provided by a specific policy can differ between countries, and there exist few policies that are universally sustainable, we can define a set of 'ideal policy sustainability principles, or elements' to govern the development of biosimilar policy.
- Biosimilar policy should be developed over time (**Figure 1**):
    - Initially, biosimilar policies should focus on ensuring the safety and quality of biosimilars, safeguarding healthy levels of supply and delivering a level of cost savings.

- As biosimilars become more established, policies should seek to optimise uptake, and combat any misconceptions regarding biosimilars.
- Ultimately, countries should aim for biosimilar policies that encourage competition, broadening treatment options and ensuring a sustainably functioning biosimilar market.

Figure 1: A 'sustainability scorecard' comprising the multi-stakeholder benefits to be realised in a sustainable biosimilar policy environment

Sustainable biosimilar policies should:

INITIALLY AND AT A MINIMUM			
1	**Ensure safe and high-quality medicines**	*Policies should ensure high quality medicines with robust and transparent evaluations, and monitoring systems to give confidence to patients and healthcare professionals*	⊕
2	**Facilitate cost savings for healthcare providers**	*Policies should facilitate cost savings for healthcare systems to ensure long-term budget sustainability*	🐷
3	**Ensure healthy levels of supply**	*Policies should minimise risks of supply shortage and ensure there is sufficient demand for biosimilars to avoid wastage or incentives to sell at unsustainable prices*	👥
4	**Maintain incentives for continued biologic research & innovation**	*Policies should ensure that sufficient incentives for manufacturers remain in place to ensure that there is continued research to launch new biologic products*	🏭
AS BIOSIMILAR POLICY MATURES			
5	**Mitigate against biosimilar misconceptions**	*Policies should seek to address common concerns surrounding biosimilars to optimise uptake and ensure informed decision-making across all stakeholders*	👥
6	**Facilitate efficient & streamlined patient access**	*Policies should encourage streamlined access procedures without compromising safety to ensure eligible patients have unrestricted access to life-saving medicines*	⊕
7	**Encourage multi-stakeholder decision-making**	*Policies should ensure that all key stakeholders (payers, physicians, pharmacists and patients) play a role within decision-making to optimise multi-stakeholder benefits*	👥
FINALLY TO ENSURE LONG-TERM SUSTAINABILITY			
8	**Facilitate sustainable levels of biosimilar competition**	*Policies should ensure that market competition is incentivised to ensure long-term predictable price levels, while delivering savings that may be reinvested*	👥
9	**Increase prescribing options for patients & healthcare professionals**	*Policies should encourage availability of multiple prescribing options to maintain flexibility in treatment regimens to address individualised patient needs*	⊕ 🩺
10	**Maintain predictable market functioning**	*Policies should ensure that market volatility is kept to a minimum and that policies are transparent to maintain attractivity of the market*	🏭

BENEFITS FOR: 👥 = All stakeholders ⊕ = Patients 🩺 = Healthcare Professionals 🐷 = Payers / Budget Holders 🏭 = Biosimilar & Originator Manufacturers

Source: CRA

2 – To what extent does existing biosimilar policy across a global selection of countries promote a long-term sustainable environment?

Across each of the nine biosimilar policy areas defined, the policies in each country have been assessed and rated according to the level of sustainability of the current biosimilar policy environment (**Table 2**). We find there is room for improvement in all 17 countries in at least one of the nine areas that determine sustainability. European countries, which tend to have more experience with biosimilar products and more developed policy, generally have higher long-term sustainability scores. Key successes include: high levels of uptake driven by acceptance and trust from physicians and patients and efficient access due to streamlined manufacturing and regulatory approaches, and exemption from health technology assessment (HTA). Conversely, the experience outside of Europe is much more mixed. In some markets there are a series of challenges reducing long-term sustainability of biosimilars. Key challenges include minimal differentiation between biosimilar and generic policies, decreased traceability, and high levels of mistrust in biosimilars based on miseducation or limited transparency and clarity in approval and regulatory processes within the market.

However, the assessment is often more nuanced, varying by patient setting and type of product. It is often the case that policies that are sustainable for biosimilars dispensed in the inpatient setting are unsustainable when considering outpatient medicines. For example, Japanese prescribing policy is significantly more sustainable in the inpatient setting given the role of indirect incentives, which promote biosimilar use in a manner not seen in the outpatient setting.

Key findings

- Generally, current approaches to biosimilar manufacturing and R&D incentives and exemptions to the application of HTA to biosimilars are sustainable.
- Across countries there is room for improvement with regards to biosimilar contracting approaches and with ensuring biosimilar education and understanding.
- European markets, which tend to have more experience with biosimilar products and more developed policy, generally have higher long-term sustainability ratings. Key successes include:
    - High levels of uptake driven by acceptance and trust from physicians and patients
    - Efficient access due to streamlined manufacturing, regulatory and HTA approaches
- Conversely, markets with more limited experience with biosimilars (e.g. Saudi Arabia, Japan) have more limited biosimilar policy, resulting in higher risks to long-term sustainability of the market. Key challenges include:
    - No differentiation between biosimilar and generic policies
    - Decreased traceability in pharmacovigilance systems
    - High levels of mistrust in biosimilars based on miseducation or limited transparency in regulatory processes within the market
- Given the differences in US markets, it is unsurprising there are some different challenges and policy solutions to promote biosimilar entry (e.g., the first biosimilar product deemed interchangeable is entitled to exclusive interchangeability for one year).

The summary of the sustainability ratings across markets in **Table 2** also allows for identification of best practice examples across each policy area. Some of these examples have been summarised in **Table 3.**

Table 2: Sustainability ratings across countries in scope for each policy area

Policy Area	AUS	BEL	BRA	CAN	FRA	DEU	GBR	ITA	JPN	MEX	NLD	NOR	SAU	ESP	CHE	UAE	USA
Manufacturing and R&D	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★
Regulatory approval	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★
Health technology assessment	★	★	Priv. & Pub. ★ / Pub. HC ★	★	★	★	★	★	★	★	★	★	★	★	★	★	★
Pricing and reimbursement	★	★	★	Pub. ★ / Priv. ★	★	★	★	★	★	★	★	Inp. ★ / Out. ★	★	★	★	★	Pub. ★ / Com. ★
Contracting	★	Inp. ★ / Out. ★	Pub. ★ / Priv. ★	Pub. ★ / Priv. ★	★	★	★	★	N/A	★	Inp. ★ / Out. ★	Inp. ★ / Out. ★	★	Inp. ★ / Out. ★	★	★	Pub. ★ / Com. ★
Biosimilar education and understanding	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★
Prescribing	★	Inp. ★ / Out. ★	★	Pub. ★ / Priv. ★	★	★	★	★	Inp. ★ / Out. ★	★	★	★	★	★	★	★	Pub. ★ / Out. ★
Dispensing	★	★	★	★	★	★	★	★	★	★	★	★	N/A	Inp. ★ / Out. ★	★	★	Pub. ★ / Com. ★
Monitoring	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★

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

Note: Further rating detail can be found in Table 7. ***Com.*** *– Commercial plans;* ***HC.*** *– High-cost biosimilars*; **Inp. –** Inpatient; **Out. –** Outpatient; ***Pub.*** *– Public sector;* ***Priv.*** *– Private sector*

Table 3: Examples of best practices by policy area

Policy area		Best policy examples
	Manufacturing and R&D	European Union (EU) legislation streamlines preparation for biosimilar entry prior to the loss of exclusivity, enabling rapid launch post patent-expiry.
	Regulatory approval	The Medicines and Healthcare products Regulatory Agency (MHRA) in the UK no longer requires clinical comparability studies for all products given latest research regarding their lack of additional value to regulatory assessments.
	Health technology assessment	Many countries like the Netherlands waive the need for biosimilar HTA provided the indications included in the biosimilar label are the same as the originator.
	Pricing and reimbursement	In the Netherlands, biosimilars can launch at the same price as their originators, encouraging entry, then competition is used to promote cost savings. Moreover, pricing and reimbursement are applied as a single process, ensuring biosimilars' automatic reimbursement.
	Contracting	In the UK, long-term supply plurality has been provided for adalimumab biosimilars, given that the market has been divided into 11 hospital groups. These groups are allocated a specific biosimilar or originator product, with degressive market shares for those products dependent on the competitiveness of the tender price they have offered.
	Biosimilar education and understanding	European educational campaigns spearheaded by the EMA are often supplemented with national-level education in European countries, for example at hospital/provider level to ensure holistic understanding of value across the country.
	Prescribing	In the UK, non-mandatory prescribing quotas still serve as an incentive for healthcare professionals. Moreover, gain-sharing mechanisms implemented at some local Clinical Commissioning Groups (CCGs) have ensured that savings driven by biosimilars are reinvested in healthcare systems, improving their perception.
	Dispensing	In France, current dispensing policies in place do not undermine physicians' autonomy but instead promote shared decision-making also with pharmacists. Moreover, substitution policies do not interfere with robust tracing systems used for safety monitoring, and patients can have their voices heard without any misconceptions around biosimilar value being able to influence dispensing decisions.
	Monitoring	US has leading pharmacovigilance systems ensuring full transparency in monitoring, for example by assigning a suffix to the biosimilar name in regulatory documents to distinguish different biosimilars.

Source: CRA analysis

3 – Can we provide countries with tangible and actionable recommendations for meaningful improvements to the biosimilar sector that consider their specific policy market archetype and different types of biosimilars?

Outputs from the two advisory board meetings were synthesised into a series of policy recommendations across each of the nine policy areas (e.g. manufacturing, regulatory approval, HTA, etc.). While the ideal set of biosimilar policies may vary from country to country, there are common themes and recommendations across each of the nine policy areas that should be followed when developing biosimilar policy to ensure a sustainable environment in the long term (**Table 4**). Additional considerations relating to country-specific archetypes have been listed as well.

Table 4: Biosimilar policy recommendations across the nine key policy areas, including specific nuances based on country characteristics and biosimilar archetypes

Policy Area		Recommendations
	Manufacturing and R&D	Biosimilar manufacturing policies should ensure the highest standard of quality and allow for prompt submission to regulatory authorities upon originator LoE while respecting intellectual property. • Countries which have previously faced supply issues (e.g. Brazil) could provide incentives for sustainable manufacturing to reduce supply shortages, and boost national economies, provided competition is encouraged, and as long as they do not penalise biosimilars manufactured in other countries, so as not to disrupt global supply chains.
	Regulatory approval	Biosimilar regulatory processes should seek efficiencies to accelerate access timelines while maintaining robust processes that will ensure safety of biosimilars. Regulators should consider the biosimilar type, number of biosimilars already available and the submitted indication to determine required evidence for submission. • Regulatory processes should be consistent and transparent across global markets, facilitating countries with smaller regulatory agencies (e.g. Saudi Arabia or the United Arab Emirates (UAE)) to leverage experience and real-world evidence generated by those with greater biosimilar presence. • Regulatory processes should ensure quality and safety but still have clear and transparent requirements. Where possible, regulatory authorities should provide additional support during regulatory processes, following the example of the US FDA, to facilitate their submission and accelerate biosimilar approval. • However, the evidence requirements should reflect the disease and associated care pathway, this may allow evidence to vary between some chronic diseases (e.g., rheumatoid arthritis), where patients stay on treatment for a significant period of time, as compared to acute oncologic treatments for example.
	Health technology assessment	Conventional HTAs should be unnecessary given the similarity of biosimilars. However, it might be warranted in cases where: the originator biologic is not reimbursed, biosimilars offer a different route of administration than the originator, or biosimilars are considered to provide added-value services compared to the originator.[13] If used, HTA should not delay access and should provide tangible benefits to the assessed product, such as ability to differentiate within tenders.

		• In countries where originator biologics are not consistently reimbursed (e.g. Brazil, Mexico), biosimilars will need to be more frequently subjected to HTAs to evaluate their benefits. HTA bodies should seek temporary reimbursement practices to avoid access delays, although accommodations may be required for patients (e.g. 'grandfathering') if the HTA is subsequently negative.
	**Pricing and reimbursement**	Policies should distinguish between biosimilars and small molecule generics. Depending on the policy landscape, either mandatory price controls or dynamic price controls (reliant on market competition) can be considered sustainable provided there are safeguards to ensure competition and sustainable price levels. • Where mandatory discounts are applied (e.g. France, Spain and Italy), policies should recognise that a one-size-fits-all approach for biosimilars may not be sustainable in the long term and consider differences across therapeutic areas, the number of competitors and population size. • Where dynamic price controls are applied (e.g. the Netherlands), policies should safeguard multiple market participants to ensure sufficient levels of competition are maintained. • This will need to be refined in the future as more orphan biologics face biosimilar competition. These are associated with smaller patient volumes and potentially fewer competitors, which may necessitate refinement of rare disease (RD) pricing policy.
	**Contracting**	Awarding of contracts (whether through direct negotiation or tendering) should include input from multiple stakeholders and allow for factors beyond price (e.g. quality and value) to contribute to decision-making. Policies should also facilitate competition between multiple suppliers for a country to minimise risk of supply shortages. • Where tendering processes are the primary procurement method (e.g. Spain and the UK), award criteria should extend beyond price and consider elements of value (e.g. added services) and ability to supply. • Where direct contracting is the main procurement method (e.g. US and Belgium outpatient), exclusionary contracts should be avoided, since this could result in limited biosimilar competition as a result of contracts with first-to-market products. • Contracts should be tailored to the type of product being procured. Where there is a goal to reduce potential treatment switching (e.g. between biosimilars with different routes of administration), products with longer treatment durations may be less suited to short-term tender contracts compared to those planned for acute treatment. • The smaller patient volumes for rare disease biosimilars may increase the importance of minimum volume guarantees in tenders.
	**Biosimilar education and understanding**	Biosimilar education is important for all key stakeholders (e.g. governments, budget holders, HCPs, pharmacists and patients) to ensure a holistic understanding of biosimilar value. The source of educational campaigns is critical to ensure trust in messaging, and peer-to-peer education is often an optimal educational method.

		• In countries where there is greater biosimilar uptake (e.g. the UK), the experience of physicians can be shared with physicians and patients in specialities newer to biosimilars. • In countries where there are persistent biosimilar misconceptions (e.g. Japan and Brazil), education of the most influential stakeholders (e.g. policymakers) should be a priority to ensure that policy supports uptake. • Education is important for all patients and HCPs but even more important for patients with chronic disease who might experience switches during their disease and require reassurance of biosimilars' efficacy/safety. Clear messaging from prescribing physicians and pharmacists about their safety and efficacy is particularly important.
	**Prescribing**	Use of the 'best value' biologic(s) should be encouraged, considering price, data on switching, prior treatment history, value added services, quality and supply. There is a role for multidisciplinary input to decision-making but with physicians ultimately responsible for ensuring the most appropriate biologic is prescribed for each individual patient. • Where there is widespread support for the use of best value biologics (e.g. Belgium, Germany), the need for long-term direct incentives should be assessed; with appropriate education, healthcare systems should indirectly encourage prescription of best value products, reducing need for formal incentives. • Where there is less consensus of biosimilar value (e.g. Japan), incentives can stimulate initial uptake but may be a temporary measure which is withdrawn as prescriber education and experience improves. • In countries where financial incentives to HCPs are seen as an unsustainable measure, due to lack of transparency (e.g. Mexico), indirect incentives could provide a more traceable system to still motivate biosimilar prescription (e.g. gain sharing).
	**Dispensing**	There is a debate regarding the role of substitution in many countries. Any decision should be based on multidisciplinary input to ensure the best outcomes for patients and best value for the healthcare system. It should be recognised that no 'one size fits all' approach will work while there variation in available switching data, setting of care (inpatient vs. outpatient) and individual therapies. • Financial incentives for pharmacists should not penalise prescription of biosimilars (e.g. through lower margins for lower-cost products) and ideally should be aligned to the incentives in place for prescribing physicians. • In markets where outpatient substitution is used (e.g. Brazil, Mexico), measures to minimise friction between different stakeholders (e.g. pharmacists and physicians) should be implemented, for example physician notification. • Chronic treatments can be more frequently dispensed in the outpatient setting compared to acute oncologic drug infusions; therefore, robust communication between physicians and pharmacists dispensing these products is especially relevant.

		• Oncology treatments in the inpatient setting require multidisciplinary decisions from a variety of experts to ensure optimal patient outcomes.
	**Monitoring**	Biosimilars should be subject to the same pharmacovigilance standards as all biologics. Any policies implemented that risk decreasing biosimilar traceability should be mitigated by additional pharmacovigilance measures. Furthermore, transparency into biosimilar supply and demand can ensure healthy levels of supply are maintained. • In those countries where pharmacovigilance systems are still developing, it is important that biosimilar policies do not undermine pharmacovigilance.

Source: CRA

Overarching learnings

The implementation of sustainable policies is very specific to each country situation. However, across the nine therapy areas, there are some overarching learnings that can be drawn out:

- The introduction of biosimilar policy should be anchored in supporting the goal of sustainability in the short and medium term, ensuring cross-stakeholder perspectives are captured.
- As a country's biosimilar landscape matures over time and stakeholder experience increases, there is a need to periodically evaluate and update policies to ensure sustainability is maintained.
- Policies are less effective when implemented in a piecemeal fashion, hence implementation should consider the existing policy environment and where synergies can be leveraged across policy areas.
- Similarly, policies should adapt to reflect the changing types of biologics losing exclusivity.
- Cultivation of a sustainable global biosimilar landscape requires sharing of learning and best practices across markets, to support accelerated development of countries with less mature biosimilar landscapes.

1 – Introduction

Organon asked Charles River Associates ("CRA") to work with a group of national and international biosimilar experts to identify the optimal, sustainable biosimilar policies and to develop actionable policy recommendations to improve biosimilar sustainability for a wide set of countries. Further, given the increasing relevance of biosimilars in the specific therapeutic areas of chronic, oncologic and orphan diseases, and the wide variation expected from sustainable policies across them, this research aimed to tailor recommendations, when applicable, to these three biosimilar archetypes. In particular, this research considers:

- The effects of individual biosimilar policies – including policies affecting biosimilar manufacturing and research and development (R&D), regulatory approval, health technology assessment (HTA), pricing, contracting, public health education, prescribing, dispensing and monitoring – on key stakeholders (patients, healthcare professionals, payers and manufacturers)
- The extent to which we can identify an 'ideal biosimilar policy landscape' to ensure sustainable conditions for long-term biosimilar competition and cost savings, supply, access and innovation
- The degree to which the findings regarding sustainable long-term biosimilar policies can be extrapolated beyond the countries in the scope of the research to tailor specific actionable recommendations to promote long-term benefits in other countries

1.1. Background

A biosimilar medicine is a biological medicine which has been shown to have no clinically meaningful differences from the originator medicine in terms of quality, safety and efficacy. Biosimilars are officially approved versions of original 'innovator' products and can be manufactured when the original product's patent expires. This possibility provides several benefits to multiple stakeholders leading to an overall increased pool of biopharmaceutical options, which improves healthcare professionals' (HCPs') and pharmacists' treatment decisions, finally resulting in an overall faster and broader access for patients to treatment.

Unlike small molecule generics, biosimilars are not identical copies of the originator molecule.[14] The manufacture of biologics from living organisms subjects them to various modifications intrinsic to biology and nature. Given such complexity, slight changes in manufacturing protocols can result in modifications to their sophisticated molecular structures, potentially affecting their effectiveness, quality or safety.[15] Complex analytical techniques are required to monitor the quality of biosimilars in order to ensure that relevant quality attributes are comparable to those of the originator.[16]

Due to the complexity of their production process, the costs of developing and manufacturing biosimilars are substantially higher than those of small molecule generics.[17] Estimates suggest generic small molecule drugs require an investment of around $2m–$3m for their development, while biosimilar development costs require an investment closer to $3bn. This is caused not only by increased manufacturing costs but also by the increased time taken to develop these products: generic drugs can reach the country in a period of two to three years, but a biosimilar drug needs approximately seven to eight years of development, due to the numerous studies currently required for their authorisation, usually including safety and efficacy studies in comparison with originator biologic molecules.[18]

Therefore, due to their inherent differences, biosimilars require specific policies to promote their sustainable use and dynamics throughout their whole life cycle. For example, while there is wide acceptance that biosimilars are indeed 'similar' to their originators, bioequivalence cannot be taken for granted.[19] This has implications for the regulatory environment. Equally, while biosimilars present an opportunity to significantly reduce spending on biologic healthcare, submitting them to equal pricing policies as small molecule generics can be considered unrealistic, and can lead to decreased competition due to manufacturers dropping the country in the long term.

Introduction

A wide range of biologic medicines are now available (with the development pipeline continuing to expand), which have provided access to treatment for a number of serious diseases.[20] The first biologic to formally see entry of biosimilars following loss of exclusivity (LoE) was Genotropin (*somatropin*) for which the first biosimilar was approved in the European Union (EU) in 2006 under the brand name Omnitrope.[21] Since then, as of 2019, the European Medicines Agency (EMA) has made 65 marketing authorisation decisions for 55 approved biosimilars for 16 different reference products.[i] The number of biosimilars authorised for use varies across countries; for example, as of 2021, the US Food and Drug Administration (FDA) has approved 30 biosimilars for 10 reference products;[ii,22] 21 of these biosimilar products are marketed in the US.[23] While some countries, such as Canada, follow a similar trend (46 biosimilars from 14 different products are currently approved in Canada),[24] official biosimilar guidelines were only developed in 2009 in Japan,[25] and in 2016 in Saudi Arabia.[26] It is therefore fair to assume that the biosimilar experience of different countries is reflected in their policy frameworks. Further to this, certain characteristics intrinsic to countries can also influence the effectiveness or impact that equal policies can have across landscapes. For example, promotion of local manufacturing policies for biosimilars can have positive implications in large countries that have seen their supply affected due to the COVID-19 pandemic but can have lower benefits in smaller geographies.

Biosimilars in different therapy areas can face different challenges owing to differences in patient numbers/epidemiology and clinical characteristics of these diseases. Currently, biosimilars marketed in the EU and US fall into therapeutic areas of inflammatory, oncology, immunology, or haematology. Not only the number of products but also the epidemiology and patient volume differs across countries or areas. For example, while chronic diseases affect a higher percentage of the global population and their treatment requires prolonged timelines, oncological therapies are normally used for shorter treatment cycles.[27,28] Higher volumes of patients can increase the number of biosimilar competitors for therapies, which can lead to unsustainable price reductions if not controlled properly. Conversely, shorter treatment cycles for oncologic products can increase the impact of non-medical switching (NMS) policies on biosimilar uptake and manufacturers. Overall, the challenges that have been faced by more recently launched oncologic biosimilars have been different to those experienced by the first biosimilars, and it is likely that as the biologic pipeline evolves, new challenges will continue to arise.

The number of biologics on the horizon of patent expiry across therapeutic areas and classes is bringing a broad range of opportunities for biosimilar entry. Five different orphan biologics are losing exclusivity in the EU and the US in the coming five years (e.g. golimumab for musculoskeletal disorders in 2024 or belimumab for musculoskeletal and haematological disorders in 2026), as well as five more biologic medicines within oncology. Moreover, the first vaccines generated through recombinant DNA technology are beginning to lose their patents (e.g. the HPV vaccine) and are expected to lose exclusivity as of 2021 (Europe) and 2028 (US).[29] Although the development of policies to promote biosimilars for vaccines are out of the scope of this research, it would surely lead to an interesting opportunity to open new debates around sustainable landscapes. This continued evolution in the biologic pipeline indicates that policy frameworks in place now, may not be fit-for-purpose to ensure a sustainable environment for newer biosimilar products in the long term. Although the number of biologics facing LoE is continuing to grow, it cannot be expected that there will be biosimilars manufactured for all of these biologic products (especially within orphan indications).[30] Furthermore,

[i] Originator biologics with biosimilar products available in Europe as of 2019: MabThera (rituximab); Eprex/Erypo (epoetin alfa); Eprex/Erypo (epoetin zeta); Herceptin (trastuzumab); Neupogen (filgrastim); Neulasta (pegfilgrastim); Remicade (infliximab); Enbrel (etanercept); GONAL-f (follitropin alfa); Avastin (bevacizumab); Humira (adalimumab); Lantus (insulin glargine); Humalog (insulin lispro); Genotropin (somatropin); Clexane (enoxaparin sodium); Forsteo (teriparatide)

[ii] Neupogen (filgrastim); Neulasta (pegfilgrastim); Avastin (bevacizumab); Herceptin (trastuzumab); Remicade (infliximab); Eprex/Erypo (epoetin alfa); Rituxan (rituximab); Lantus (insulin glargine); Enbrel (etanercept); Humira (adalimumab)

not all biosimilars approved by the EMA are available in the majority of European countries, reflecting potential sustainability limitations across existing policy frameworks. It will be important that adaptations to existing policy frameworks are managed such that they create a sustainable environment for newer biosimilar products in the long term.

As a result, the definition of an ideal sustainable environment for biosimilars might be currently outdated, and will need to evolve in parallel to the biosimilar pipeline. Furthermore, such an ideal environment must account for intrinsic differences across countries and understand that the one-size-fits-all approach is not always the best exercise to promote long-term sustainability for biosimilars.

1.2. What is 'sustainability' of biosimilars and why may it be an issue?

Many publications regarding the off-patent biological and biosimilar market reference the importance of sustainability with regards to policy development, application and execution with the objective of ensuring wider uptake of biosimilars in the short and long term. While many do not define sustainability explicitly, concepts common across papers include: '*balance between incentives for all key stakeholders/multi-stakeholder benefits',*[31,32,33,34] '*cost savings/sustainability for budgets*',[35,36,37] '*sustainable price competition*', '*increased/broader patient access*',[38] '*sustained innovation',*[39,40,41] '*increased levels of competition and choice*',[42,43,44,45] '*attractivity for continued investment*',[46] and '*sustainable supply*'.[47,48]

Given the expected increasing role for biosimilars, it is not surprising that there is a growing literature on the long-term sustainability of market for biosimilars. A number of existing studies have sought consensus on how to define sustainability:

- ***Vulto et al. (2020):*** *Defines a sustainable biosimilar market: "All stakeholders, including patients, benefit from appropriate and reliable access to biological therapies. Competition leads to a long-term predictable price level, without compromising quality, while delivering savings that may be reinvested".*[49]
- ***The Pugatch Consilium (2019):*** *Defines the three pillars of a sustainable European market for off-patent biologics: (1) rewarding and incentivising biopharmaceutical innovation and biosimilar development; (2) recognising the need for health system efficiencies; (3) providing patients and health care providers with freedom of choice and improved access to treatment.*[50]
- ***IQViA (2018):*** *Defines a sustainable biosimilar environment as one that "improves patient access and physician prescription choice of safe and high-quality biologic medicines, provides a means to manage existing healthcare budgets while safeguarding a healthy level of competition and supply", thus considering the needs of all key stakeholders (patients, healthcare professionals/providers, payers and manufacturers).*[51]

There are a number of reasons why 'sustainability' is seen as a significant issue for the biosimilar market:

- **Variation in biosimilar uptake:** As of 2021, biosimilars capture 10% of the total biologic pool in Europe, 7% having been achieved in the last five years, demonstrating their growth.[52] However, biosimilar uptake in countries such as Japan, the US and Canada has been significantly lower. From this it can be inferred that, in some countries, policies to increase patient use of biosimilars might not be efficient enough, limiting the total benefits they can have (e.g. on payers' budget).
-

- **Country confidence:** Misconceptions persist around the safety of biosimilars as non-identical molecular entities, resulting in mistrust among physicians and even patients, which can affect usage.[53]

- **Uncertainty regarding biosimilar practices and policy:** Policies in some countries have been subject to legal battles between payers/governments and manufacturers questioning the rules applied to biosimilars. For example, inconsistent contracting practices for biosimilars in Mexico have led to a lack of stable and transparent procurement methods.[54]

- **Conflation of the application of policy issues to biosimilars and generic small molecules:** Many biosimilar policies draw on the experience of the small molecule generic market. Moreover, many countries do not differentiate between these two very different products. There is a concern that applying small molecule policies to the biosimilar market is unsustainable and will reduce the number of biosimilar launches within specific markets, potentially resulting in higher prices and increased risk of supply shortages.

  This paper builds on these analyses, synthesising the key components highlighted in this literature to develop a series of multi-stakeholder benefits that should be realised in the long term in a sustainable biosimilar environment, and seeks to address three key questions:

  (1) Can we define an 'ideal' biosimilar policy toolkit that will ensure long-term sustainability?

  (2) To what extent does existing biosimilar policy across a global selection of countries promote a long-term sustainable environment benefitting all stakeholders?

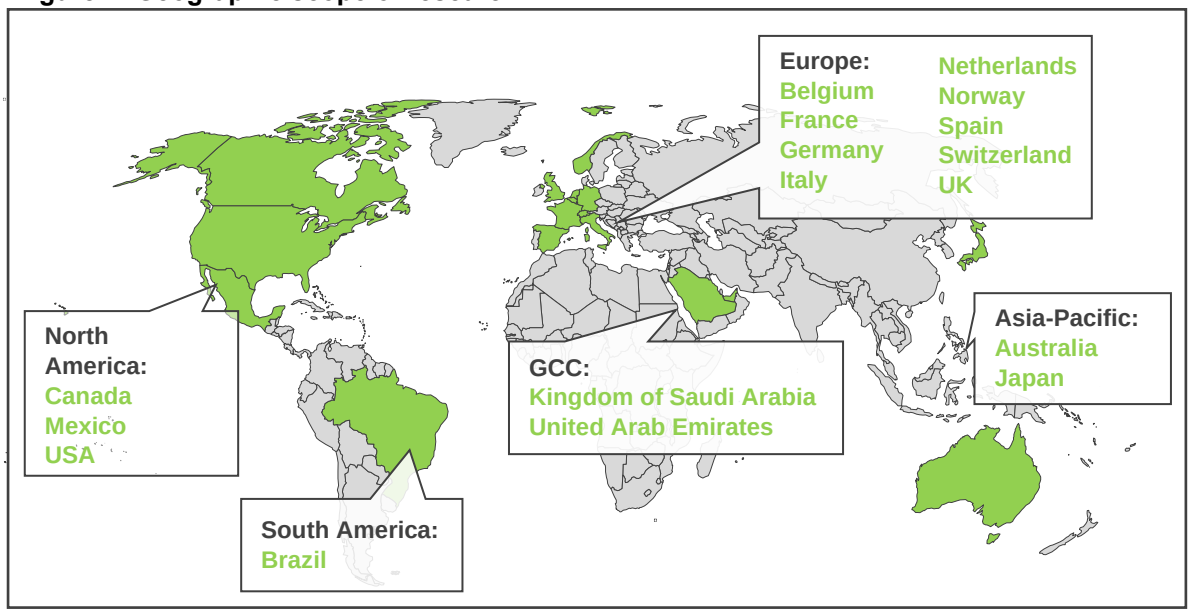
  (3) Can we provide countries with tangible and actionable recommendations for meaningful improvements to the biosimilar sector that consider their specific policy country situation and different types of biosimilars?

1.3. Geographic scope of the analysis

Given the focus on developing a global assessment of sustainability, we adopted a wide geographic scope with 17 countries across the globe, including the regions of both Americas, Asia-Pacific, Europe and countries from the Gulf Cooperation Council (GCC). The full list of countries included is depicted in **Figure 2**.

Such selection was made to ensure coverage of countries in different stages of development with regards to penetration of biosimilars, and countries from many different policy archetypes (e.g. public insurance vs. strong presence of the private sector; wide use of tendering procedures vs. direct contracting agreements) ensuring a broad selection of biosimilar policies are assessed. This selection also ensures that policy recommendations developed in this white paper are based on expertise from several archetypes, increasing the relevance of said recommendations for countries that are not included in this study.

Figure 2: Geographic scope of research



Source: CRA analysis

The biosimilar policy history of the countries in scope is captured in **Table 5**, showing that they range from those that pioneered biosimilar policy (e.g. the European Medicines Agency introduced their first policies in 2006) to those that are just beginning to develop their biosimilar policy (e.g. Swissmedic recently introduced Switzerland's first set of biosimilar policies in 2017).

Table 5: Year of introduction of biosimilar-specific policy across countries in scope of research

AUS	BEL	BRA	CAN	FRA	DEU	GBR	ITA	JPN	MEX	NLD	NOR	SAU	ESP	CHE	UAE	USA
2008	2006	2010	2009	2006	2006	2006	2006	2009	2009	2006	2006	2010	2006	2017	2019	2010

Source: CRA analysis

1.4. Structure of the white paper

The rest of the white paper is structured as follows:

- In Chapter 2, we outline the research methodology used to develop this white paper. This white paper is based on a structured literature review first conducted to collect information regarding the biosimilar policy landscape in each country in scope and subsequently looking at the existing evidence that different policies support a sustainable biosimilar environment in the long term. Hypotheses regarding the most sustainable policies for biosimilars, including specific considerations for different country situations and types of biosimilar, were then tested with biosimilar experts consulted during a series of engagements in 2021 and 2022, including individual country interviews and two advisory board meetings.
- Chapter 3 describes the policy framework and our hypotheses regarding the sustainability of the different biosimilar policies in place across countries, including specific considerations for different country situations and types of biosimilar.
- Chapter 4 summarises the biosimilar policy landscape of the countries in scope and the perceived sustainability of each country as validated by biosimilar country experts.
- Chapter 5 summarises actionable policy recommendations for countries to support a sustainable biosimilar environment in the long term, including specific recommendations for different country situations and types of biosimilars.

2 – White paper methodology

The research had three stages, with each stage composed of both a structured literature review and expert validation. The stages are summarised below and in Figure 3:

- **Stage 1 – A literature review was undertaken to develop a 'sustainability scorecard'**. Based on existing literature regarding sustainability for biosimilars, a 'sustainability scorecard' was developed comprising 10 elements that characterise a sustainable environment for biosimilars in the long term. The 10 elements on the 'sustainability scorecard' were validated through expert review and in-depth 1:1 discussions, which indicated that biosimilar policy sustainability should be developed over time. Initial elements of policy should provide a strong foundation for future biosimilar launches, and as biosimilars become more integrated in countries over time, policy should evolve to ensure long-term sustainability within the market.
- **Stage 2 – Country policy landscape assessments were based on secondary research and local interviews.** A research framework was developed to guide a consistent landscape analysis across countries to summarise the biosimilar-specific policies in place in each country through country-specific literature reviews, and validated with country experts. The long-term sustainability of the biosimilar policy environment in each country was then assessed using the sustainability scorecard developed in Stage 1. This allowed for the identification of the policy areas where sustainable practices provided broad benefits, as well as the areas with room for improvement. The assessments were validated through expert review and in-depth 1:1 discussions.
- **Stage 3 – Two international advisory board meetings were held to inform the development of actionable policy recommendations for long-term biosimilar sustainability.** Given the broad and global scope of the research, two meetings were held in order to accommodate time zones, bringing together international experts to discuss recommendations for an ideal, long-term sustainable policy environment for biosimilars. Findings obtained in these meetings led to the development of actionable policy recommendations, including specific recommendations by country situation and type of biosimilar.

Figure 3: Three stages of the white paper development methodology

Source: CRA analysis

2.1. Stage 1 – A literature review was undertaken to develop a 'sustainability scorecard'

A structured literature review of existing publications regarding biosimilar sustainability was conducted. Papers were selected according to their technical robustness and relevance to the topic, with the most recent definitions of biosimilar sustainability used preferentially over those in older papers (**Table 6**).

Table 6: Structured literature review of biosimilar sustainability

Topic	Description
Key search terms	'biosimilar', 'sustainability', 'definition', 'policy', 'long term'
Search engines	Google Scholar, Google, PubMed
Date range	Earliest date of publication was limited to 2014.
Search language	English
Reviewing process	Peer-reviewed papers and white paper reports with relevant titles and abstracts were first selected for thorough reading and consideration for development of the sustainability scorecard
Selection process	The search included academic journals and articles, governmental official sources, media reports and formal white papers from national/pan-national/international regulatory authorities

A total of 27 papers / white papers (**Appendix 1**) were assessed in depth to synthesise a 'sustainability scorecard' comprising 10 elements that are consistently used across literature to characterise a sustainable biosimilar policy environment. Input from experts across countries indicated that biosimilar policy sustainability should be built over time, starting with ensuring basic elements that provide a strong foundation for future biosimilar, and as biosimilars become more integrated in countries over time, policy should evolve to eventually ensure long-term sustainability of the market (**Figure 4**).

Figure 4: A 'sustainability scorecard' comprising the multi-stakeholder benefits to be realised in a sustainable biosimilar policy environment

Sustainable biosimilar policies should:

INITIALLY AND AT A MINIMUM			
1	**Ensure safe and high-quality medicines**	*Policies should ensure high quality medicines with robust and transparent evaluations, and monitoring systems to give confidence to patients and healthcare professionals*	⊕
2	**Facilitate cost savings for healthcare providers**	*Policies should facilitate cost savings for healthcare systems to ensure long-term budget sustainability*	🐷
3	**Ensure healthy levels of supply**	*Policies should minimise risks of supply shortage and ensure there is sufficient demand for biosimilars to avoid wastage or incentives to sell at unsustainable prices*	👥
4	**Maintain incentives for continued biologic research & innovation**	*Policies should ensure that sufficient incentives for manufacturers remain in place to ensure that there is continued research to launch new biologic products*	🏭
AS BIOSIMILAR POLICY MATURES			
5	**Mitigate against biosimilar misconceptions**	*Policies should seek to address common concerns surrounding biosimilars to optimise uptake and ensure informed decision-making across all stakeholders*	👥
6	**Facilitate efficient & streamlined patient access**	*Policies should encourage streamlined access procedures without compromising safety to ensure eligible patients have unrestricted access to life-saving medicines*	⊕
7	**Encourage multi-stakeholder decision-making**	*Policies should ensure that all key stakeholders (payers, physicians, pharmacists and patients) play a role within decision-making to optimise multi-stakeholder benefits*	👥
FINALLY TO ENSURE LONG-TERM SUSTAINABILITY			
8	**Facilitate sustainable levels of biosimilar competition**	*Policies should ensure that market competition is incentivised to ensure long-term predictable price levels, while delivering savings that may be reinvested*	👥
9	**Increase prescribing options for patients & healthcare professionals**	*Policies should encourage availability of multiple prescribing options to maintain flexibility in treatment regimens to address individualised patient needs*	⊕ 🩺
10	**Maintain predictable market functioning**	*Policies should ensure that market volatility is kept to a minimum and that policies are transparent to maintain attractivity of the market*	🏭

BENEFITS FOR: 👥 = All stakeholders ⊕ = Patients 🩺 = Healthcare Professionals 🐷 = Payers / Budget Holders 🏭 = Biosimilar & Originator Manufacturers

Source: CRA analysis

The aim of these elements was to develop an objective rating system to evaluate the level of sustainability of biosimilar policy environment in each country in scope. Therefore, a 'sustainability rating scale' was developed to rate the extent to which the 10 multi-stakeholder sustainability benefits are met. This scale was designed to allow for clear comparison across policy areas and across countries, allowing differentiation between sustainable areas that grant full benefit for all stakeholders (five stars) and policy areas / countries that might lag behind in some of the elements and can therefore be further improved (four stars or lower) (**Table 7**).

Table 7: Sustainability rating scale

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

Source: CRA analysis

2.2. Stage 2 – Country policy landscape assessments were based on secondary research and local interviews

An assessment framework was developed to guide a consistent landscape assessment of each country. This assessment framework is based on the nine key stages of the biosimilar life cycle, starting with manufacturing and then regulatory approval policy considerations through to pricing and reimbursement measures before going through prescribing and dispensing practices and ending with policy considerations on the monitoring of biosimilar products (**Table 8**). Within each of the nine policy areas, different policies specific to biosimilars were characterised and subsequently assessed. In addition, we investigated whether different policies are considered for different types of biosimilars (e.g. biosimilars of orphan drugs).

Table 8: Policy area assessment framework

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

Source: CRA analysis

Landscape assessments of the 17 countries in scope were conducted to populate the policy assessment framework. Initial secondary research was conducted through country-specific literature reviews. Papers were selected according to their technical robustness and relevance to the topic (**Table 9**). The review of academic literature included peer-reviewed articles contained in open-source and academic databases. In order to prompt a more accurate research, relevant information was tailored via keyword search.

Table 9: Literature review approach for country-specific landscape assessments

Topic	Description
Key search terms	'[country]', 'biosimilar', 'policy', 'manufacturing', 'regulatory assessment', 'HTA', 'health technology assessment', 'reimbursement', 'pricing', 'price discounts', 'launch pricing', 'contracting', 'tendering', 'provision', 'prescribing', 'prescribing incentives', 'prescribing practices', 'switching', 'dispensing', 'substitution', 'education', 'campaigns', 'misconceptions', 'monitoring', 'pharmacovigilance'
Search engines	Google Scholar, Google (including local Google sites), PubMed
Date range	Earliest date of publication was limited to 2014
Search language	English and local languages (e.g. Portuguese, Spanish)
Reviewing process	Papers with relevant titles and abstracts were first selected for thorough reading, although only those with robust content specific for biosimilars were finally kept for the white paper

Selection process	The search included academic journals and articles, governmental official sources (e.g. legislation and health policy plans), media reports and formal white papers from national/pan-national/international regulatory authorities

Source: CRA analysis

Research findings were then validated with industry experts and 23 international and local non-industry experts. One to three biosimilar non-industry experts in each country were selected based on their previous publication history, contribution to current biosimilar policy and level of expertise (**Table 10**). Across countries, a range of experts with different backgrounds were selected to ensure a range across patient representatives, physicians, pharmacists and payers / health economists.

Table 10: Non-industry country experts and experience

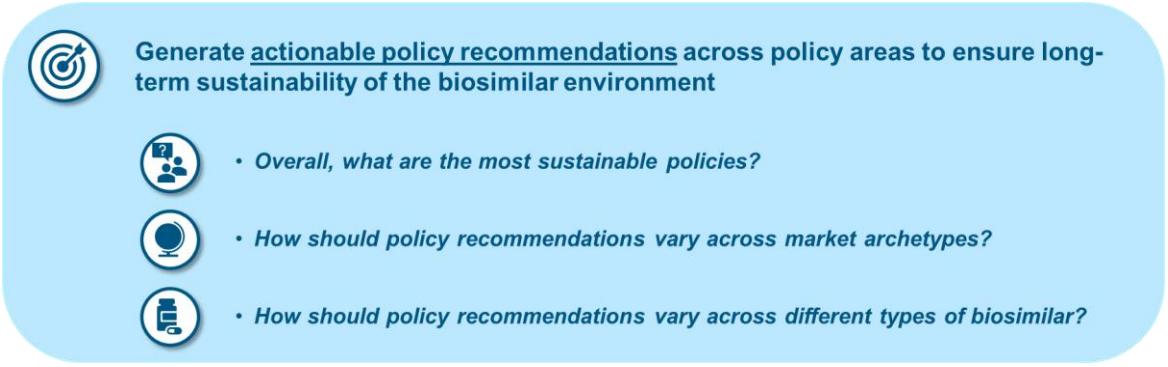
Geographical background	Expert experience
Australia	Current Chair of the Australian Biosimilars Academy; former President of the Pharmacy Guild of Australia
Belgium & the Netherlands	Professor of Health Economics, KU Leuven
Brazil	Assistant Professor Medical Oncology, Hospital São Lucas da PUCRS
	Associate Professor of Rheumatology, Federal University of Minas Gerais (UFMG)
Canada	Founder and President of Arthritis Consumer Experts
France	Hospital pharmacist
	Founder of Nile
	Consultant at Nile
Germany	Chief of Gynecology and Gynecological Oncology, Agaplesion Markus Hospital, Frankfurt
Italy	Professor of Health Economics and Microeconomics, EEHTA-CEIS Director, University of Rome “Tor Vergata”; President of Italian Society of Health Technology Assessment (SiHTA)
Japan	Specially Appointed Professor, Showa University
Mexico	Executive Director UDIMEB, CEO UDIBI, Research Professor of Immunology
	Senior Investigator of Pharmacology, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional (CINVESTAV)
Norway	Consultant Clinical Oncologist
	Professor of Pharmaceutical Chemistry
Spain	Director of Hospital Pharmacy in the Son Espases University Hospital, Palma de Mallorca
	Pharmacist and Deputy Director of Catalan Oncology Institute, Barcelona
	Head of Medical Oncology, Hospital Gregorio Marañon, Madrid
Switzerland	Independent consultant, previously member of Swiss Federal Commission of Drugs
UAE	Consultant & Chief of Rheumatology, Tawam hospital, UAE Clinical Assistant Professor, College of Medicine & Health Sciences, UAE University, United Arab Emirates
UK	Commissioning pharmacist within an integrated care system (ICS)

USA	CEO, Matrix Global Advisors; Senior Fellow, American Enterprise Institute

2.3. Stage 3 – Two international advisory board meetings were held to inform the development of actionable policy recommendations for long-term biosimilar sustainability

A comparison of the expert-validated country policy landscapes was brought together, and two international advisory board meetings held where experts were asked to discuss the key areas for biosimilar policy improvement across countries. Overall, the key objective of the advisory boards was to develop actionable policy recommendations. This was guided by three key questions regarding the overall trends for biosimilar sustainability, any considerations of country situation, and any key differences for various types of biosimilar (**Figure 5**).

Figure 5: Overall objective and key questions for advisory board discussion



Source: CRA analysis

Outputs from the advisory board meetings were synthesised into a series of policy recommendations across each of the nine policy areas (e.g. manufacturing, regulatory approval, HTA etc.). Any specific considerations for country situations or different biosimilars were specified. These outputs were reviewed offline by attendees to ensure alignment across all stakeholders and refined for the purposes of this white paper. However, the development of recommendations and their tailoring to different contexts (e.g. adaptation based on different biosimilar types) should be understood as a starting point for achieving biosimilar sustainability. Integration of further expert input across different biosimilar contexts will be required in order to identify the best approach to implement these recommendations.

3 – Biosimilar policy evaluation for long-term biosimilar sustainability

This chapter provides an overview and a sustainability analysis of different biosimilar policies in place across countries in scope of this research. A long-list of biosimilar policies has been developed based on country-specific secondary research conducted by CRA and validated by country experts. Subsequently, an assessment of the pros and cons of each policy regarding long-term sustainability for biosimilars has been conducted. This assessment leverages key 'policy sustainability elements' synthesised from definitions of long-term biosimilar sustainability in recent literature.

The chapter is structured in nine sections, reflecting the nine policy areas of focus for this white paper. For each section, an introduction and overview of relevant policies in the countries in scope is summarised, followed by the assessment of the pros and cons of each policy identified, supported by case study examples and existing literature. This analysis results in hypotheses for the 'ideal long-term sustainable policy environment' for biosimilars within each area, and how this may vary across different archetypes and/or different types of biosimilars.

3.1. Manufacturing and R&D

The production of biologics (and, consequently, of biosimilars) is more complex than that of most small molecule medicines. This increased level of complexity arises from the nature of biological molecules, where small batch-to-batch differences at the manufacturing level, if undetected, can affect originator or biosimilar efficacy, safety or stability. Therefore, strict manufacturing standards have been established for biologics and biosimilars. In addition to the regulatory policies that have been implemented to guarantee the quality of the manufacturing process, a couple of biosimilar-specific policies have been implemented across the studied countries to promote local production.

Biosimilar policies regarding manufacturing and R&D observed across countries include (Table 11):

- Local manufacturing incentives
- Manufacturing exemption waivers: allowing for biosimilar manufacturing licenses to be obtained ahead of originator LoE

Table 11: Manufacturing and R&D policies observed across countries in scope

AUS	BEL	BRA	CAN	FRA	DEU	GBR	ITA	JPN	MEX	NLD	NOR	SAU	ESP	CHE	UAE	USA
Local manufacturing incentives																
O	O	✓	O	O	O	O	O	O	O	O	O	O[iii]	✓	✓	O	O
Early biosimilar manufacturing license																
O	✓	O	O	✓	✓	✓	✓	O	O	✓	✓	O	✓	✓	✓	O

✓ Policy applied in the country | O Policy not identified or not applied

Source: CRA analysis

Local manufacturing incentives

Pros: Policies to incentivise the local manufacturing of biosimilars have been used by some countries not only as a way to improve their uptake and boost healthcare access, but also to enhance the industry growth within the country. A clear example of this is the industrial policy for the creation of Productive Development Partnerships (PDP) in Brazil, which promotes the close collaboration of international manufacturers and local laboratories for the production of biosimilars. Other countries, such as Switzerland, have included local production of biosimilars in the criteria for awarding tenders, allowing for wider elements of value to drive decision-making.[55] The benefit of these types of policies is that they can reduce import costs in the long term, and also reduce the risk of supply shortages (especially in larger countries such as Brazil), while supporting national manufacturers and boosting the country's biotechnological industry.[56] Benefits and savings obtained through local manufacturing could partly be reinvested in the innovative biopharmaceutical industry, contributing to further progress on research and development of new therapeutic targets and driving the industry forward. In this way, benefits obtained from biosimilars can ensure long-term incentives for continued biologic innovation.

[iii] Current initiatives and investments within the Kingdom of Saudi Arabia aim at establishing a minimum of 40% of medicinal products to be produced inside the country. These policies include, but are not specific to, biosimilars.

Generally, policies that have resulted in the preferential treatment of foreign suppliers have been widely criticised as they can represent a deterrent to local manufacturing. This has been the case in Mexico, where policies to facilitate international supply and avoid shortage ended in unequal approval conditions for local companies, which need to undergo longer licensing processes (180–240 days) than foreign manufacturers (5 days).[57]

Cons: On the other hand, the importance of global supply cannot be disregarded, and local manufacturing incentives could penalise foreign importation if not applied appropriately. Given the tight margins for off-patent biologics and the barriers they often need to overcome for market access, international collaboration and global supply chains play an important role in ensuring efficient access. Foreign import is still needed and can benefit countries where local manufacturing capabilities are limited. Moreover, it is critical to continue to prioritise the assurance of biosimilars' comparative quality, efficacy and safety to their originator. For this, manufacturing requirements need to be consistent across biosimilar producers, and authorities need to ensure that manufacturing guidelines are transparent and clear, as they should not present a barrier to timely biosimilar entry. As a result, any local manufacturing should be accompanied by strong, secure regulation and enforcement to guarantee these three principles, and countries that are to encourage local manufacturing practices should also promote well-established regulatory frameworks in order to safeguard sustainability of local manufacturing.

Sustainability evaluation: Local manufacturing incentives provide an alternative to boost countries' economies and reduce dependencies on importation for supply. This is especially relevant for larger countries which are geographically distant from the main global manufacturing hubs (e.g. Brazil). However, to establish sufficient local manufacturing, incentives may be required to support a national manufacturing industry which is competitive against internationally established manufacturers. Moreover, it can allow for easier monitoring of supply and quality and improve the understanding of value and perception of biosimilars in the country, as well as driving innovation forwards when savings are reinvested in the biopharmaceutical industry. Nevertheless, implementation of such incentives can be limited in most countries, and international supply chains still provide a solid approach to maintain market competition and provide alternative sources to avoid procurement shortages, providing sustainable criteria are used for such contracts. Policies encouraging foreign manufacturing solely on the basis of price can demotivate certain manufacturers to commercialise their products in the country, impacting competition and limiting cost savings and treatment options for patients. Such an unsustainable environment can also lead to an overall long-term erosion of the biosimilar industry in the country. Therefore, an ideal sustainable environment will find the balance between local and international supply in order to benefit all stakeholders, providing fair criteria for global procurement.

Manufacturing exemption waivers

Marketing authorisation for medicinal products can require long periods of time, which can also vary across countries and depending on the health authorities responsible for their revision – from a maximum of 240 days by Mexican COFEPRIS,[58] a median review time of 303 for the US FDA, or up to a median of 369 days for the EMA.[59] Given this situation, biosimilars can sometimes face slow processes for their authorisation, despite their generally streamlined regulatory (and other, e.g. HTA or reimbursement) assessment requirements in most countries.[60, 61]

Pros: A potential way to accelerate access to biosimilars is to enable biosimilar manufacturing licenses to be obtained ahead of patent expiry of the originator so that biosimilars can seek regulatory approval soon after originator LoE (with appropriate protections to ensure that entry does not occur prior to loss of exclusivity). Theoretically, faster access can lead to the multi-stakeholder benefits of biosimilars to be realised sooner. This is the case for the United Arab Emirates (UAE), where manufacturers can apply for regulatory approval of biosimilars two years before their originator has lost its exclusivity in the

country.[62] Similarly, the EU allows for the manufacturing of biosimilars for storing during the six months prior to the expiration of Supplementary Protection Certificates (SPCs), therefore allowing biosimilars an immediate launch on day-one after SPC expiring.[63] With these waivers, originators' exclusivity needs to be respected, and there could be an advantage if transparency in this process allows them to plan in advance their post-LoE strategy. Moreover, earlier realisation of savings obtained from biosimilars, as explained above, can serve as a way to support investment in R&D if savings are used appropriately, driving forward innovation in the health and biopharmaceutical industry.

Cons: However, there are concerns about such rules and how they are implemented to avoid unintended consequences.[64] Further, it was also highlighted that such waivers are not common in other jurisdictions resulting in incompatibility across Free Trade Agreements (FTAs) with key international partners such as the US, Japan and South Korea, as well as others, potentially introducing additional competitive biases across international biosimilar markets.[65]

Sustainability evaluation: Policies to encourage early biosimilar entry, ensure originators are able to benefit from their full exclusivity period, while simultaneously fast and efficient access for biosimilars is facilitated. Manufacturing waivers could provide advantages in some markets, but they need to be designed with care taking into account market circumstances so that they are not anticompetitive and in conflict with existing FTAs with countries/jurisdictions that do not allow for such waivers.

3.2. Regulatory Approval

Biosimilars are not like generics in that their development requires additional quality and comparability studies, as well as clinical studies of immunogenicity, safety and efficacy, due to the inherent biological variability associated with such large and structurally complex molecules.[66] Therefore, specific policies can be implemented on the regulatory approval level in order to grant a sustainable environment to safeguard biosimilars' quality and to promote accelerated access to ensure that the multi-stakeholder benefits of biosimilars are realised as quickly as possible.

Biosimilar policies regarding regulatory approval observed across countries include (Table 12):

- Streamlined evidence requirements
- Simplified regulatory approval through international collaboration
- Regulatory support for biosimilar submission

Table 12: Regulatory approval policies observed across countries in scope

AUS	BEL	BRA	CAN	FRA	DEU	GBR	ITA	JPN	MEX	NLD	NOR	SAU	ESP	CHE	UAE	USA
Streamlined evidence requirements																
✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Simplified regulatory approval through international collaboration																
O	O	O	O	O	O	O	O	O	✓	O	O	O	O	O	O	O
Regulatory support for biosimilar submission																
O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	✓

✓ Policy applied in the country | O Policy not identified or not applied

Source: CRA analysis

Streamlined evidence requirements

At the regulatory level, the process is streamlined compared to the authorisation of the originator, but biosimilar policies should ensure rapid approval while still guaranteeing safety and efficacy standards.

Pros: Regulatory requirements are needed to ensure there have been sufficient safety and efficacy assurances but these should reflect the risks and benefits of the technologies being assessed. One clear example of such regulatory approaches and how they can be tailored for the approval of biosimilars is found in the UK. The Medicines and Healthcare products Regulatory Agency (MHRA) has recently announced an innovative new approach to biosimilar approval which will not require *in vivo* studies in animals to support biosimilar approval, and the comparative efficacy trial requirements have been changed in most cases. This approach is grounded in both science and real-world experience and reportedly takes "a pragmatic approach to biosimilar approvals". It has been reported that this change in legislation could lead to a "biosimilar boom".[67,68]

This has been supported by retrospective reviews, where in 95% of biosimilar development programs requiring a comparative efficacy study, this information was reported as adding no scientific value to

the review process.[69] The white paper concludes that moving away from routinely requiring comparative clinical efficacy studies will ensure that the assessment of quality, safety and efficacy of a biosimilar will remain uncompromised, while contributing to a sustainable multi-source medicine environment.[70]

While the MHRA is the first agency to routinely take this innovative approach to biosimilar approvals, some other agencies allow for comparative clinical efficacy studies to be waived in some instances. For example, in Switzerland, biosimilar manufacturers can apply to Swissmedic for 'submission with reduced documentation', which may be granted based on an individual assessment of the type of biosimilar, the employed analytical and manufacturing methods and available experience from the reference product.[71] Similarly, in the US the FDA waived the need for comparative clinical efficacy trials in the case of Retacrit (erythropoietin), Nivestim (filgrastim), and Udenyca (pegfilgrastim).[72] Overall, the implementation of these policies could result in an overall more streamlined process to grant biosimilars approval without increasing safety risks, by leveraging others' experience if applied appropriately, as proven in the described studies.

Lastly, streamlined evidence requirements are also implemented by some regulatory agencies (e.g. Swissmedic, MHRA, ANVISA) for biosimilar indication expansions where clinical comparability to the originator only needs to be proven for one indication (e.g. that with the largest patient population), and indication expansions can happen more efficiently thereafter. There are studies showing that these policies can avoid unnecessary duplicated comparability assays and provide a way to broaden the access of biosimilars to more patients, which can be of greater interest in high-volume therapy areas like inflammatory disease.[73]

Cons: If based on as assessment of the risks and benefits of a given products, and applied appropriately, there are no negative effects on long-term sustainability for biosimilars have been identified for this policy; however, it has been highlighted during expert discussion that this needs to reflect market circumstances. Waiving the need for comparative clinical effectiveness studies across the board could exacerbate existing mistrust of biosimilar products among some prescribers and pharmacists. Without appropriate education, this could further limit uptake due to a lack of understanding of the differences between originator biologics and biosimilars.

Sustainability evaluation: Streamlining approval processes, in particular waiving clinical comparative effectiveness studies, can accelerate biosimilars' access to a broader range of patients without compromising their quality and safety when used appropriately. These measures can also result in streamlined broadening of access if applied to indication expansions as well as initial launch indications. However, studies proving equal clinical effectiveness between originators biologics and biosimilars can improve the public understanding and perception of biosimilars.

Simplified regulatory approval through international collaboration

Another potential way to accelerate biosimilars' access without compromising their quality and safety can be the sharing and use of scientific evidence already generated by other international organisations. Countries with smaller national regulatory agencies could consider an 'abbreviated regulatory approval' process that can be used when other larger or pan-national regulatory agencies (e.g. EMA and US FDA) have granted approval to the medicine in question.

Pros: An abbreviated route would enable national regulatory authorities with more limited capacity and typically longer timelines to leverage foreign assessment reports to form the basis of their own evaluation, requiring only adaptation for the expected use and target population in the new market. For example, in Singapore, regulatory legislation allows the Health Sciences Authority (HSA) to leverage foreign reports to grant marketing authorisation. The HSA accepts reference reports from the EMA, US FDA, Health Canada, Australia's Therapeutic Goods Administration (TGA) and MHRA. New drug

applications that have received prior approval from at least two of these agencies can be assessed through an abbreviated route called the 'Verification Route (VR)', which takes 60 days (excluding clock stops) instead of the standard 270 days.[74]

A way to further facilitate such extrapolations of approvals would be granting better reproducibility across regulatory processes. Manufacturers have called for greater uniformity in requirements across regulatory agencies, which would provide benefits to better understand other regulatory agencies' rationale and criteria, leveraging this information for the described purposes. With new regulatory legislation coming into force from the UK's MHRA and different requirements across the EMA and US FDA, variation will remain in the requirements from different regulators.

Cons: No negative effects on long-term sustainability for biosimilars have been identified as long as the simplified regulatory approval provision is applied in agreement with the biosimilar's manufacturer.

Sustainability evaluation: Leveraging evidence from the regulatory assessments of other authorities can provide a way to accelerate biosimilar approval and therefore access to the market. By accelerating the approval of biosimilars, multi-stakeholder benefits of biosimilars can be realised more quickly by all stakeholders. Further, an environment that allows for increased collaboration will allow for increased transparency in regulatory assessments, therefore facilitating greater understanding of biosimilars among key stakeholders.

Regulatory support for biosimilar submission

Complexities in the process of attaining marketing authorisation and the requirements needed for submission are reported to be a regulatory barrier for manufacturers, especially those with minimal experience of the regulatory process.[75]

Pros: Policies in place that encourage regulatory support to be provided to biosimilar manufacturers can result in fewer misunderstandings in the long term, provide better clarity around legislation, and ultimately lead to more efficient access. Across countries, just one regulatory body has established a specific support program for biosimilar manufacturers: the US FDA has established a Biosimilar Product Development (BPD) Program where all manufacturers (of both new and already marketed biosimilars) are able to enrol and receive detailed, product-specific advice to support them to meet the FDA's regulatory requirements.[76] The adoption of these policies by further regulatory agencies could provide better ways to optimise support programs and encourage manufacturers to undergo approval processes, facilitating wide approval for a same product in different geographical scopes, especially in those countries where manufacturers struggle with the national requirements.

Cons: Providing enhanced support programs might require significantly increased time and resource commitments for regulatory authorities; hence, increased assessment or submission fees might be required by authorities in order to ensure their robust assessment procedures are not compromised.

Sustainability evaluation: Receiving support directly from regulatory authorities on the requirements needed for approval can lead to faster biosimilar access in the long term. Additionally, this support may enable manufacturers to more accurately communicate their biosimilar's value, supporting perceptions of its quality. Overall, this regulatory support will be most relevant for manufacturers which are less established and might be launching their first biosimilar product.

3.3. Health Technology Assessment

Generally, HTA is used to inform decision-making about innovative therapeutic options and whether they add therapeutic benefit and represent value for money.[77] Assessments of a specific technology's impact on health and the related social, economic, organisational and ethical aspects are conducted.

Given the similarity of biosimilars to their originators, which themselves will likely have undergone an HTA, the value of repeating HTA for biosimilar products needs to be articulated.

Biosimilar policies regarding health technology assessments observed across countries include (Table 13):

- Lack of full-length HTA requirements for biosimilars
- Simplified assessments specific to biosimilars

Table 13: HTA policies observed across countries in scope

AUS	BEL	BRA	CAN	FRA	DEU	GBR	ITA	JPN	MEX	NLD	NOR	SAU	ESP	CHE	UAE	USA
Lack of full-length HTA requirements for biosimilars																
O	O	✓*	O	O	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Simplified HTA submission requirements																
✓	O	O	O	✓	O	O	O	O	O	O	O	O	O	O	O	O

✓ Policy applied in the country | O Policy not identified or not applied

Source: CRA analysis

Lack of full-length HTA requirements for biosimilars

Most countries do not apply HTA to biosimilars. Given that manufacturers need to undergo a process to determine similarity and safety, it is established that there is little role left for HTA bodies as the value the biosimilar is expected to bring to the patients is the same as the originator.

Pros: By not conducting an HTA, the barriers for launching a biosimilar (e.g. administrative) are reduced, increasing the attractiveness of launch and accelerating the timelines. Consequently, more biosimilars are likely to enter the country, promoting competition. This was recognised by the Canadian Agency for Drugs and Technologies in Health (CADTH), following an internal review which assessed the streamlined biosimilar review processes that had been introduced in 2018. The conclusion of this internal review was that their assessments were non-essential and delayed the country access to biosimilars.[78]

Cons: Biosimilars are normally reviewed from a non-inferior therapeutic perspective, and their cost-effectiveness is assumed, removing the need to undergo full HTA processes to grant access and reimbursement. However, there can be some value to conducting an evaluation of biosimilars to quantify their impact on systemic cost savings. It has been suggested that these evaluations could be conducted retrospectively or in the form of multiple technology assessments once several biosimilar products for the same originator are available. This might enable biosimilars to launch in indications for which the originators were not previously deemed cost-effective. Discussions held among experts also emphasised the value of such analyses to consider during contracting discussions, as it is currently regarded in the Italian budgetary law and *'accordo quadro'.*

Sustainability evaluation: Conducting a full-length HTA for a biosimilar launching into the same indication as the originator product is largely considered as unnecessary, adding an additional hurdle for biosimilar access and decreasing the long-term sustainability of the biosimilar market. However,

developing certain analysis to understand the extent of biosimilars' organisational impact can provide better comprehension of the benefits they can provide to the system, improving their uptake among stakeholders.

Simplified HTA submission requirements

In countries where HTA for biosimilars is conducted, policies usually involve streamlining the submission (e.g. evidence) requirements, given the existence of a previous HTA report for the originator that can allow for efficiencies in the process.

Pros: Development of certain economic evaluation of biosimilars might add specific value in those cases where **(1)** the originator biologic is not reimbursed, **(2)** biosimilars present a different form of administration than its originator, and **(3)** biosimilars are considered to provide added-value services compared to the originator.[79] This reduces the burden for both the assessment agency and the submitting manufacturer, promoting increased biosimilar competition and hence providing additional prescribing options for physicians. Though not always the case, reducing this burden normally leads to accelerated reimbursement. In Australia, biosimilars that do not apply for indications beyond those of the originator are eligible to make a 'Category 3' submission to the Pharmaceutical Benefit Advisory Committee (PBAC) prior to their assessment. Although this submission route still results in an assessment of clinical need and effectiveness, it excludes the economic evaluation. Furthermore, this submission route also requires a lower application fee, reducing the cost for the manufacturer.[80] Similarly, in Quebec, Canada, the Institut national d'excellence en santé et en services sociaux (INESSS) conducts abridged HTAs in the form of 'mini-HTAs'.[81] These streamlined assessments exclude the need to conduct systematic reviews of clinical evidence or of the potential risk of biases.[82]

In some countries, HTAs are only conducted when a biosimilar launches in an indication for which the originator has not been assessed. In the UK for example, given the lower pricing of biosimilars relative to originators, biosimilars are often considered to be more cost-effective. Consequently, it is possible for the National Institute for Health and Care Excellence (NICE) to approve biosimilars for use in earlier lines of treatment than the originator is recommended for (within the same disease area), following a streamlined assessment of the indication extension. For example, biosimilar filgrastim was moved to first-line cancer treatment in the UK as a result of its improved cost-effectiveness when compared to alternative (originator) treatments.[83]

Cons: There are some instances where HTAs are required for biosimilars without a clear rationale for their requirement, thus resulting in additional administrative hurdles without added value, delaying time to biosimilar access. This is exemplified in France, where the Commission de la Transparence (CT) conducts rapid biosimilar HTA reviews on behalf of Haute Autorité de Santé (HAS). The assessment process is meant to be accelerated by removing cost-effectiveness and economic modelling, as well as critical appraisals of the quality of evidence and considerations of ethical implications.[84] Furthermore, biosimilars are predefined with an *amélioration du service médical rendu* (ASMR) designation prior to the HTA without requiring CT advice release. However, although HTA for biosimilars is accelerated, this still introduces a certain delay compared to the complete absence of HTA, without granting additional benefit.

Sustainability evaluation: The outcomes of HTA processes can provide designations for biosimilars beyond 'non-inferiority' or 'cost saving' status and potentially increase better understanding of biosimilar value. This can help improve their uptake and lead to broader access of biosimilars and long-term cost savings.[85] However, when HTA is conducted for biosimilars without clear benefits for any stakeholders obtained from the assessment, this procedure can be considered an additional and unnecessary hurdle

to access. Importantly, there can be value to conducting an HTA if the biosimilar is launching in an indication in which the originator has not launched yet.

3.4. Pricing and reimbursement

Biosimilars are also playing an important role in supporting budget management in many countries.[86] Given the opportunity that biosimilars represent for healthcare cost savings, pricing and reimbursement policies are a high-profile topic; however, it is critical that policies in place are mindful of a long-term sustainable environment for all stakeholders, ensuring cost savings but also prioritising patient access, physician choice and predictability for manufacturers. In this regard, it is also necessary to consider the impact of biosimilar policies on originator pricing and long-term incentives for continued biologic innovation.

Reimbursement policies

Biosimilar policies regarding reimbursement observed across countries include (Table 14):

- Automatic reimbursement following regulatory approval and submission
- Full coverage or partial coverage of the cost of the biosimilar for the healthcare provider
- Exclusionary contracts preventing sales from biosimilar competitors

Table 14: Reimbursement policies observed across countries in scope

	AUS	BEL	BRA	CAN	FRA	DEU	GBR	ITA	JPN	MEX	NLD	NOR	SAU	ESP	CHE	UAE	USA
Automatic reimbursement following regulatory approval and submission	O	O	O	O	✓	✓	✓	✓	O	O	✓	✓	O	✓	O	✓	✓
Full coverage vs. partial coverage	O	✓	O	✓	O	✓	O	✓	O	O	✓	O	O	O	✓	✓	O
Exclusion contracts	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	✓

✓ Policy applied in the country; O Policy not identified or not applied

Source: CRA analysis

Automatic reimbursement

Reimbursement of biosimilars is often automatic provided pricing rules are applied to the list price.

Pros: In countries where no HTA is required, automatic reimbursement following regulatory approval facilitates fast or immediate access to biosimilar products. Alternatively, where biosimilar automatic reimbursement is subject to administrative requirements, certain streamlining in the reimbursement process could still accelerate biosimilars entry (e.g. earlier initiation of negotiations). However, such streamlined processes should present certain value and utility, and be avoided if their outcomes are predefined. For example, the EU transparency directive sets a maximum of 180 days for member states to approve reimbursement of biosimilar products arriving in the market.[87] Considering that this

reimbursement process has already occurred for the originator product within its approved indications, this bureaucratic burden in EU member states should be reduced to the minimum possible to assure faster reimbursement for biosimilars. In certain countries where some bureaucracy needs to be submitted to grant biosimilar reimbursement, criticism has been raised given the lack of value of such processes. For example, submission of documents to grant biosimilar reimbursement in Belgium, though reduced to 90 days for biosimilars compared to the 120 days required for originators, is still believed to be unnecessary.

Cons: In certain countries, it was discussed that potential issues could arise with automatic reimbursement if the timelines that support approval processes are not transparent and there is no notice of upcoming launch until the biosimilar enters the market. Biosimilar entrance with little-to-no warning for existing therapeutic alternatives (both other biosimilars on the market and originator products) can impact their supply management, potentially resulting in sudden drops in demand and wasted stock. This is currently a hypothetical issue, not observed in any of the countries in scope.

Sustainability evaluation: To accelerate patient access, automatic reimbursement is favoured in most countries. However, there should be a transparent regulatory process regarding upcoming products to provide enough predictability for biosimilar and originator manufacturers with marketed products and inform their supply decisions. Better visibility into ongoing regulatory assessments should be prioritised in countries where these processes are currently opaque (e.g. Australia and Mexico) as this can allow marketed competitors to forecast potential impacts on their supply chain and adapt their strategies to new market dynamics. As a result, automatic reimbursement of biosimilar products without additional delay can be ensured while avoiding short-term over-supply.

Full coverage vs. partial coverage

Reimbursement/coverage can range from 100% to partial reimbursement, depending on the country. Reimbursement of the biosimilars is often consistent with the price of the innovative products, although some countries have set fixed reimbursement levels aligned to lowest-cost treatment options. As a result, any product having a higher price than the lowest-cost options would be subjected to certain co-payments either by the patient or the healthcare provider (e.g. hospital or pharmacy). In other countries, such as Spain, prices of originators and biosimilars are unified through a reference pricing system, so full (100%) reimbursement can be maintained for both of them.

Pros: Setting reimbursement levels to the lowest-cost option is intended to drive uptake of biosimilar products and can therefore improve their adoption. This provides an incentive for patients where they would otherwise have to cover the excess cost of a more expensive originator therapy. Implementation of such policies has shown to increase cost savings, as with outpatient small molecule generics in Italy.

Alternatively, other regulations have established fixed reimbursement percentages (rather than numerical levels) for originator vs. biosimilar drugs. This also acts to provide an incentive for patients to receive the biosimilar, since prescription is associated with lower co-payments. For example, this case has been observed in Switzerland, where co-payment rates can be higher for drugs for which a cheaper option is included in the specialities list (SL) (e.g. originator products). A price limit is calculated by adding 10% to the average ex-factory price of the cheapest one third of all drugs on the specialities list with the same active ingredient composition.[88] If the originator exceeds such limit, patients need to pay 20% of costs in excess of the annual deductible compared to the normal 10%. This situation does not apply if the physician specifically prescribes the originator.[89]

Fixed reimbursement percentages do not have to be equivalent across biosimilars and originators. In the US, multiple biosimilar manufacturers have proposed that a higher reimbursement percentage for biosimilars could provide an incentive for biosimilar uptake.

A similar principle applies in countries that use fixed reimbursement levels for providers. For example, in Japanese hospitals, the Diagnostic Procedure Combination (DPC) reimburses hospitals with a fixed amount of the fee per inpatient day. The system does not set any specific requirements on the drug selected for inpatient treatment and, therefore, hospitals tend to use biosimilars as the cheapest therapeutic options, to profit from the system as much as possible. This is the reason why inpatient biosimilars, such as filgrastim, are leaders in the country.[90]

Cons: Although it encourages utilisation of the biosimilar, setting reimbursement levels to the lowest-cost options has been reported to destabilise competitive countries, especially for higher-cost biologics, and discourage manufacturers' participation/launch into a country.[91,92]

Sustainability evaluation: While policies limiting the level of reimbursement to the cheapest alternative can drive considerable cost savings to the system, this can encourage prescribing that is not in line with medical rationale and remove the potential for physician/patient choice (e.g. in situations where a specific mode of administration is linked with patient compliance). Further, continuous changes in reimbursement levels upon entrance of cheaper alternatives to the market can affect patients already initiated on a treatment and prompt excessively frequent switches, as well as suddenly affecting demand for marketed products, which could lead to over supply or shortages. In order to provide a fully sustainable environment, establishment of fixed reimbursement percentages can still benefit biosimilars and drive cost savings, in the end broadening their access and accelerating their uptake.

Exclusionary contracts

In some countries, 'exclusionary contracts' have been made between originator manufacturers or manufacturers of first-to-market biosimilars and payers that can inhibit the subsequent reimbursement and access of other biosimilar products. For example, in the US, some commercial plans require patients to receive access to originator products prior to a biosimilar.[93,94]

Pros: No positive effects on long-term sustainability for biosimilars have been identified with exclusionary contracts.

Cons: Exclusionary contracts are set up in such a way that payers (e.g. commercial plans in the US) derive higher benefits through confidential rebates/discounts applied by contracted manufacturers, provided an agreed level of market share is retained by the originator. The extent of the discount applied is not known, given the confidentiality of the agreements, but the net prices are expected to be significantly lower than the original list price and therefore perceived to be good value for payers. However, these exclusionary contracts limit the ability of biosimilar products to be successful in the country, thus resulting in limitations on the extent of cost savings that can be realised and decreased available market share for biosimilar products. Further to this, exclusionary contracts can restrict the ability of physicians to prescribe certain biosimilar products. Overall, exclusionary contracts have been criticised as obstructive policies, inhibiting access to biosimilars, and sometimes referred to as 'rebate traps'.[95]

Sustainability evaluation: The implementation of exclusionary contracts might be beneficial for certain manufacturers, but if they have the effect of reducing potential for biosimilar success, the overall effect on the market leads to decreased competition, negating basic cost savings and ultimately reducing the variety of available treatment options for HCPs and patients. This may also have negative impacts on the attractiveness of the market for future biosimilars in other therapeutic areas, eroding competition and increasing potential pricing.

Pricing policies

In some countries there are policies governing the list price of a biosimilar (and sometimes also originator) at time of biosimilar launch. Approaches to list-price setting ranges from free-pricing policies to pre-agreed price reductions.[96] It is critical that pricing policies in place are mindful of a long-term sustainable environment for all stakeholders, ensuring cost savings but also prioritising patient access, physician choice and predictability for manufacturers. In particular, list-pricing policies should be mindful of subsequent practices within the country such as tendering or further contracting negotiations. When combined with net price discounts, aggressive list-pricing policies could result in unsustainable levels of price reduction, leading to manufacturers' withdrawal from the market.

Biosimilar policies regarding pricing observed across countries include (Table 15):

- Mandatory discounts for biosimilars and/or originators
- Tiered price discounts for subsequent biosimilar products
- Progressive price discounts, applied over time
- Implementation of reference pricing (both internally and internationally)

Table 15: Pricing policies observed across countries in scope

	AUS	BEL	BRA	CAN	FRA	DEU	GBR	ITA	JPN	MEX	NLD	NOR	SAU	ESP	CHE	UAE	USA
At launch – mandated fixed discounts for biosimilars	✓	o	o	o	✓	o	o	✓	✓	o	o	o	o	✓	✓	✓	o
At launch – mandated fixed discounts for originators	✓	✓	o	o	✓	✓	o	o	o	o	o	o	o	o	o	o	✓
At launch – tiered discounts for biosimilars	o	o	o	o	o	o	o	o	o	o	o	o	✓	o	o	o	o
Over time – progressive price discounts	✓	o	o	o	o	o	o	✓	o	o	✓	o	o	o	o	o	o
At launch – reference pricing mechanisms	✓	✓	✓	o	o	✓	✓	✓	o	o	✓	✓	o	✓	o	o	✓

✓	Policy applied in the country	o	Policy not identified or not applied

Source: CRA analysis

Discounts applied at launch

Mandated fixed discounts for biosimilars: In order for biosimilar products to secure reimbursement, they are often required to launch with a list price at a certain discount from the existing originator's list price. For example, in Italy, biosimilars must launch with a list price of at least a 20% discount to the

originator list price in order to be reimbursed,[97] and in France biosimilars in the retail setting must be discounted by 40%.[98] In the majority of cases, this discounted list price is subject to further confidential price reductions through tendering and/or contracting mechanisms.

Mandated fixed discounts for originators. In addition to mandating discounts for biosimilars, many countries also mandate originator discounts when a biosimilar launches**.** For example, in France, originators are required to discount their list price by 20% in the retail setting and 30% in the hospital setting upon biosimilar launch. In countries where originator discounts are not mandated, manufacturers are able to voluntary decrease their product's price, but this is a decision made by the manufacturer.

Tiered discounts for biosimilars at launch: An extension of mandated list-price discounts for biosimilars is the concept of tiered discounts. For example, in the Kingdom of Saudi Arabia (KSA), discounts applied at launch vary from entrant to entrant, with the first biosimilar being subject to smaller discounts than later entrants (the first biosimilar marketed cannot exceed 75% of the originator's list price, and the second and third biosimilars cannot exceed 65% and 55%, respectively).[99]

Pros: Discounts applied at time of biosimilar launch can be effective ways for payers to guarantee cost savings in the short term. Through these mechanisms, many countries have seen significant cost savings to healthcare expenditure. This can be useful in small countries (e.g. the KSA) where high levels of competition are not expected in subsequent contracting mechanisms, or patient volumes are also significantly smaller. In order to realise biosimilars' benefits to the system, set discounts at launch in these smaller countries can mimic the same force that would drive net price discounts in bigger ones, where more competition is expected. Moreover, list-price discounts set at launch can serve as a means to ensure predictability for manufacturers.

Cons: While mandated price reductions might lead to a downward trend in pricing, fixed discount levels can sometimes be seen as arbitrary and do not allow for differentiation across therapy areas where a smaller or larger discount may be more appropriate (depending on, for example, the clinical value of the product, available market share or originator list price). Moreover, list-price discounts may be particularly problematic in those countries where biosimilars are not perceived as a specific category within pricing guidelines (e.g. Brazil), which can lead to unfair, and hard to achieve, discounts closer to the range for generic chemical medicines.

List prices are often not the final prices paid for a biosimilar, and therefore, in some countries, these mandatory list-price discounts have instead resulted in unsustainable levels of price reduction in the long term.[100] For example, the recent retraction of the filgrastim biosimilar Zarzio from the Belgian market in 2019 and the absence of insulin (lispro and aspart) or teriparatide biosimilars have been reported as the first indications of a non-sustainable situation in the retail setting where there are no limits on discount level and no volume guarantees applied.

Similarly, tiered discounts can incentivise fast access of biosimilars, but they can also disincentivise subsequent competition by disincentivising later entrants, which are accepted to be necessary to achieve sustainable levels of cost savings within a country. With limited competition within the country, the incentive to reduce pricing is minimal.

Overall, significant mandatory price reductions for both biosimilar and reference products limit the space for further price competition. Without volume guarantees for biosimilar products, ongoing and unrestricted price revisions at regular intervals are not likely to be sustainable in the future as biosimilar manufacturers might opt out of the market.

Sustainability evaluation: Although they might be useful for certain smaller countries with lower expected levels of competition, overall, significant mandatory price reductions for both biosimilar and reference products limit the space for further price competition. Without volume guarantees for biosimilar products, ongoing and unrestricted price revisions at regular intervals are not likely to be

sustainable in the long term. Fixed discounts do not account for market dynamics and can have a more negative impact in therapy areas with smaller volumes and competitors expected (e.g. rare diseases). Moreover, list-pricing discounts can further jeopardise biosimilar sustainability when their differences with respect to generic medicines are not understood and gathered in pricing mechanisms. Additionally, mandated discounts for originators can disincentivise manufacturers to invest in innovation and development of new drugs.

Discounts applied over time

Progressive price discounts: List prices can continue to be lowered over time, based on either new entrants, time or market dynamics. For example, in Norway, the original price set for biosimilars when they enter the country is not static. The discount level continues to increase with time and as the country competition gets higher.[101]

Reference pricing mechanisms: In other countries, revisions to the list price are mandated over set periods of time and are applied through the creation of reference price groups or price disclosure mechanisms, as seen for example in Australia.

Pros: Discount levels that are dictated by market dynamics instead of arbitrary thresholds/rules have been praised as more sustainable discounting options that allow for differences in therapy areas to be recognised. These policies can incentivise competition and, in the long term, result in sustainable levels of cost savings, although it should also be highlighted that achieving the lowest possible price for biosimilars should not be the goal, to safeguard the sustainability of the market.[102]

This is the case in the Netherlands, where biosimilars can officially launch at the same price as their reference biologics, although subsequent reference pricing mechanisms sets the conditions for both and can lead to price decrease.[103] Internal reference pricing also applies in certain countries, such as Spain, where products are gathered in unified groups by their active compound and their prices are agreed depending on the basket average.[104]

Cons: However, these additional progressive discounts can often be seen to lead to unsustainable prices, especially in cases where volumes / market share of products is not guaranteed. Moreover, reference-pricing policies can homogenise pricing across all products with the same active ingredient, thus not allowing for differentiation across entrants (e.g. citrate-free, low-volume adalimumab).

Reference pricing mechanisms can sometimes be too aggressive and equally result in dramatic cost reductions that could jeopardise long-term sustainability. In Belgium, for example, 'the cliff' cost containment policies allow for steep price decrease of products when certain criteria are met (e.g. certain market share). In the case of the 'biocliff', both originator and biosimilar undergo high price discounts upon the market entrance of the latter, leaving room for unpredictability.[105] Therefore, reference pricing systems must still safeguard fair mechanisms and realistic criteria to drive cost containment.

Sustainability evaluation: Although internal reference pricing can equalise competition between biosimilars and originators and establish fair basis for cost savings, it also does not allow for any price differentiation and can result in unsustainable price reductions if volumes are not guaranteed. Pricing over time, based on market dynamics, allows for differences across therapy areas to be recognised in ways that fixed discount levels do not, but fair levels of price reduction need to be ensured to maintain incentives for competition and innovation, and to ensure predictability for businesses.

3.5. Contracting

Pricing and reimbursement policies set the baseline for list-price discussions. However, further contracting agreements are often made to determine access and net prices. Contracting mechanisms vary across countries and are often agreed via direct negotiation or through tenders. Given that these contracting mechanisms often agree additional price discounts, there is also the potential for excessive price erosion, which in some cases can be significant enough to affect most stakeholders involved, causing manufacturers to leave the market, and potentially resulting in supply shortages, affecting treatment access for HCPs and patients. Therefore, it is necessary that contracting policies provide clear limitations to ensure a sustainable long-term environment for biosimilar access and supply, ensuring cost savings are realised but not in a manner that is unsustainable for manufacturers.

Biosimilar policies regarding contracting observed across countries include (Table 16):

- Direct contracting with providers
- Tendering procedures

Table 16: Contracting policies observed across countries in scope

	AUS	BEL	BRA	CAN	FRA	DEU	GBR	ITA	JPN	MEX	NLD	NOR	SAU	ESP	CHE	UAE	USA
Direct contracting with providers	✓	✓	✓	✓	O	O	O	O	O	O	O	O	✓	O	✓	✓	✓
Tendering practices	✓	✓	✓	O	✓	✓	✓	✓	O	✓	✓	✓	✓	✓	✓	✓	O

✓ Policy applied in the country | O Policy not identified or not applied

Source: CRA analysis

Direct contracting with providers

Signing of contracts for the supply of biologics directly with manufacturers is an established trend in the US, where health plans and private insurance providers can reduce their costs via direct negotiations to include certain drugs on their formulary.[106] Additionally, other countries can enter into contracts directly with suppliers, such as private sector providers in Brazil and Mexico, or outpatient providers in Belgium. Direct contracting can take place at the national or sub-national level.

Pros: National direct contracts can enable faster (and potentially broader) access to treatments, providing equal supply for all regions across the country. However, competition needs to be at all times ensured. One way of maintaining competition is for contracts to be agreed between manufacturers and sub-national authorities, as contracts can vary from one region to the other and offer a wider opportunity for manufacturers to gain a portion of market share.[107] Moreover, committing to contracts for regional populations can decrease risk of supply issues and provide opportunities for smaller manufacturers to hold a position in the market, although regions need to be large enough to also provide a fair division.

Countries which do not practice tendering for biosimilars, such as Canada, can realise additional benefits relative to tendering markets. For example, price negotiations led by the pan-Canadian Pharmaceutical Alliance (pCPA) resulted in greater reductions in biosimilar pricing than were seen in the EU, once their negotiators became aware of the level of discount conceded in the EU as a result of tenders.

Cons: While these contracting practices, on both the national and sub-national level, can offer long-term savings to the system, they may also disadvantage second-to-market biosimilars where there is a perceived lower need to arrange additional agreements if providers are satisfied with the first arrangement. Experts believe that establishing several different sub-national contracts can be limiting, given the increased administrative burden for suppliers, which can result in access delays. This is especially relevant in cases where contracts are agreed for very small patient populations (e.g. at individual hospital levels), further reducing incentives for contract agreements to be made and driving disparities in product access within a single country. Moreover, monitoring and regulation enforcement where there are numerous sub-national contracts is likely to be more difficult, as different criteria might apply across fragmented regions and therefore impede governmental authorities from easily ensuring that suppliers are sticking to the requirements.

It has been reported that, theoretically, originator manufacturers can participate in direct procurement negotiations shortly before the market launch of biosimilar competitors, potentially excluding these biosimilars due to their advantage position as incumbents.[108] As a result, direct contracts need to avoid exclusionary, anticompetitive behaviours, and regulations must apply to consider certain dynamics on their renewals, giving chances for all new biosimilar entries to gain market shares.

Lastly, direct contract decisions between suppliers and payers tend to leave out the input from healthcare professionals and pharmacists, who are the ultimate stakeholders who will decide on biosimilar treatment to better benefit the patient. As a result, multidisciplinary decision-making involving all key contributors of the healthcare system is a rare practice, and prescribing/dispensing treatment options are often reduced, resulting in less autonomy for professionals and reduced patient access to novel biologics.

Potential sustainability benefits: While national contracts can provide fairer and more unified treatment alternatives for HCPs and patients, they might reduce competition if the number of selected suppliers is not enough. Regional contracts can ensure multiple suppliers within any given country but can lead to increased administrative burden, access delays and more complex monitoring and regulation efforts. Further, if sub-national agreements are made at a too-small scale, disparities in access across a country can emerge. Independent of geographical level of the contract, agreements must always ensure proper integration of HCPs' and pharmacists' opinions into decision-making.

Tendering practices

Many countries use tendering as their preferred procurement approach for biosimilars. These tenders generally occur at the national level, but can be managed regionally, allowing for regional variation. It is possible to identify certain common factors to ensure long-term sustainability of biosimilars across countries. Such factors can be gathered under three main categories: **(1)** the number of winners allowed, **(2)** criteria used for their awarding, and **(3)** the length of the awarded contracts.[109] Tendering procedures, when set up appropriately, can be useful mechanisms to ensure not only cost savings but also good levels of supply and an environment where competition and broad access are safeguarded.[110]

- ***Number of granted awards***

The number of manufacturers selected for the national/regional supply of biosimilars on awarded contracts can be crucial and determine the correct functioning of biosimilar procurement in countries.

Pros: Awarding tenders to multiple suppliers has been shown to enhance competition and it provides noticeable cost savings without driving unsustainable price reduction.[111] In particular, the organisation of multiple tenders per region to encourage multiple manufacturers to operate in the country has proved to drive competition and maximise patient access to affordable treatments.[112] For example, in the UK,

authorities have allowed multiple winners in tenders, either through one national tender or through smaller sub-national tenders, each allowing for at least one winner, as seen for adalimumab biosimilars.[113] This practice has supported competition through guaranteed degressive market shares based on the competitiveness of proposed tender pricing. Additionally, this tendering strategy supported sustainability through the division of the market into 11 hospital groups, with staggered tenders providing multiple opportunities to win, each of which was allocated a specific originator or biosimilar product.[114] On a similar trend, in some other countries, such as Spain, tenders are awarded to a main supplier, but a recommended list of ranked suppliers can be also provided for those cases where the main selected winner fails to supply, or in order to distribute market shares according to ranges of price.[115] This can provide a sustainable environment where several biosimilar providers can share a certain percentage of the market without requiring aggressive strategies to steeply reduce price.

Cons: Multiple winner tenders can still be unsustainable when volume guarantees are not made to winners. This can result in cases of over-supply or supply shortage and have even more unpredictable results for manufacturers that are not successful in tenders at all. Awarding tenders to a single winner can negatively impact the participation of manufacturers and competition between them, and reduce physicians' prescribing choices.[116]

For instance, some countries, such as Norway, have encountered supply problems when tenders have been awarded to only one pharmaceutical company, which in the end has struggled to provide enough product.[117] Such processes can even be worsened, taking into consideration national contracts where a single winner must supply a whole country and market share is completely taken away from the rest of participants. Lessons learnt from this situation have evidenced that the awarding of national tenders to single winners provides an unsustainable environment for biosimilars, which has led the Norwegian Pharmaceutical Industry Association (LMI) to propose the winning of two suppliers in tendering contracts in order to avoid a second supply shortage.[118]

Sustainability evaluation: When deciding on the contract criteria for awarding tenders, a healthy level of competition must always be ensured. There is evidence that the selection of a single supplier can be effective in the short term and in encouraging significant price competition. However, this is unlikely to be sustainable, as it can disincentivise participation. By selecting multiple winners, healthier volumes of supply will be required from a number of suppliers, improving predictability and avoiding any unforeseeable shortages, such as have happened in previous examples.

- ***Awarding criteria***

Of equal importance to ensure sustainability are the criteria considered for tender awarding, which should consider multiple factors to avoid the award of tenders being completely weighted on a single consideration such as price.

Pros: Weighting the awarding of tenders on multiple factors as opposed to the consideration of price can avoid unsustainable price erosion and encourage participation of a good number of manufacturers in tenders.[119] Several countries, like Switzerland, have added extra criteria to be considered when selecting tender winners, such as manufacturers' ability to supply or local manufacturing.[120] In the case of the Netherlands, despite insurance companies' pressure on price, tenders can also account for periodic updates from manufacturers on stock availability.[121]

The correct implementation of these policies, however, must be thoroughly controlled to ensure that additional criteria are indeed equally considered, and price does not fully govern tender award decisions. For example, in Italy, budgetary law requires consideration of additional elements beyond price (e.g. quality, organisational impact) for tender awarding. However, poor enforcement and regulation of the law has led regional authorities still to consider price as the main decision factor.

Therefore, monitoring of the correct implementation of laws ruling tenders can ensure that new included criteria are equally considered.

Equally important, the inclusion of HCPs and pharmacists into decision-making can improve the awarding criteria used in tendering practices. This is the case observed in Norway, where physicians can determine which treatments can be considered of equal clinical benefit to include in a tender. The procurement of such products will then be decided on tenders, where multidisciplinary decisions will also evaluate HCPs' clinical opinion, opening a window for the application of better awarding criteria.

Finally, in the same way that manufacturers can be required to monitor their capabilities, tenders should provide reliable estimates of volume to ensure a predictable environment, guaranteeing a minimum volume and defining a maximum cap. Covering an unexpected increase in demand may be difficult for manufacturers, as it is complicated and lengthy to increase the production scale due to the complex manufacturing process of biologics.[122] Similarly, in cases where no minimum volumes are guaranteed, tenders could lead to a risk of unused stock and issues with scaling. Suppliers with overstock may go for highly competitive offers in pending or subsequent tender procedures, which may lead to unsustainable market dynamics.[123]

Cons: Price is usually the main, sometimes the single, factor that decides a winner. In countries like Spain or Italy, regional tenders are still heavily awarded on price,[124,125] which has led to such high discounts for biosimilars that price levels have even reached those of generic drugs.[126] Unsustainable awarding criteria in Spain have led to the majority of tenders being awarded to suppliers with no existing track record in the country, discouraging good levels of participation, especially from local participants.[127] This goes against the recent 'Action Plan for Science & Innovation' of the national government, which places R&D and innovation at the centre of Spain's recovery strategy.[128]

Sustainability evaluation: The inclusion of criteria beyond price for awarding tenders can encourage increased competition and long-term cost savings owing to a more sustainable market. Criteria regarding supply and local manufacturing / existing presence in the country can help to avoid supply shortages and facilitate greater trust within a country. Considerations of value-added services can provide multi-stakeholder benefits from tendering procedures (e.g. opportunities for patients to benefit).

- ***Contract length***

Finally, the contract length for awarded tenders can also be important for establishing a predictable but competitive environment and can therefore influence participation. The reopening of tenders upon new entries in the market can have different levels of benefits and drawbacks between stakeholders, so policies to regulate this need to be thoroughly considered.

Pros: While short tender durations can be important to promote competition, as shorter periods can mean a more frequent renewal of suppliers, longer contracts provide better predictability for manufacturers and HCPs/patients. In order to find a balance between the two, sustainable tender guidance for implementation following first biosimilar entry has proposed reopening of tenders within 6 months to enable competition versus originators while ensuring business predictability. On the other hand, contracts of up to 12 or 24 months have been considered if multiple biosimilars are expected to launch in a short period of time. These longer awards can better contribute to sustainability in more mature countries, once a certain number of competitors is already established.[129] Long-term tenders which require an annual price improvement have also been proposed as a more sustainable practice compared to current practices where excessive competition among manufacturers can lead to unsustainable price reductions without following any criteria.

Cons: Policies allowing for the constant reopening of tenders upon the entrance of new competitors in the market (e.g. within 60 days in Italy) are indicative of unsustainability, resulting in further discounts

and conditions different to what was previously agreed.[130] Further to this, constant reopening of tenders can jeopardise predictability for manufacturers as well as HCPs, if available treatment options are subjected to tendering practices.

Potential sustainability benefits: Debates on the adequate duration of tender contracts need to consider not only opportunities to boost competition and drive cost savings but also the potential harms that this might bring. Shorter contracts can also mean constant switching of patients' treatments, which is equally unsustainable in the longer term.[131] As a potential alternative, contracts could account for differences within therapeutic areas when deciding on their length – e.g. those therapy areas where longer treatment periods are expected, such as chronic disease, might require longer tenders. Independently of the country context, policies that can contribute to predictability and grant efficient access for biosimilars can also be ensured when tender operators commit to making a decision in a timely manner.

3.6. Biosimilar education and understanding

If biosimilars are to compete on a level playing field with originator products there needs to be confidence and trust in them from all key stakeholders. The concept of biosimilarity is fairly new for the majority of countries and has only affected a limited number of therapeutic areas.[132] It is therefore unsurprising that public understanding still needs to be increased. The lack of complete knowledge among stakeholders, from HCPs to patients, has led to mistrust and misconceptions regarding biosimilars, on the grounds of associating cheaper alternatives with lower quality. It is also important that education targets the full range of stakeholders with influence over key access and uptake decision makers, including prescribing physicians, pharmacists and patients. Moreover, for countries where access to biosimilars is decided through contracting (e.g. Spain and Italy), educational efforts focused on payers and other decision makers is critical as these decisions often provide little additional flexibility for physicians and pharmacists with regards to prescription and/or dispensation.

Biosimilar policies regarding public health education observed across countries include (Table 17):

- HCP and pharmacist educational programs
- Patient educational programs

Table 17: Biosimilar education and understanding campaigns/policies observed across countries in scope

AUS	BEL	BRA	CAN	FRA	DEU	GBR	ITA	JPN	MEX	NLD	NOR	SAU	ESP	CHE	UAE	USA
HCP- and pharmacist-targeted educational programs																
✓	✓	O	✓	✓	✓	✓	✓	O	O	✓	✓	✓	✓	✓	O	✓
Patient-targeted educational programs																
✓	✓	O	✓	✓		✓	✓	O	O	✓	✓		✓	O	O	✓

✓ Policy applied in the country | O Policy not identified or not applied

Source: CRA analysis

HCP-targeted educational programs

Healthcare professionals can resist the use of biosimilars, which on certain occasions can be a key driver behind limited uptake of biosimilars. Reasons for this include the availability of long-term safety data and real-world evidence that is often perceived as being relevant only for the originator product and also that well-established originator products are linked to pharmaceutical companies with better visibility among HCPs and with overall higher revenues that allow for stronger marketing campaigns.

Pros: Given that HCP misconceptions are often key limiting factors for biosimilar success, specific HCP- and pharmacist-targeted campaigns can help to build trust in biosimilar products, resulting in equal consideration of biosimilars with originators in the long term. When developing such campaigns, leveraging help from people within the same career can prove essential to accurately reach the target population – this means, programs delivered by HCPs to educate their peers will have a better outcome, and the same principle applies for pharmacists. Educational efforts can also arise from within hospitals to educate their staff as needed, as much as leveraging governments' resources (e.g. regulatory agencies, HTAs and public drug programs) and/or materials created by the pharmaceutical industries,

professional associations and patient groups to educate stakeholders. Moreover, such efforts must be a continuum, and campaigns must therefore happen on a regular basis and through different communication channels in order to keep the scientific community constantly updated and engaged. Further to educational campaigns, certain countries like the UAE have implemented policies to counteract incorrect misconceptions and to avoid preferential treatment of originators from HCPs.[133]

Cons: No negative effects on long-term sustainability for biosimilars have been identified.

Sustainability evaluation: The implementation of educational campaigns for healthcare professionals can improve their perception about biosimilars and provide better understanding of the additional value these can provide. Given HCPs and pharmacists are the final stakeholders between the product and the patients, targeted education can have benefits for a wider group of stakeholders in the same way that their miseducation can result in extremely high barriers for biosimilar success.

Patient educational programs

There is often a direct correlation between the uptake of off-patent medicines in a country and the level of understanding of its patient population, which can be targeted via different communication channels.[134] Therefore, for cost savings and benefits obtained from biosimilars to be realised, there is a need for a policy framework which considers patient-targeted educational programs within its priorities.

Pros: Educational campaigns to target patient segments can provide a way to overcome the last barrier for biosimilars access. Knowledge about biosimilars' added values can empower patients, particularly in countries where HCPs especially consider patients' perspectives. While certain countries, like the Netherlands, have shown good approaches in their patient-targeted educational campaigns,[135] others, such as Belgium, still struggle with the proper targeting of the relevant population.[136]

The involvement of different stakeholders in leading educational campaigns can also determine their level of success. Thus, educational efforts can come from both national organisations and pan-national/international bodies. As an example of the first, the influence of French patient associations in policy creation has resulted in a plan to achieve 80% penetration by 2022.[137, 138]

Cons: Political will has also been regarded as beneficial and proven to be a key element driving education in certain countries. However, the involvement of governmental bodies in such campaigns can also act as a burden in countries where there was a previous lack of trust, and government's efforts tend to be regarded as a means for costs savings only. The same can be true with regards to manufacturer-sponsored educational campaigns, which can be considered less trustworthy due to existing biases in public perception. In these cases, educational programs could be better accepted if led by other, more neutrally perceived bodies and based on clear, clinical and real-world evidence. This can be the case for educational campaigns launched by supra-national corporations like the EMA and directed to HCPs and patients,[139] or independent associations without government affiliation, as in the case of BioSim in Spain or Egualia in Italy.[140, 141]

Sustainability evaluation: Increasing HCPs' and patients' understanding of the benefits of biosimilars can improve their public perception and provide a way to promote their uptake, especially in the outpatient sector. Greater knowledge about biosimilars can increase their uptake among patients and broaden their access, resulting in cost containment on the long term.

3.7. Prescribing

Policies which influence the prescription of biosimilars are key to determining their uptake, often the 'last hurdle' faced by patients to access biosimilars. Policies can promote or mandate usage through formal/informal recommendations or incentives/penalties. While increased use of biosimilars is a clear goal of prescribing policies, they can also have wider implications for the ability to monitor downstream usage of biosimilars (e.g. from a pharmacovigilance perspective).

Biosimilar policies regarding dispensing observed across countries include (Table 18):

- Clinical recommendations for prescriber-initiated prescription of biosimilars
- Mandated switching to cheapest alternative
- Prescription quotas for volume of biosimilar prescription
- Financial incentives linked to volume of biosimilar prescription
- Financial penalties linked to volume of biosimilar prescription
- International non-proprietary name (INN) prescribing

Table 18: Prescribing policies observed across countries in scope

AUS	BEL	BRA	CAN	FRA	DEU	GBR	ITA	JPN	MEX	NLD	NOR	SAU	ESP	CHE	UAE	USA
Clinical recommendations for prescriber-initiated prescription of biosimilars																
✓	O	O	O	✓	✓	✓	✓	O	O	✓	O	✓	✓	✓	✓	O
Mandated switching to cheapest alternative																
O	O	O	✓	O	O	O	O	O	O	O	✓	O	O	O	O	O
Prescription quotas for volume of biosimilar prescription																
O	✓	O	O	✓	✓	✓	✓	O	O	O	O	O	✓	O	O	O
Financial incentives linked to volume of biosimilar prescription																
O	✓	O	O	✓	✓	✓	✓	✓	O	O	O	O	O	O	O	O
Financial penalties linked to volume of biosimilar prescription																
O	O	O	O	O	✓	O	O	O	O	O	O	O	O	O	O	O
de facto INN prescribing																
✓	O	O	O	O	O	O	O	O	✓	O	O	O	✓	✓	O	O

✓	Policy applied in the country	O	Policy not identified or not applied

Source: CRA analysis

Clinical recommendations for prescriber-initiated prescription of biosimilars

In some countries, clinical guidelines consider cost-effectiveness principles and make recommendations to prescribe cheaper biologic products where it is medically safe and appropriate to

do so. However, these guidelines are used as recommendations and still require the physician to decide about the prescription of biosimilars.

Pros: Recommendations to use biosimilars in clinical guidelines are a means of promoting their use in a non-mandatory fashion and maintaining physicians' prescribing autonomy. For instance, in Australia, the 2017 update of the National Budget involved a commitment from the Government to Medicines Australia, the Generic and Biosimilar Medicines Association and the Pharmacy Guild of Australia to implement biosimilar uptake drivers. Recommendations to encourage the prescription of biosimilars rather than the reference, originator brand were included as part of these drivers.[142]

If switches systematically occur, the resulting cost savings benefit the health system and continue to support broad access and increased biologic competition, and ensure that prescribers have access to a variety of treatment options.

Cons: Conversely, non-mandatory switching and recommendations may not be strong enough, especially in countries or therapy areas where there are pervasive misconceptions surrounding the value of biosimilars. Therefore, non-mandatory measurements must always be complemented with educational campaigns to fight misconceptions around biosimilars and, ideally, interventionalist policies. Ultimately, policies that support prescribing decisions towards '*best value biologics*' would establish equal grounds for competition between biosimilars and their originators.

Sustainability evaluation: Recommendations to prescribe biosimilars based on their cost-effectiveness are largely a sustainable practice that can support wider use of biosimilars. However, in some countries, such measures may not be sufficient to guarantee equal opportunities for biosimilar products, and therefore, the introduction of temporary interventional policy may be required to stimulate biosimilar use.

Mandated switching to cheapest alternative

Some policymakers choose to mandate lowest-cost switching policies. By limiting reimbursement of higher-cost originators and biosimilars, these policies ensure only the lowest-cost treatment is (initially or exclusively) prescribed.

Pros: Mandated switching to lowest-cost alternatives has the effect of rapidly driving biosimilar uptake, capturing cost savings for the healthcare system. Examples of these switching policies are observed in some Canadian provinces, where patients are required to switch from their originator biologic treatment to a biosimilar, reducing overall costs for the insurance plan.[143] British Columbia introduced its non-medical switching (NMS) policy in May 2019, and this has triggered other provinces (e.g. New Brunswick and Quebec) to implement and review potential implementation of NMS policies.[144,145] Following introduction, patients are typically given six months to consult with their physician before their treatment is switched to the lowest-cost treatment. Importantly, however, there are often medical exceptions to the mandatory switch – e.g. patients under 18 years or pregnant women.

Cons: Mandated switching policies can create less-competitive market environments if just one product is deemed the 'lowest-cost option' and no other biosimilars are allowed in the market (e.g. as the result of a single-winner tender). Depending on the notice period given to patients regarding switching, this can result in multiple switching over short time periods resulting in confusion and also increased challenges in monitoring practices. Further to this, promotion of the use of the cheapest product diminishes the ability of manufacturers to predict their business, given the risk of being undercut and rapidly losing sales volume. The same way, leaving all the country to be supplied by a single option might further increase the chances of suffering from supply shortages.

Potential sustainability benefits: A mandated switch to the lowest-cost alternative might act as a driver for biosimilars uptake but it sets the grounds for diminishing competition opportunities for other stakeholders in the country. Moreover, this practice decreases the responsibility of physicians within prescribing and sends a message of cost savings above all other criteria, which can be harmful for the understanding and perception of biosimilar value. Lowest-cost switching can also result in frequent and multiple switching as prices evolve, promoting a 'race-to-the-bottom' effect with regards to price, leading to unsustainable levels of price erosion.

Prescription quotas for volume of biosimilar prescription

Quotas define a fixed volume or proportion of prescriptions that must be made for the biosimilar. They often apply to a certain active ingredient, but they can consider a physician's prescriptions within a therapy area or their overall prescriptions.

Pros: Given that biosimilars are typically priced below their originator products, introduction of these quotas is a direct means of reducing healthcare spending. Depending on whether quotas are mandatory or not, their introduction can encourage or ensure that physicians consider switching/initiation where it is safe to do so.

In Germany, the National Association of Statutory Health Insurance Funds (GKV-SV) and the National Association of Statutory Health Insurance Physicians (KBV) annually define prescribing targets across therapy areas. These targets are non-binding and act as a guideline for the formation of prescription quotas at the regional level. Based on this, regional physician associations (KVs) can then define their own quotas; these quotas vary considerably between federal states.[146] Generally, quotas implemented at the regional level are binding, and some are even more stringent than the national prescribing targets. Consequently, this contributes to the relatively high biosimilar penetrations observed in some states, such as the 87% biosimilar infliximab market share observed in Lower Saxony (Q4 2018).[147]

Prescription quotas that have been implemented in other countries, such as the UK, have not been binding. The NHS 'Commissioning Framework for Biological Medicines (including biosimilar medicines)' established non-mandatory biosimilar quotas in 2017.[148] Goals included a target to initiate 90% of treatment naïve patients on the 'best value biological medicine' within three months of the launch of a biosimilar, and at least 80% of existing patients within 12 months.[149]

Conversely to lowest-cost switching, quotas for biosimilars more broadly still enable health price competition among biosimilars and provide equal opportunities in legislation for price differentiation, leaving biosimilar prescriptions ultimately at the choice of the physician.

Cons: Quotas have been criticised for not ensuring a level playing field for biosimilars and biologics to compete freely. Further, quotas are not always seen as effective measures to promote use of biosimilars if needed to achieve savings in the short term. For example, in the UK, non-mandatory quotas were not initially met for biosimilars of Remicade (taking 28 months to reach 80% of market share) and Enbrel (taking 12 months to reach 50% of market share). However, implementation of financial incentives in addition to quotas eventually drove further uptake for subsequent biosimilar launches.[150] Thus, while non-binding quotas do support biosimilar uptake, coupling them with other incentives (e.g. financial) increases their impact.

Sustainability evaluation: Prescribing quotas can boost biosimilar uptake in the short term only if correctly implemented with other prescribing incentives, but are not necessarily measures for a sustainable biosimilar market in the long term as they do not foster natural competition between the originator and the biosimilars. As an extension of this, prescribing quotas need to consider differences

across therapy areas and how competition and perception of prescribers within therapy areas evolves over time.

Financial incentives linked to biosimilar prescribing

Similar to biosimilar quotas, provision of incentives to prescribe lower-cost products can serve as an encouragement for driving biosimilar uptake in the short term, supporting fast and efficient broadening of access to treatment.

Pros: Implementation of financial incentives in the UK had a marked impact on the rate at which biosimilar quotas were met in the short term. NHS England adopted the Commissioning for Quality and Innovation Scheme (GE3 Hospital Medicine Optimisation). This provided a target payment of 1% of contract value (based on the total hospital spending on the high-cost drugs) for tariff-excluded high-cost drugs, where providers met the prescribing quotas outlined in the NHS 'Commissioning Framework for Biological Medicines' (90% of naïve and 80% of existing patients).[151] Coupled with quotas for biosimilar medicines, these incentives have resulted in the UK having some of the highest market shares for biosimilar products globally.

In addition to direct financial incentives for physicians, an alternative means of incentivising biosimilar prescribing is through the introduction of indirect gain sharing mechanisms which can provide other benefits linked to the level of cost savings realised through prescribing. These have been observed in Germany, where agreements between some insurers and groups of physicians have enabled payer savings to be shared between groups of, and individual, physicians. An example is the BioLike initiative launched by the sick fund Barmer GEK with groups of gastroenterologists and rheumatologists, which allowed for relatively higher (>50%) penetration in the tumour necrosis factor α inhibitor market by sharing savings realised between the sick fund and the physician association.[152]

Cons: As with biosimilar quotas, prescribing incentives have been criticised for being short-term solutions appropriate to boost biosimilar uptake but not long-term solutions for an equal and sustainable market. Implementation of physician incentives to drive biosimilar uptake has demonstrated to be efficient in the short term but cannot be the ultimate goal to achieve in the long run. Educational campaigns need to be developed in parallel, to ensure that biosimilar benefits sink into the scientific community as physicians obtain direct incentives from them. As educational campaigns start proving their effectiveness for biosimilar uptake, and always considering the country context, physicians' incentives can be slowly (and never abruptly) retrieved, always safeguarding that biosimilar prescribing levels do not go back to previous levels.

Sustainability evaluation: Incentivising biosimilar prescribing through financial bonuses can indirectly improve the understanding of their value, as physicians can realise the equal efficacy and safety of off-patent biologics. However, these measures must be considered as short-term measures to boost biosimilar uptake, while long-term durable solutions establish fundamental trust in biosimilars to drive their uptake (e.g. educational campaigns). As a result, it is always necessary to evaluate biosimilar uptake levels and consider slowly decreasing financial incentives as other sustainable policies take over.

Financial penalties linked to biosimilar prescribing

Financial penalties act as a deterrent for physician prescribing of higher-cost originator biologics, providing cost savings for the healthcare system in a similar way to financial incentives. Penalties are implemented less frequently than incentives across countries.

Pros: In the same way as financial incentives linked to cost savings, financial penalties can act as mechanisms to encourage uptake of biosimilars in the short term to ensure that prescription quotas are met.

Cons: These policies can be seen as more obstructive than constructive and negate flexibility in prescribing by reducing physicians' treatment options. For example, in Germany, a physician's prescribing history can be audited, and if they cannot justify their use of higher-cost originators, they may face a penalty of reduced remuneration.[153] However, these audits and penalties are loosely enforced, indicating that they have lesser support as an incentive mechanism when compared to 'positive' incentives, which are generally considered to be a more sustainable means of driving biosimilar uptake.

Sustainability evaluation: While financial incentives maintain physicians' freedom to prescribe, financial penalties can reduce it, also affecting patients' access to broader options. Despite driving cost savings, the negative sentiment generated by these financial penalties can actually have a negative impact on biosimilars' perception and result in lower uptake in the long term.

de facto INN prescribing

INN prescribing describes the practice by which physicians write prescriptions using only the name of the product's active compound and the pharmacist then has the opportunity to dispense their choice of a brand biologic of that INN (the originator or a biosimilar).

Pros: From an optics perspective, INN prescribing can support an increase in biosimilar uptake in the short term and encourages prescribers, pharmacists and patients to understand that biosimilars contain the same active ingredient as originator products.

Cons: However, INN prescribing also means that the differences across biosimilars (e.g. excipients) may not be considered during prescribing. Further to this, INN prescribing reduces traceability of prescribed products if no additional brand identification is recorded on pharmacovigilance systems. Many countries use INN prescribing but with the ability to differentiate between products using full INNs that include unique identification codes. For example, in Switzerland, INN prescribing is required by Swissmedic (surveillance authority for medicines), but in order to support pharmacovigilance efforts, the INN must be followed by a unique biosimilar-specific identification code, as recommended by the WHO.[154]

Sustainability evaluation: INN prescribing can support an increase in biosimilar uptake in the short term and facilitate a better understanding of biosimilar products. However, this practice also raises some further challenges to a sustainable market by increasing the opportunity for non-medical switching and by reducing traceability of products. There are policy measures (e.g. unique INN suffixes) that can be put in place to overcome these situations, but this is a policy to be approached with caution and not to be implemented on its own.

3.8. Dispensing

In order to ensure broad access to biosimilars, it is also critical that the appropriate incentives are given to pharmacists who act as key 'gatekeepers' for access. While switching should remain a medically driven decision, adequate responsibility should be given to pharmacists to support healthcare systems to realise cost savings in a sustainable and fair manner through fair dispensation practices.

Biosimilar policies regarding dispensing observed across countries include (Table 19):

- Automatic substitution
- Regressive retailer markups
- Reduced patient co-payments

Table 19: Dispensing policies observed across countries in scope

AUS	BEL	BRA	CAN	FRA	DEU	GBR	ITA	JPN	MEX	NLD	NOR	SAU	ESP	CHE	UAE	USA
Automatic substitution																
✓	O	O	O	✓	✓[iv]	O	O	O	O	✓	O	O	O	O	O	✓
Regressive retailer markups																
✓	✓	O	O	✓	O	✓	O	O	O	✓	O	O	O	✓	✓	✓
Reduced patient co-payments																
O	O	O	O	O	O	O	O	✓	O	O	O	O	O	O	O	O

✓ Policy applied in the country | O Policy not identified or not applied

Source: CRA analysis

Automatic substitution

Substitution is defined as the dispensing of one medicine instead of another equivalent and interchangeable medicine at pharmacy level without consulting the prescribing physician.[155] The results obtained from such a measure can present different benefits, but all of which are associated with challenges.

Pros: On the one hand, it has been reported that automatic substitution of biosimilars could be a method to increase knowledge about biosimilars, foster trust and increase the tendency among patients, prescribers and dispensers to use biosimilar medicines.[156] In some countries, automatic substitution is enabled through 'interchangeability' statuses awarded at the regulatory level. The US FDA designates biosimilar 'interchangeability' (i.e. enabling automatic switching)[157] and the same practice is implemented by Australia's PBAC through 'a-flag' designations which are awarded on a case-by-case basis to biosimilars deemed interchangeable at the pharmacy level. However, in both countries, certain restrictions are still placed on interchangeability: in the US further limitations are placed on substitution at the state level (as of mid-2018, 41 states and Puerto Rico have laws restricting automatic substitution)[158] and in both the US and Australia, physicians can indicate if brand substitution is not

[iv] The implementation of the GSAV in 2022 will allow for automatic substitution at the pharmacy level in Germany.

permitted at the pharmacy level when prescribing. These restrictions ensure that ultimate decision-making regarding prescribing lies with the physician. Other countries are introducing additional legislation to mandate physician consultation before substitution is permitted (e.g. Brazil).[159]

Cons: On the other hand, it is also widely thought that automatic substitution can be a bad practice which can result in greater treatment switching, negatively impacting pharmacovigilance and traceability, and hence potentially eroding long-term safety.[160] Where there are multiple or uncontrolled substitutions, it can become increasingly difficult to accurately trace the product and batch that was dispensed, which can have safety implications if adverse events need to be reported. Automatic substitution reduces this visibility with additional checks of dispensing required in addition to prescribing records; this is particularly true in countries that promote the use of INN prescribing and whose electronic prescription systems do not allow for specific differences in INNs (sometimes introduced by regulatory authorities) to be recorded.

In addition, automatic substitution has the potential to adversely affect treatment outcomes, for example through the introduction of the nocebo effect.[161] This effect can arise from negative patient sentiment and unwillingness to switch, where an automatic substitution is not perceived to be medically justified, in turn impacting patients' expectations of treatment efficacy. There has been recent controversy in Germany, where the enforcement of the GSAV (a new proposed biosimilar regulation) in mid-2022 will introduce automatic substitution without notification of the physician for non-bioidentical biosimilars unless explicitly stated by physicians in prescription.[162]

Sustainability evaluation: The decision to substitute a treatment must be made by a multidisciplinary team, and must also account for the patient's preference. Therefore, automatic substitution of therapies without common input from both prescribing physicians and dispensing pharmacists is viewed as an unsustainable practice. Their dialogue must be guaranteed to ensure that none of the following are compromised: physician's ultimate prescribing autonomy, traceability from a monitoring/pharmacovigilance perspective, existing volume / market share agreements.

Regressive retailer markups

Markups are described as certain percentages of products' price that are provided for retailers as a bonus for their dispensing. In some cases, markups are regressive, meaning the magnitude of the markup decreases as the price of the product increases.

Pros: Many countries can benefit from significant cost savings by encouraging the dispensing of off-patent biologics. Some countries apply regressive markups to encourage dispensing of lower-cost drugs (e.g. France, Belgium and Norway). However, given their lower price, in many other countries the bonuses obtained from biosimilar dispensation are also consequently lower, which has imposed a disincentive for pharmacists to dispense cheaper medicines. As a result, higher percentage markups for cheaper medicines (e.g. biosimilars) ensure that lower-priced products are not penalised at the pharmacy level. The same principle can be applied through reduced markups for originator brands that have biosimilar alternatives. While this policy should not necessarily favour biosimilars over originators, it ensures that pharmacists profit equally from both products and are not incentivised to stock higher-cost products.

Cons: Regressive markups can actually result in better benefits for manufacturers of higher-cost medicines if not implemented properly. In the US, Medicare has tried to address the differential profit for originators vs. biosimilars by ensuring that providers are reimbursed with the same 6% margin that the originator product is eligible for (i.e. increased biosimilar markups). While this does ensure providers are not penalised for using biosimilar products, the policy also provides incentives for originators to maintain high prices and therefore does not facilitate cost savings.[163]

Sustainability evaluation: Regressive markups provide an opportunity to drive biosimilars uptake, and have demonstrated to be of higher benefit than direct bonuses or incentives paid to retailers by manufacturers. Given originators' higher revenues, these direct incentives can disequilibrate the competition balance between them and biosimilars. Conversely, fair regressive markups provide a more equalised system and can improve retailers' perception of biosimilars, given the direct benefits they obtain through their dispensing. As a result, pharmacists can self-evaluate added values that biosimilars can have for the healthcare system and base their dispensing decisions on *'best value biologics'* and their clinical/organisational benefits, rather than financial incentives.

Reduced patient co-payments

Other pharmacy-level policies incentivising use of biosimilars are related to patient co-payments.

Pros: In countries where co-payments are required, offering biosimilars with a lower co-pay than originators can incentivise their widespread use (and broad access for patients) while ensuring cost savings. In Australia, schemes intended to increase the uptake of generic medicines exists, where patients are required to pay extra for the branded product when there is a cheaper, generic alternative.[164] Consequently, there have been proposals to update policy to provide an equivalent incentive to drive biosimilar use (e.g. 50% of the originator co-payment), but this has not yet been implemented in Australia. These schemes have come under criticism for the same reasons as automatic substitution, e.g. that they can undermine physicians' prescribing autonomy. However, it is also possible to implement this policy in a sustainable manner, with appropriate measures in place to notify physicians of proposed substitution or to provide them with the option to 'opt out' of substitution practices (as in Australia). By implementing proper regulation, this will provide multi-stakeholder benefits.

Cons: The benefits obtained by lower patient co-payments can be banned if other unsustainable practices are in place. In some countries, patient co-payment policies are established in such a way that patients only have to pay up to a certain fixed numerical threshold (e.g. a maximum 700 CHF in Switzerland[165]). While these regulations set fair limits for patients and the amount of out-of-pocket money they need to pay for healthcare, they might also avoid the incentivisation of biosimilar prescribing. This is also the case in Japan, where once the patient co-payment cap is reached three times, the maximum amount allowed for co-payments is further decreased. This benefits higher-cost biologics over biosimilars, as the cap is reached faster with more expensive products.

Sustainability evaluation: Lower patient co-payments applied for biosimilars can serve as a sustainable option to favour their dispensing over originators without unfairly affecting competition. Moreover, such policy can result in cost savings not only for payers but for a broader range of stakeholders including patients.

3.9. Monitoring

All drugs, including biological drugs, need to prove their safety prior to commercialisation. In the case of biosimilars, most comparability assays to demonstrate similar characteristics also include monitoring for immunogenicity and anti-protein antibodies (APA). However, given the complexity of these molecules, biologics and biosimilars need to be further monitored after their launch, to keep a long-term measure of any potential adverse events (AEs).[166] Systematic monitoring of usage also has a role in ensuring there is consistent biosimilar supply, hence manufacturing and procurement issues can also be tracked.

Biosimilar policies regarding monitoring observed across countries include (Table 20):

- Post-commercialisation pharmacovigilance measures
- Transparency in usage reporting
- Monitoring of product ability to supply

Table 20: Monitoring policies observed across countries in scope

AUS	BEL	BRA	CAN	FRA	DEU	GBR	ITA	JPN	MEX	NLD	NOR	SAU	ESP	CHE	UAE	USA
Post-commercialisation pharmacovigilance measures																
✓	✓	✓	✓	✓	✓	✓	✓	✓	O	✓	✓	✓	✓	✓	✓	✓
Supply and usage monitoring																
✓	O	O	O	O	O	✓	O	O	O	✓	O	O	O	O	O	O

✓	Policy applied in the country	O	Policy not identified or not applied

Source: CRA analysis

Pharmacovigilance measures

As a general rule, pharmacovigilance measures across countries are applied equally to both biosimilars and their originators. Special requirements for biosimilars are applied in certain countries regarding additional documentation to accompany the product for its commercialisation. This is the case for the EU, where the EMA has also served as an example for other countries like Switzerland (Swissmedic). In such countries, biosimilars need to provide additional information in the documentation for their approval (e.g. an inverted black triangle stating that the product is a biosimilar).[167]

Pros: The purpose of pharmacovigilance measures is to ensure traceability of molecules upon development of AEs, to assess their safety for the patient. This process must be equally ensured for both innovative biologics and biosimilars, and therefore equivalent procedures with same requirements are deemed sufficient. Differences in the documentation accompanying biosimilars and their originators can serve as a way to increase traceability and differentiate between two molecules with the same active ingredient. Some countries, such as the US, have introduced pharmacovigilance measures to give specific identifiers to biosimilar medicines, which allow for the direct identification of the product. In the case of the Kingdom of Saudi Arabia, commercial names must accompany INNs, and biosimilars are specifically identified as such in the hospitals' order entry screens.[168] The monitoring system implemented in Norway goes even a step beyond, recognising batch-dependent differences inside these unique identifiers. These are included in a patient's history upon switching or biosimilar treatment initiation, to enable traceability of the prescribed product.[169]

Policies must ensure that when AEs are reported, all stakeholders involved in the biosimilar pathway are included. This way, patients as well as manufacturers and HCPs should be responsible for the reporting of AEs associated with biosimilars. The establishment of simplified protocols by the authorities and their support with understandable guidance would ease the approach for this process, potentially establishing certain hierarchy (i.e. HCPs serving as a bridge between patients and authorities). Alternatively, some countries like the UAE, currently looking to enhance their biosimilars' markets, are advocating for a rather direct approach. Here, patients can directly report back to the Ministry of Health and Prevention (MOHAP).[170] This could, nevertheless, produce certain complications, as manufacturers do not get a notification of such reports. To avoid this, pharmacovigilance reporting systems must ensure transparency between the parts involved. An example of this latter is the KSA, where producing companies do get notified.

Cons: No negative effects on long-term sustainability for biosimilars have been identified.

Sustainability evaluation: Monitoring of adverse events after commercialisation is a common requirement for all marketed drugs. The use of such measures for biosimilars can provide a way of showing real-world evidence to different stakeholders and improve biosimilars' perception, demonstrating their equal efficacy and safety. Placing biosimilars at the same level of biologics sets a good environment for competition and perception of biosimilars in the long term.

Supply and usage reporting

In order to maintain a sustainable market in the long term for all key stakeholders, commitment to market shares for biosimilar products should be ensured to avoid unsustainable levels of price erosion and to safeguard enough levels of supply without shortages. To facilitate this, transparency in supply and usage should be considered across the supply chain as a best practice policy.

Pros: Transparency in supply and usage can support sustainable contracting procedures. On the one hand, tenders/contracts can be arranged between payers and providers providing realistic estimates on biosimilar market shares, leveraging historical performance and country trends as reference. On the other hand, manufacturers entering tenders/contracts need to understand the level of market share they are bidding for, so they can enter at a sustainable price and commit to a realistic level of supply that will not result in supply shortages. In many cases, unsustainable contracting processes have resulted in sudden supply shortages, which can affect the pharmaceutical industry at many different levels. If medicinal products are not widely available, patient care and treatment can be compromised, leading to disease progression or an increase in AEs.[171]

Further to providing benefits at the contracting stage, ongoing supply and usage monitoring can be a policy to manage sudden shortages of medicines. This is the case for the Netherlands, where suppliers need to provide weekly updates on biosimilar availability status, or have delivery information available on their own webpage.[172] Additionally, further measures are taken in the UK: if a manufacturer fails to supply in line with its tender, the corresponding authority will compensate the shortage with other competitors, adding extra pressure on the first's supply chain.[173] Increased visibility into usage of biosimilars, uptake following contracting and projections on long-term demand can help biosimilar manufacturers to scale up or scale down their supply chain as appropriate.

Cons: No negative effects on long-term sustainability for biosimilars have been identified.

Sustainability evaluation: Transparency in both supply (from manufacturer side) and usage (from healthcare system side) ensures a high level of predictability for all stakeholders and minimises the risk of sudden supply shortages as it can allow countries to foresee any upcoming issue and provide timely

solutions. This can also support sustainable levels of competition, if additional manufacturers can be selected to support with the supply of their products to compensate for any foreseen shortages.

4 – Cross-country sustainability assessment

In order to obtain an overview of the current biosimilar policy environment, this chapter provides a comparison of the sustainability ratings (**Table 21**) for each policy area across the range of countries included in the scope of this project. A rationale for each rating has been included to highlight the common themes across countries with the same rating, including the key points for improvement that could drive a more sustainable long-term environment for biosimilars. This cross-country comparison allows for identification of those policy areas with the most room for improvement and also the countries where the current biosimilar policy is unlikely to be conducive to long-term sustainability (**Table 22**).

Individual country assessments and ratings are explained in more detail in specific country landscape and sustainability assessment documents also generated as part of this research.[v] The ratings have been informed by secondary research and subsequent discussions with biosimilar policy experts from each country.

Table 21: Sustainability rating scale

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

Source: CRA analysis

[v] Charles River Associates (2022). "Biosimilars: A global roadmap for policy sustainability". Available at https://www.biosimilarsroadmap.com.

Table 22: Sustainability ratings across countries in scope for each policy area

Policy Area	AUS	BEL	BRA	CAN	FRA	DEU	GBR	ITA	JPN	MEX	NLD	NOR	SAU	ESP	CHE	UAE	USA
Manufacturing and R&D	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★
Regulatory approval	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★
Health technology assessment	★	★	Priv. & Pub. ★ / Pub. HC ★	★	★	★	★	★	★	★	★	★	★	★	★	★	★
Pricing and reimbursement	★	★	★	Pub. ★ / Priv. ★	★	★	★	★	★	★	★	Inp. ★ / Out. ★	★	★	★	★	Pub. ★ / Com. ★
Contracting	★	Inp. ★ / Out. ★	Pub. ★ / Priv. ★	Pub. ★ / Priv. ★	★	★	★	★	N/A	★	Inp. ★ / Out. ★	Inp. ★ / Out. ★	★	Inp. ★ / Out. ★	★	★	Pub. ★ / Com. ★
Biosimilar education and understanding	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★
Prescribing	★	Inp. ★ / Out. ★	★	Pub. ★ / Priv. ★	★	★	★	★	Inp. ★ / Out. ★	★	★	★	★	★	★	★	Pub. ★ / Out. ★
Dispensing	★	★	★	★	★	★	★	★	★	★	★	★	N/A	Inp. ★ / Out. ★	★	★	Pub. ★ / Com. ★
Monitoring	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★

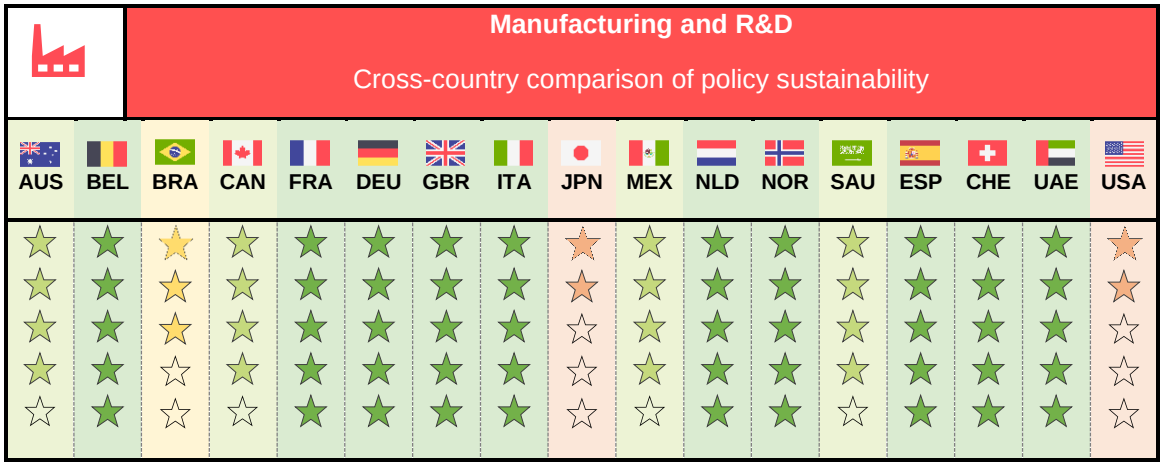
★	The policy area is considered to be sustainable for all stakeholders	★	Some minor areas for improvement were identified to result in a fully sustainable environment; however, no unsustainable policies impact the area	★	Some major areas for improvement were identified to result in a fully sustainable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

Note: Further rating detail can be found in Table 21. ***Com.*** *– Commercial plans;* ***HC.*** *– High-cost biosimilars*; **Inp. –** Inpatient; **Out. –** Outpatient; ***Pub.*** *– Public sector;* ***Priv.*** *– Private sector*

4.1. Manufacturing and R&D

Manufacturing and R&D policies are sustainable in the majority of the countries; however, there is some variation across countries and there are some specific challenges in Japan, the US and Brazil (**Table 23**).

Table 23: Sustainability of manufacturing and R&D policies across countries



Source: CRA analysis

★★★★★ – Manufacturing standards for biosimilars are the same as for the originator and therefore product quality is maintained through clear guidance. Further, to accelerate access to biosimilars, some regulators provide manufacturing exemption waivers to biosimilars that allow for manufacturing prior to originator LoE. This facilitates efficient supply at launch while still observing the full exclusivity period of the originator product. *For example, European legislation allows for the efficient production of biosimilars, limiting delays to market launch.*

★★★★☆ – Biosimilars are held to the same manufacturing standards as originator products, and therefore quality is maintained. However, manufacturing can only begin after originator LoE, which can result in slower access to the country and delay in the benefits realised by biosimilar entry. *For example, there are no manufacturing exemption waivers currently in place in Mexico that allow for biosimilars to be manufactured prior to originator LoE. However, the recent modification of the Federal Law of Industrial Property Protection has strengthened the rules for extension of patents to avoid granting of second patents without a justified reason.*

★★★☆☆ – There is room for improvement in the regulation around safety in manufacturing of biosimilars. Moreover, transparency in the regulations governing manufacturing practices could be improved. *For example, in Brazil the limited amount of transparency behind Productive Development Partnerships (PDP) contracts has led to some premature cancelation of partnerships without clear justification, leading to the loss of large amounts of invested money.*

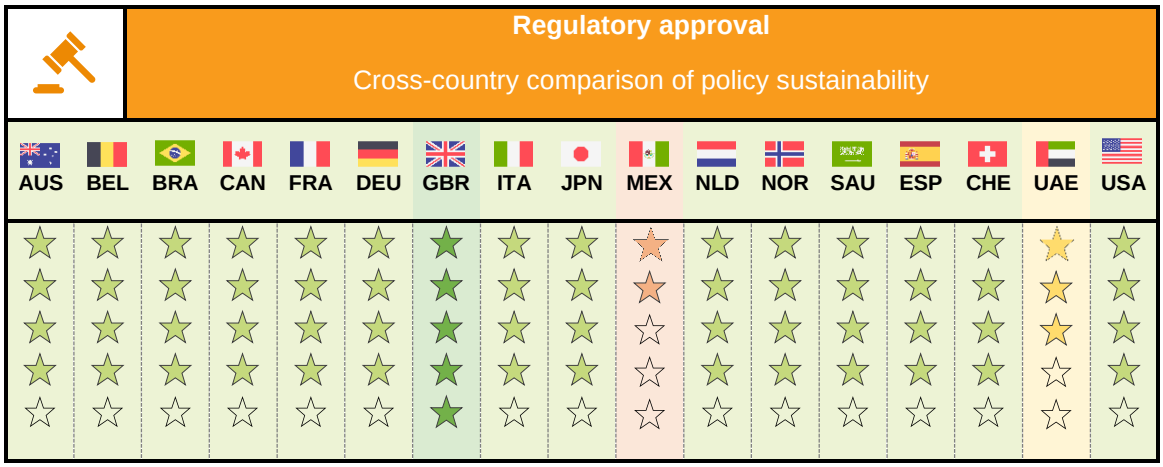
★★☆☆☆ – Regulations allowing for loopholes regarding originator patenting can increase barriers to entry for biosimilars, for instance through extension of originator patents or implementation of secondary patents. *For example, in Japan, patenting of innovative biologics per individual indications can further burden biosimilars' entry in the country. Similarly, the existing patenting environment in the US can impede biosimilar entry where reference product manufacturers erect 'patent thickets' around biologics.*

★☆☆☆☆ – No countries have been found to fall within this category. However, this would be a potential scenario where biosimilars are not subjected to the same manufacturing standards as originators, increasing risks to safety and quality associated with biosimilars.

4.2. Regulatory approval

Regulatory approval policies are sustainable in the majority of the countries; however, there are some specific challenges in Mexico (**Table 24**).

Table 24: Sustainability of regulatory approval policies across countries



Source: CRA analysis

★★★★★ – Regulatory assessment for biosimilars is accelerated and adjusted to the latest scientific consensus regarding the utility of clinical comparative studies, requiring comparative clinical effectiveness trials when they meaningfully add value to the submission. *For example, the MHRA in the UK no longer require clinical comparability studies given latest research regarding their lack of additional value to regulatory assessments.*

★★★★☆ – Streamlined regulatory assessments are used to prove biocomparability to an originator although both non-clinical and clinical studies are still required. Though these procedures are faster than the requirements for innovative biologics, further acceleration of assessments (e.g. through exclusion of clinical comparative assays where relevant) result in faster biosimilar approval without compromising quality or safety. *For example, European countries following EMA's guidelines are subjected to such streamlined processes. Other countries like Canada, Australia or Switzerland created their guidelines for biosimilars approval with a strong influence from the EMA (although in Canada the review time of the regulatory process is the same for both originators and biologics).*

★★★☆☆ – There are no streamlined evidence requirements but there are policies in place that encourage more accelerated assessments. *For example, in the UAE manufacturers can submit for regulatory approval 2 years prior to originator LoE to facilitate efficient access at launch.*

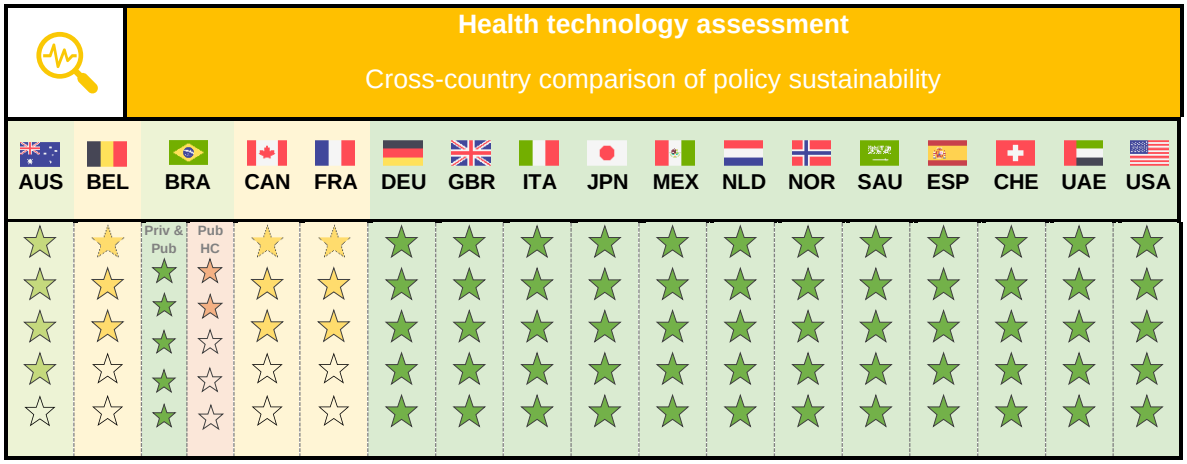
★★☆☆☆ – Streamlined regulatory assessments are used to prove biocomparability to an originator via non-clinical and clinical studies. However, the existence of other unsustainable regulatory policies finally results in disadvantages for biosimilars. *For example, in Mexico policies initially thought to incentivise biosimilar international import have resulted in an unfair delayed revision process for national manufacturers.*

★☆☆☆☆ – No countries have been found to fall within this category. However, this would be a potential scenario where there is no distinction between innovative biologics and biosimilars in terms of the requirements for their approval, which leads to unnecessary assessments for biosimilars, delaying their access.

4.3. Health technology assessment

HTA policies are sustainable in the majority of the countries; however, there are some specific challenges in Belgium, Canada and France (**Table 25**).

Table 25: Sustainability of HTA policies across countries



Pub. *– Public sector;* ***Priv.*** *– Private sector;* ***HC.*** *– High-cost biosimilars*
Source: CRA analysis

★★★★★ – HTA is not required for biosimilars, provided the indications included in their label are the same as their originators' and therefore have been already assessed. When HTA is used, it does not delay access and is used to inform healthcare systems regarding the organisational impact and economic value of biosimilars. No HTA requirements to determine access are regarded as a means for accelerating biosimilars' entry in the healthcare system, thus avoiding unnecessary bureaucracy with no added value. *For example, most of the countries in the EU (except France and Belgium) do not require HTA for biosimilars.*

★★★★☆ – Though HTA procedures are still required, they are streamlined, therefore potentially resulting in accelerated biosimilar entry and/or they are used to assign uptake drivers (such as interchangeability statuses) to biosimilar products. *For example, in Australia streamlining of such procedures can sometimes exclude pharmaco-economic evaluations.*

★★★☆☆ – Certain evaluation is required for biosimilars in order to grant reimbursement and inclusion in the system. Although there is intention to streamline assessments versus the process for innovative biologics, they still result in an additional burden for biosimilars to gain entry to some or all of the country. *For example, in France biosimilars are granted a 'non-clinical improvement rating' compared to the originator, but they are still required to go through HTA revision, leading to unnecessary patient access delays.*

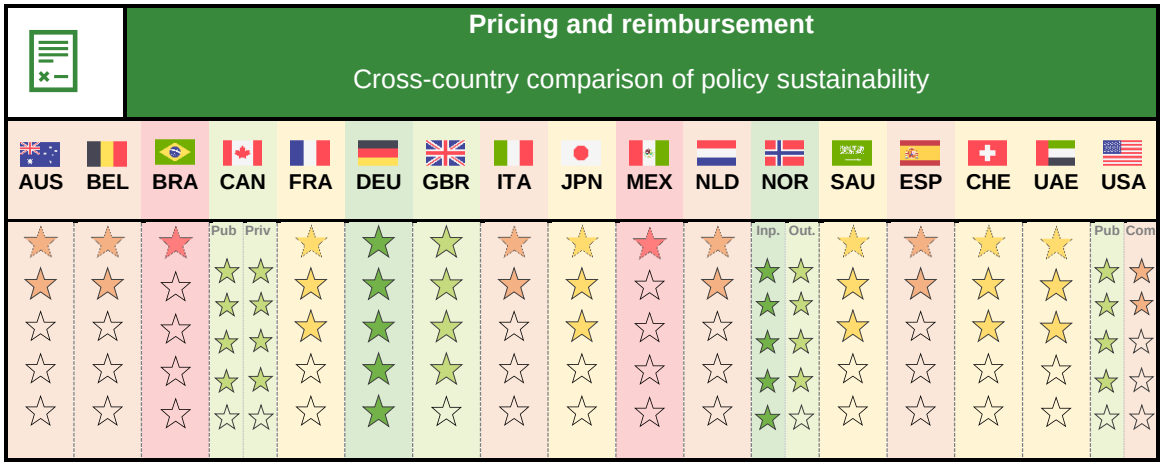
★★☆☆☆ – Specific rules are applied distinctively depending on the type of biosimilar, resulting in unequal disadvantages for access. *For example, high-cost biosimilars in Brazil need to undergo an extra step of economic evaluation and are contracted through centralised alternative procedures, finally resulting in poorer access of patients to these treatments.*

★☆☆☆☆ – No countries have been found to fall within this category. However, this would be a potential scenario where HTA requirements for biosimilars are the same as for originators, resulting in unnecessary delay to the country.

4.4. Pricing and reimbursement

The level of sustainability provided by pricing and reimbursement policies varies across countries, with Brazil, Mexico and the UAE facing the biggest challenges (**Table 26**).

Table 26: Sustainability of pricing and reimbursement policies across countries



Source: CRA analysis

★★★★★ – A transparent automatic reimbursement system ensures good predictability for the stakeholders involved. Moreover, price setting at launch is primarily influenced by country dynamics, providing a fair competitive environment without mandating arbitrary discounts at launch. *For example, in Germany, the creation of pricing reference groups ensures fair competition without directly affecting originators, and binding of biosimilars' automatic reimbursement to EMA's authorisation safeguards transparency and predictability.*

★★★★☆ – Automatic reimbursement is accepted for biosimilars, provided they undergo specific mandatory discounts. However, these pricing requirements account for volumes, competition and manufacturer's profit levels, supporting business predictability and still maintaining the potential for subsequent net price competition without driving unsustainable levels of price reduction. *For example, in Canada's public sector, pCPA negotiates mandatory biosimilar list-price reductions and incremental confidential rebates accounting for the different context for different biosimilars (e.g. molecule complexity, number of competitors, market share, etc.).*

★★★☆☆ – Reimbursement of biologics is often limited, and mandatory price discounts are required for biosimilars and/or originators. Such discounts are imposed by the authorities without guarantee on volume, maximum allowed discount, or potential further price decrease through subsequent tendering procedures. This decreases predictability for the involved stakeholders and reduces fair competition baseline between biosimilars and their originators. *For example, mandated discounts for biosimilars apply in Japan, Switzerland, UAE and KSA. Moreover, originators are also required to lower their prices in the KSA.*

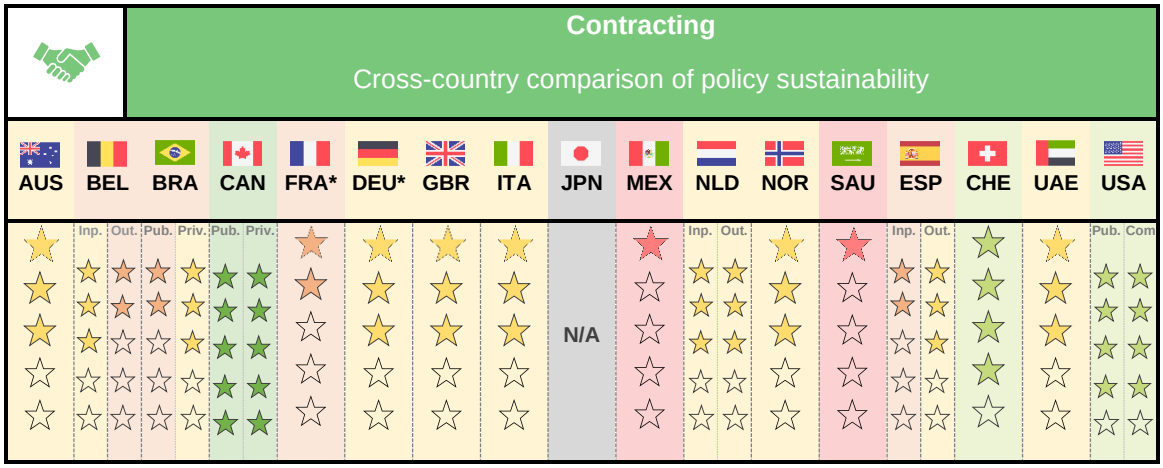
★★☆☆☆ – Reimbursement of biosimilars is limited and/or pricing systems subject biosimilars to significant and frequent revisions that can lead to further discounts in short periods of time after launch. Moreover, in some markets the implementation of list-price discounts does not account for subsequent price reductions from tendering practices. This can increase the risk of reaching unsustainable levels of price reduction in the short term and decrease the viability and predictability of the market for manufacturers. *For example, in Spain biosimilar prices are re-negotiated on an annual basis, and the application of further discounts through tendering practices has exacerbated biosimilar price reductions. In Australia biosimilar price benchmarks are reduced every five years due to progressive originator discounts and the price disclosure system.*

★☆☆☆☆ – Biosimilar pricing is not differentiated from the approach taken with generic small molecules, resulting in significant price reductions and reduced viability for manufacturers to remain in the country. *For example, in Brazil both biosimilars and generics are regarded as molecules to "increase market concurrence", which has led biosimilars to undergo discounts even up to 88%.*

4.5. Contracting

Contracting policies vary across countries, therefore showing some variation in sustainability. Mexico and Saudi Arabia face the biggest challenges in this area (**Table 27**).

Table 27: Sustainability of contracting policies across countries



Pub. *– Public sector;* ***Priv.*** *– Private sector;* ***Com.*** *– Commercial plans;* ***Inp.*** *– Inpatient;* ***Out.*** *– Outpatient*

***** *Rating potentially subject to change upon implementation of upcoming substitution policies*

Source: CRA analysis

★★★★★ – Contracting procedures fulfil five essential requirements to support sustainability: supply, fair price levels, predictability, multidisciplinary input, and enforcement of the regulations. Policies ensure healthy levels of supply shared between various providers to avoid shortages. Moreover, price does not govern the decision-making of contracts, with more elements being considered during tender/contracts award decision-making (e.g. ability to supply, value added services, local manufacture when applicable). Contracts' length provides a predictable environment for suppliers, avoiding unexpected reopening, and contracting decisions receive input from all stakeholders as a multidisciplinary team, also considering HCPs and pharmacists, therefore resulting in best outcomes for the patients. Finally, all the previous requirements are clearly established in law and thoroughly monitored. *In Canada, direct negotiation at a provincial level with individual providers ensures that multiple biosimilars have market share across the country. Provinces use their own methodologies for negotiating contracts, incorporating considerations of biosimilar value.*

★★★★☆ – Sustainable criteria are in place for contracting procedures: they ensure healthy levels of supply between multiple suppliers within a country (either through multiple/varied direct contracts or multi-winner tenders), and product attributes beyond price are considered, as well as input from multiple stakeholders. However, poor monitoring and enforcement of these regulations results in contracting practices still applying unsustainable criteria. *For example, multi-winner tenders are used in Switzerland and include criteria other than price (e.g. local manufacture) to select winners.*

★★★☆☆ – The process followed for contract awarding combines both sustainable and unsustainable criteria, with only part of the requirements described above fulfilled. *For example, in*

Australia single winner contracts risk supply shortages. In Spain, tenders for outpatient biosimilars consider price as the main requirement for awarding, driving excessive price reduction. Additionally, in Italy, current law promotes the use of HTA and cost effectiveness and price-quality considerations however, regions tend to award tenders solely on price despite the law.

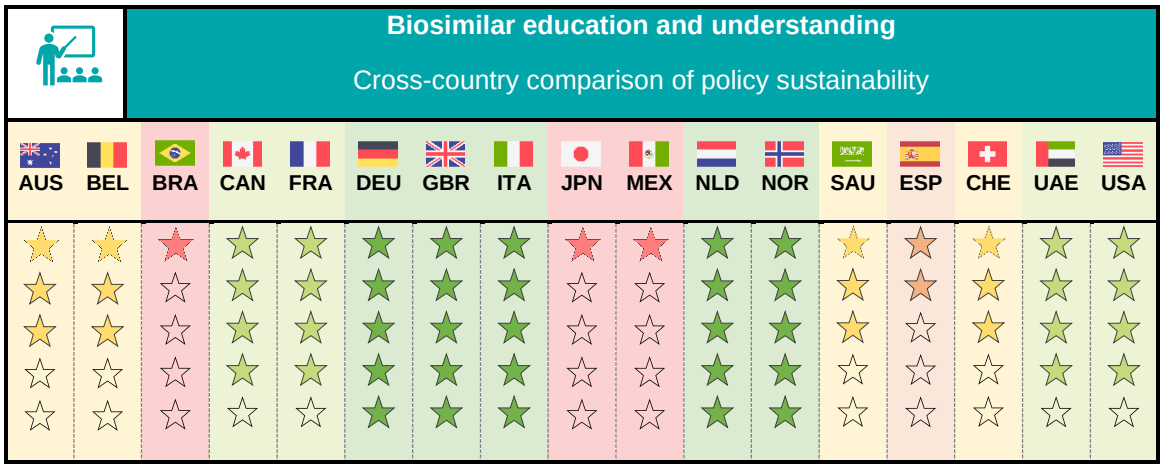
★★☆☆☆ – The combination of unsustainable contracting requirements and list-pricing policies promotes issues with supply shortages and/or unsustainable levels of price reduction through tendering. Moreover, input from different stakeholders is not accounted for, in such contracting decisions. *For example, exclusionary contracts are allowed in the US, which increase likelihood of supply shortages.*

★☆☆☆☆ – Requirements for sustainable contracting practices are highly disregarded. Moreover, the lack of (consistent) policies in place results in regional disparities in access to biosimilar products and can increase the risk for exclusionary contracts. There is also a lack of competition and / or there are frequent price revisions (e.g. through reopening of contracts). *For example, recent detachment from previous contracting systems thought inefficient in Mexico has led to a currently uncertain environment where no robust regulation is in place nor applied.*

4.6. Biosimilar education and understanding

Biosimilar education and understanding policies are sustainable in the majority of the countries, with Brazil, Japan and Mexico facing the greatest challenges (**Table 28**).

Table 28: Sustainability of biosimilar education and understanding policies across countries



Source: CRA analysis

★★★★★ – Educational programs target key stakeholders and are effective in reaching target audiences via different communication channels, contributing to an overall good understanding and resulting in good uptake of biosimilars. While there is always a need to continue education, misconceptions among patients, physicians, pharmacists and policymakers are minimal. *For example, educational campaigns in the Netherlands are organised periodically and delivered through different channels, therefore ensuring efficient targeting of the population.*

★★★★☆ – Educational programs are in place and developed in a consistent repetitive manner, therefore respondent to evolving challenges. However, there is still room for improvement to efficiently target groups of stakeholders and make the most of educational efforts in place. *For example, the use of more varied channels for educational programs has been proposed in Canada (e.g. online resources, media, congresses) to gain better coverage.*

★★★☆☆ – Educational campaigns are in place, but rather sporadically without continued efforts. This has led to insufficient levels of education, resulting in certain misconceptions among stakeholders. *For example, more frequent and repeated educational campaigns have been suggested in Belgium as a method to improve uptake.*

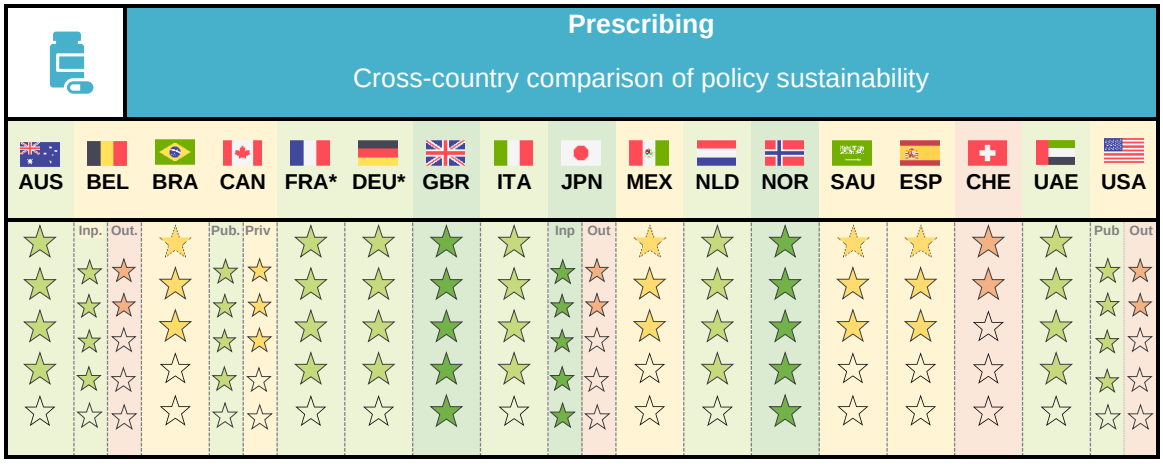
★★☆☆☆ – Sporadic and/or limited educational efforts have been further worsened due to limited input from national authorities, which means that there is a higher degree of misconceptions and mistrust of biosimilars across key stakeholders. *For example, in the UAE education around biosimilars is limited given the lack of continued efforts from the government to promote these.*

★☆☆☆☆ – No educational support from national authorities or governments and messaging only from innovator or biosimilar manufacturers results in limited uptake. Furthermore, previous misinformation or bad experiences with biosimilars results in persistent lack of trust among some or all stakeholders. *For instance, quality issues with intended copies launched in Mexico resulted in physicians' mistrust in the quality of biosimilars. This was furthered by innovator manufacturers who gave out information to bias the perception of physicians and regulatory authorities against using any biosimilar regardless of its quality.*

4.7. Prescribing

Prescribing policies still show a slight room for improvement in most countries, with differences applying between the public and private sector, and the inpatient and outpatient setting (**Table 29**).

Table 29: Sustainability of prescribing policies across countries



Pub. *– Public sector;* ***Priv.*** *– Private sector;* ***Com.*** *– Commercial plans;* ***Inp.*** *– Inpatient setting;* ***Out.*** *– Outpatient setting*
**Rating in DEU and FRA likely to be different upon implementation of proposed legislation regarding automatic substitution*
Source: CRA analysis

★★★★★ – Prescribing of biosimilars is encouraged through clinical recommendations, and additional incentives are in place where required (e.g. quotas, gain-sharing, indirect incentives). Moreover, biosimilar prescription considers multidisciplinary perspectives with a role for pharmacists, budget holders and patients as well as prescribing physicians to ensure maximum value for all parts of the healthcare system. *For example, in Norway physicians can provide their input on contracting decisions for biosimilars, therefore avoiding a reduction in their prescribing options.*

★★★★☆ – Physicians retain prescribing autonomy either completely or within certain limits (e.g. formularies with two or more options), and biosimilar uptake is good due to implementation of policies encouraging uptake (e.g. incentives, recommendations, quotas). However, there is room for

improvement in other fields – with regards to either multidisciplinary input or the implementation of additional uptake drivers to support biosimilar uptake (e.g. incentives, gain sharing, quotas). *For example, recommended quotas and incentives in France could be supplemented with better clinical recommendations and guidance for HCPs. Conversely, recommendation of biosimilars and their inclusion into Australian clinical guidelines could be further improved through financial incentives.*

★★★☆☆ – Lower uptake rates for biosimilars due to either the implementation of policies that reduce physicians' autonomy to prescribe, or the lack of policies targeting physicians to motivate their prescription in addition to limited multidisciplinary input. *For example, in Spain reimbursed biosimilars are decided on the contracting level (e.g. via tenders), generally without input from physicians, and thus treatment options are decreased.*

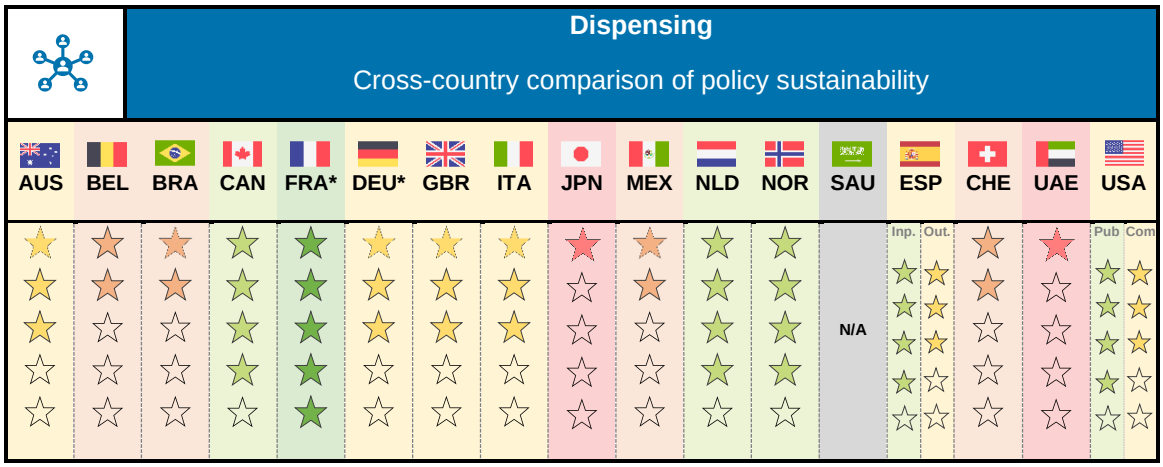
★★☆☆☆ – Biosimilar prescription among physicians is not outstanding and their low uptake is further worsened by other legislation that can undermine the long-term sustainability in previous/subsequent policy areas. *For example, the absence of prescription quotas for physicians in Switzerland, combined with a margin system disincentivising pharmacists, results in overall low uptake. Similarly, unfair co-payment mechanisms for outpatient lower-cost biosimilars in Japan disadvantages their use.*

★☆☆☆☆ – No countries have been found to fall within this category. However, this would be a potential scenario where there is low uptake of biosimilars due to policies in place that discourage their use or penalties for physicians who do not meet prescribing quotas.

4.8. Dispensing

Dispensing policies show margin for improvement in most countries, with Japan, Germany, Switzerland, and the UAE facing the biggest challenges (**Table 30**).

Table 30: Sustainability of dispensing policies across countries



***** *Rating potentially subject to change upon implementation of upcoming substitution policies*

Source: CRA analysis

★★★★★ – Dispensing policies in place do not undermine physicians' autonomy but instead promote shared decision-making between them and pharmacists. Further, policies ensure that these stakeholders are fairly incentivised (i.e. to the same extent) to use biosimilars. Where substitution policies are in place, there are clear requirements to inform prescribing physicians, which are adhered to and not often opposed unless detailed clinical rationale is provided. Moreover, substitution policies do not interfere with robust tracing systems used for safety monitoring. Where relevant, patients also

realise benefits from being treated with a biosimilar through reduced patient co-payments*. For example, in France current regulations ensure constant communication between pharmacists and HCPs to drive the best decision for patients.*

★★★★☆ – Policies are in place to ensure that dispensation of biosimilars vs. originator does not penalise the pharmacist (e.g. through lower margins). Moreover, pharmacists can receive incentives from biosimilars dispensing. However, more multidisciplinary decision-making and communication between all parties involved could increase transparency and allow for the best patient outcomes. *For example, in both the UK and the Netherlands clawback systems are implemented to provide incentives to pharmacists dispensing biosimilars.*

★★★☆☆ – Certain inconsistency on dispensing mechanisms can result in unequal patient access to biosimilar treatments, depending on practice setting or region/province. *For example, contracting procedures in Australia might result in different drug procurement between community and hospital pharmacies, limiting patients' choices across settings.*

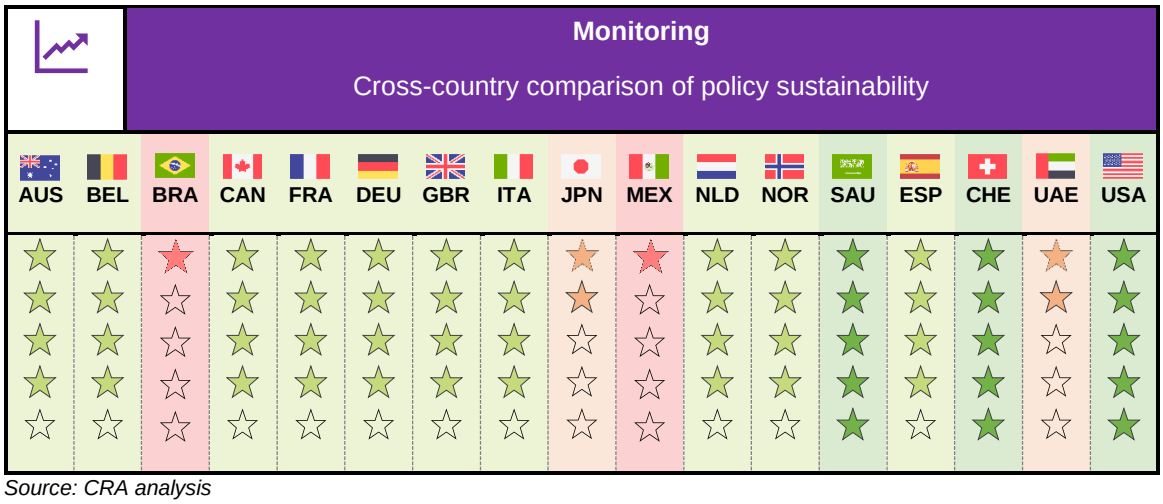
★★☆☆☆ – Regulation currently in place does not promote substitution, but common practices among pharmacists can result in continuous switching and reduce monitoring. *For example, pharmacists in Brazil and Mexico can substitute patient's treatment based on their stock availability instead of a medical-based decision, decreasing system transparency.*

★☆☆☆☆ – Policies have resulted in limited uptake of biosimilars, sometimes incentivising originators' dispensing and reducing incentives to prescribe lower cost biologics (e.g. biosimilars). Furthermore, unclear substitution policies can provide an unpredictable environment, impeding proper traceability. *For example, dispensing policies in Japan result in higher co-payments in the long term for patients using biosimilars. In the UAE, originators' use is promoted through allowed indirect bonuses from their manufacturers to pharmacists.*

4.9. Monitoring

Monitoring policies are sustainable in the majority of the countries; however, there is much room for improvement in Brazil and Mexico (**Table 31**).

Table 31: Sustainability of monitoring policies across countries



Source: CRA analysis

 – Biosimilars and originators are required to follow the same rigorous pharmacovigilance requirements and provide risk management plans to the same standards, which allows for accurate and transparent tracing of adverse events. Further to this, biosimilars are distinguished from originators in their INN (i.e. using a suffix in regulatory documents) that allows for full transparency during the monitoring process. *For example, the US FDA has adopted a unique naming approach for all biosimilars in the US, which involves the addition of a unique four-letter suffix at the end of each biologic's international non-proprietary name (INN).*

 – Biosimilars and originators are required to follow the same rigorous pharmacovigilance requirements and provide risk management plans to the same standards. Improved or simpler protocols implemented at the national/sub-national level could improve efficiency and transparency in monitoring systems, particularly in the outpatient setting. Alternatively, better regulation or enforcement of reporting by physicians would improve results of robust pharmacovigilance requirements in place. Finally, INN-based differentiation between originators and biosimilars is not observed. *For example, in Europe, despite the EMA's pharmacovigilance guidelines, there could be improved systems at the prescribing and pharmacy levels, where treatment switches are made. In Australia, improved traceability of batch-dependent differences would improve risk management plans*.

 – No countries have been found to fall within this category. However, this would be a potential scenario where risk management plans are in place, but there is lack of transparency in nomenclature of products, limiting the differentiation between biosimilars and originators and the AEs raised by each.

 – There are measures in place to facilitate monitoring of biosimilars, but an overall weak pharmacovigilance system, with unclear practices for physicians, can limit AE reporting. *For example, in the UAE pharmacovigilance needs to be improved, given that adverse events are not always communicated to manufacturers.*

 – Transparency is undermined by unclear pharmacovigilance monitoring systems, or the effectiveness of these is reduced as a result of substitution practices at the pharmacy level that do not require notification of the physician, change of the prescription in paper or electronic systems, or INN prescribing. *For example, vague pharmacovigilance requirements in Brazil result in low rates of AE reporting by HCPs. In Mexico, treatment substitution based on pharmacy stock availability impedes transparency in the reporting system.*

5 – Policy recommendations for a sustainable long-term biosimilar environment

These policy recommendations are intended to provide tangible and actionable recommendations for meaningful improvements to sustainability within the biosimilar sector. Where possible, recommendations have been tailored to account for broader country caveats, specific country situations and different types of biosimilars (e.g. inpatient/outpatient, rare disease (RD) and high-volume biosimilars). These outputs were reviewed offline by attendees to ensure alignment across all stakeholders and refined for the purposes of this white paper.

For each policy area, the recommendations provided following the following structure:

- Overall recommendations to ensure an ideal, long-term sustainable environment
- Recommendations for specific country situations
- Recommendations for specific-biosimilar archetypes

In the tables below, biosimilar-specific archetypes are represented with the following icons:

	High-volume products used in chronic indications		Oncology products		Rare disease products

5.1. Manufacturing and R&D

Biosimilar policies should ensure the highest standard of quality but facilitate prompt market access. Importantly, the intellectual property rights (i.e. market exclusivity) of the originator should be protected, and policies should act to mitigate the risk of potential supply shortages (**Table 32**).

Table 32 – Key recommendations for manufacturing and R&D

 **Manufacturing and R&D*** *Key recommendations*

For an ideal sustainable long-term biosimilar policy environment:
• Biosimilar products should be subjected to the same high manufacturing practices and safety standards as innovative biologic medicines.
• Manufacturing legislation should be transparent and provide clear guidance for biosimilar producers, and should also be enforced from relevant authorities.
• Manufacturing rules should not be a barrier to prompt biosimilar entry. Manufacturing exemption waivers (e.g. approval of biosimilar manufacturing licenses prior to originators' LoE) could be considered to support efficient biosimilar access but must ensure that:
  ○ The full period of originator exclusivity is respected.
  ○ There are no infringements on patents covering manufacturing processes.
  ○ There are tangible benefits, from patient access to the efficient availability of the biosimilar.
  ○ The agreement is not in conflict with existing free-trade agreements (FTAs).
• Financial benefits obtained from the use of biosimilars should be further invested into the system, allowing for continued research and innovation in the biosimilar industry and leading to improved patient benefits.

Best practice examples
• European legislation allows for the efficient production of biosimilars without delay to entry in the country, applying equivalent manufacturing standards for biosimilars and originators and maintaining product quality.
Country characteristics

Countries with a history of supply issues					
• In countries of sufficient scale, where there have been historical supply issues due to reliance on foreign importation, local manufacturing incentives could be considered as a potential opportunity to reduce supply shortages and boost national economies, provided competition is encouraged, and global supply chains are not interrupted. • The biotechnological industry should leverage the benefits obtained from biosimilar use, encouraging further research and development, and contributing to the long-term increased treatment options for physicians and ultimately patients.					
Biosimilar archetypes					
	N/A		N/A		N/A

** Manufacturing and R&D was not discussed in depth during the advisory board meetings, but takeaways and recommendations were still developed based on the input gathered from individual discussions with experts.*

5.2. Regulatory approval

Acceleration of regulatory approval for biosimilars is critical as it ensures that patients benefit from these more cost-effective treatments at the earliest time point, while allowing payers to capture savings. Smaller agencies can derive significant benefit (e.g. improved efficiency and learnings) from referencing the decisions of larger, well-established regulatory agencies. Across biosimilar product archetypes, the need to streamline evidence requirements can vary depending on the expected population size, duration of treatment and unmet need. For instance, in the case of rare diseases, although there are small populations, the unmet need experienced by patients may warrant greater streamlining in order to support rapid market entry to alleviate the burden of disease more quickly (**Table 33**).

Table 33 – Key recommendations for regulatory approval

 **Regulatory approval** *Key recommendations*

For an ideal sustainable long-term biosimilar policy environment:
• Regulatory assessment should be robust and transparent (i.e. available to the public while preserving confidential data), to instil confidence in the efficacy and safety of approved biosimilar products.
• Robustness of regulatory guidance should ensure safety and efficacy of biosimilars without loopholes or a lack of clarity.
  ○ Regulatory agencies could provide direct support to elucidate the processes around submission of required documentation for companies new to the procedure.
• Consistent methods, metrics and assays should be used to assess biosimilar characteristics (e.g. immunogenicity) by all regulatory agencies, supporting comparability of different biosimilars where assessments are shared.
• Regulatory approval timelines should be formally accelerated where possible (compared to typical innovative medicines) to align with the streamlined evidence requirements.
• With regards to evidence requirements on efficacy, regulatory agencies should adopt the latest scientific consensus regarding the utility of clinical comparative studies and require comparative clinical effectiveness trials when they will meaningfully add value to the submission.
  ○ While HCP/public confidence in biosimilars is being developed, comparative clinical effectiveness requirements may be required, but these requirements should be relaxed as confidence improves.
  ○ However, even then biosimilars should only be required to prove biosimilarity in one of the originator's indications.

- Assessments and real-world evidence (e.g. from registries) should be shared between regulatory agencies, increasing transparency, ultimately to support confidence in new medicines and technologies.

Best practice examples

- In the UK, the MHRA no longer requires clinical comparability studies given latest research regarding their lack of additional value to regulatory assessments, streamlining the assessment process.

Country characteristics

Large, international regulatory agencies	Smaller, national regulatory agencies
• It is particularly important for large, international regulatory agencies (e.g. EMA and US FDA) to establish a precedent in applying consistent methods, metrics and assays in assessments, in order to ensure consistent decision-making and support timelier/streamlined submissions from manufacturers.	• Increased international collaboration among regulators could be explored in order to leverage relevant foreign evaluations in abbreviated procedures, in particular for regulatory bodies that have longer timelines or more limited capacity. • However, leveraging international decisions should not come at the expense of developing national competencies and ensuring that regulatory standards within each country continue to evolve.

CA US DE BE FR ES

IT NL NO CH GB JP

MX BR AU SA AE

Biosimilar archetypes

	There can be perceptions (e.g. among physicians) that greater care should be taken to demonstrate safety of products indicated for longer-term use.		Conversely, products which are not expected to be used in the long term (e.g. shorter oncologic infusion cycles) can be perceived to be better suited to streamlined evidence requirements.		Accelerated regulatory processes for RD / orphan products could be explored in indications of highest unmet need.

5.3. Health technology assessment

HTA should not act as a barrier to biosimilar market entry and should only be conducted in a streamlined way in specific instances where it provides additional value (**Table 34**).

Table 34 – Key recommendations for health technology assessment

	Health technology assessment *Key recommendations*

For an ideal sustainable long-term biosimilar policy environment:

- Conventional HTA should be unnecessary, given that the therapeutic benefits provided for biosimilars will be similar to the originator, and these assessment processes can be considered an additional barrier to entry raising costs and delaying access.
    - In instances where biosimilar HTA is currently a formality or results in an automatic decision, policies to provide access during that period or to minimise access delay should be considered.
- However, there are certain scenarios where HTA for biosimilars can still be necessary or add value for healthcare systems:
    - When biosimilars launch or expand into indications that are different to the originator's
    - When the originator product has not been reimbursed in all or certain indications
    - In order to quantify the organisational and economic value of different treatment options to inform subsequent formulary decisions, treatment guidelines and prescribing practices (however this should not be a barrier to country entry)
        - In countries where such capabilities and capacity exist, multiple technology assessments could be considered to support this
- Where HTA is conducted, HTA bodies should seek to streamline and accelerate traditional processes to ensure efficient access to biosimilars.

Best practice examples

- The majority of countries in the sample do not require HTA for biosimilars if they have the same label as the originator; this applies to in-scope markets from the EU (except France and Belgium), the Americas (except for Canada), the UAE, Saudi Arabia and Australia.

Country characteristics

Limited Originator Reimbursement	Traditional HTA not Required
• In countries where originator biologics are typically not reimbursed, biosimilars will be more frequently subjected to HTAs to evaluate their benefit. HTA bodies should seek temporary reimbursement practices to avoid access delays.	• Where traditional HTA for all originator products is not conducted, there is no need to implement additional HTA for biosimilar products.
MX BR	US JP SA AE CH

Biosimilar archetypes

	N/A		N/A		HTA for rare biologics is more likely to be streamlined, given the additional challenges that small patient populations can give to develop a full package of evidence, facilitating their market entry.

5.4. Pricing and reimbursement

Differentiation of biosimilar and small molecule generic pricing policy is critical to maintaining sustainable price benchmarks for biosimilars. Automatic reimbursement or streamlining of decision-making processes will support more rapid market entry and hence, earlier realisation of biosimilar value. Finally, where implemented, pricing and reimbursement policies should reflect countries' market characteristics (e.g. the level of competition) to ensure a sustainable long-term biosimilar environment (**Table 35**).

Table 35: Key recommendations for pricing and reimbursement

Pricing and reimbursement *Key recommendations*

For an ideal sustainable long-term biosimilar policy environment:
• Policies should distinguish between biosimilars and small molecule generics, accounting for the differences between these products and the fact that typical generic policies are unlikely to result in a sustainable pricing solution for biosimilars in the long term.
• Automatic reimbursement systems which operate in a transparent manner (e.g. as seen in Germany) support more efficient country access for biosimilars.
• Where automatic reimbursement is not used, measures to streamline P&R pathways and drive more efficient access to biosimilars should be considered, such as:
  ○ Early initiation of negotiations (e.g. as done by the pCPA in Canada)
  ○ Acceleration of existing processes
• Country characteristics (e.g. total patient volume, number of competitors or tendering) dictate the degree to which competition will work effectively and whether it will be sustainable. Ideally, sufficient net price competition will determine prices. Mandatory discounts may have a role in some countries in ensuring predictable cost savings and avoiding unsustainably excessive price reductions.

Best practice examples
• In Germany, the creation of biosimilar reference pricing groups (which align pricing across biosimilars) ensures fair competition without directly affecting originators, and binding of biosimilars' automatic reimbursement to EMA's authorisation safeguards transparency and predictability.
Country characteristics

Mandatory price controls	**Dynamic price controls**
• Magnitude of mandatory discounts, if applied, should consider differences across therapeutic areas and products, including typical treatment duration, manufacturing processes, number of competitors and population size: policies should recognise that a one-size-fits-all approach for biosimilars may not be sustainable in the long term. • Policies should consider safeguards to ensure discount levels are not unsustainable. For example, frequency of price revisions should be monitored to avoid a 'race to the bottom' and instead policies should look to promote a sustainable, long-term cost savings.	• Policies should safeguard multiple country participants to ensure that sufficient levels of competition exist to capture long-term cost savings for the healthcare system. • Biosimilars and off-patent originator products can have access to the same negotiation tactics to ensure fair and equal competition.
FR, AU, CA, JP, DE, BE, IT, ES, CH, SA, NO	BR, NL, US, MX, GB

Biosimilar archetypes					
	N/A		N/A		Smaller patient volumes and potentially fewer competitors may necessitate refinement of rare disease pricing policy to ensure a market for biosimilars is viable.

5.5. Contracting

Participation of multiple suppliers in tenders drives sustainability by fostering competition and decreasing the likelihood of supply shortages. The processes and requirements for tender or contract participation should be transparent, to ensure equal opportunity, and selection criteria used should be designed to prioritise product quality and value (**Table 36**).

Table 36: Key recommendations for Contracting

Contracting
Key recommendations

For an ideal sustainable long-term biosimilar policy environment:

- Competition within a country should be preserved by ensuring and safeguarding multiple country participants:
  - Single-winner/supplier situations at the national level should be avoided.
  - Where single-winner/supplier contracts operate regionally/locally, measures should be in place to ensure multiple winners/suppliers across a country at the national level.
- Supply issues and withdrawal due to unsustainable revenues should be avoided by increasing transparency during contracting procedures, providing market share guarantees to individual suppliers over a set period of time. Both suppliers and payers should be held to these contractual agreements with appropriate enforcement measures.
- Transparent, equal opportunity setting must be granted for all suppliers with an appropriate and consistently applied use of contract decision-making criteria, including criteria that ensure quality and value.
  - Further, these considerations should contribute meaningfully to final contractual decisions.

Best practice examples

- In Canada, direct negotiation at a provincial level with individual providers ensures that multiple biosimilars have market share across the country. Provinces use their own methodology for negotiating contracts, incorporating considerations of biosimilar value.

Country characteristics

Tendering Procedures *Often inpatient setting*	**Direct Contracting** *Often Outpatient Setting*	**Hybrid Countries**
• Tender award criteria should extend beyond price and consider elements of value (e.g. added services) and ability to supply. • Tender criteria should be monitored and enforced to ensure proper adherence and predictability for future suppliers.	• Second-to-country biosimilars should not be excluded through the conditions/terms agreed in contracts with first-to-market products. • Any exclusionary or anticompetitive contracting practices should not be permitted as they can restrict the level of benefits derived from biosimilar competition.	• There should be guidance on use of tenders vs. direct contracting. Opportunities should be applied consistently through a set of clear regulations (i.e. how this applies in inpatient vs. outpatients setting or if affected by number of biosimilars are available) to ensure predictability for manufacturers.
NOR ESP CHE UAE GBR DEU AUS	AUS CAN BEL BRA JPN	CAN MEX BRA AUS
FRA ITA NLD BRA MEX BEL SAU	MEX SAU UAE USA CHE	BEL CHE SAU UAE

Biosimilar archetypes

	Products used for chronic diseases with longer periods of treatment may lend themselves more to		Complex molecule structures which may be more commonly found in oncologic disease areas		The need for volume guarantees for rare disease biosimilars is likely to be amplified

	additional value considerations during tendering/contracting. Furthermore, tendering (especially where contracts are shorter-term) may be less attractive, given the goal of reducing treatment switching (e.g. between different routes of administration).		could require greater considerations of additional services (e.g. physicians' training) during tendering/ contracting. Although, given the shorter treatment duration, it may be simpler to field tenders of shorter duration.		given smaller overall market share. Furthermore, there are likely to be fewer competitors, simplifying negotiations.

5.6. Biosimilar education and understanding

A multidisciplinary approach to education is key to maximising the sustainability of a country's biosimilar environment. This applies not only to the design of educational materials but also to the targets of educational policy, as stakeholders ranging from payers to patients can all benefit. As stakeholders' experience with biosimilars increases over time, the role education plays shifts, but ultimately it is likely to support greater biosimilar usage (**Table 37**).

Table 37: Key recommendations for biosimilar education and understanding

Biosimilar education and understanding
Key recommendations

For an ideal sustainable long-term biosimilar policy environment:

- All key stakeholders (e.g. governments, budget holders, HCPs, pharmacists and patients) should be educated on the value of biosimilars to avoid bottlenecks or barriers at one point in the chain.
- Educational materials should be independently developed (from a credible source) in order to support evidence-based education.
- Biosimilar advocates should work together in a multidisciplinary manner to ensure that messaging across all channels is consistent and strong.
- Education of patients can improve their involvement in treatment decision-making and overcome myths around biosimilars (e.g. perception of different efficacy between intravenous (IV) and subcutaneous (SC) biosimilars).
- Educational campaigns should be carried out through peer-to-peer discussions to ensure that trust is maintained and the message reaches the target population.
    - Pharmacists play a key role in education due to their close contact with patients and (in some countries) their influence over formulary decision-making/prescribing options.
    - Educational messages led by patient organisations could have greater impact to combat misconceptions among patients.
- As well as consistent and strong messaging, some specific tactics can also be used to maximise effectiveness of educational campaigns:
    - Following a simple 'myth-busting' approach can increase receptivity to messaging.
    - Educational campaigns must be presented through different communication channels (e.g. online, at hospitals).
    - Messaging should be consistently repeated over a significant period of time to ensure durability of messaging.

Best practice examples

- In the Netherlands, government-led educational campaigns are organised periodically and delivered through different channels, therefore ensuring efficient targeting of the population.
- Similarly, in the UK and Germany, educational materials capture multi-stakeholder perspectives and are tailored to target specific groups, ensuring broad education.

Country characteristics

Countries with long history and good uptake with biosimilars	Countries with more limited history and uptake of biosimilars
• Governments and other biosimilar advocates can leverage physicians who have experienced greater biosimilar uptake to share experiences with physicians in specialities newer to biosimilars. • Therapeutic areas where novel biosimilars are launching (e.g. nephrology) can leverage long-term real-word evidence from other examples to educate their HCPs and patients.	• A top-down approach to education and addressing misconceptions is critical to ensure that stakeholders with the largest influence over biosimilar policy (and therefore uptake) are supportive of their use. Education should start with governments and policymakers, then go on to budget holders, HCPs pharmacists and finally patients.

BEL	CAN	ESP	GBR	ITA	BRA	CHE	JPN	SAU	UAE	USA
NLD	NOR	AUS	DEU	FRA	MEX					

Biosimilar archetypes					
	Chronic patients, who might need several switches during their disease, can benefit from clear messaging from prescribing physicians and pharmacists about the safety and efficacy of all biosimilars.		The need for increased education of HCPs and regulatory bodies around biosimilar safety can be amplified for more complex biologics (e.g. oncologic monoclonal antibodies).		Additional HCP- and patient-targeted campaigns may be required for RD biosimilars where there is likely to be greater originator loyalty.

5.7. Prescribing

The value of products (e.g. from a cost and benefit perspective) should be considered to determine the 'best value' biosimilar. A multi-stakeholder approach should be leveraged to make this consideration, but regardless of the outcome, this should not limit prescribing physicians' autonomy in making clinical treatment decisions. In some cases (e.g. where there is biosimilar miseducation), the use of (in)direct prescribing incentives may be justified to support increased use of the 'best value' product (**Table 38**).

Table 38: Key recommendations for prescribing

Prescribing *Key recommendations*

For an ideal sustainable long-term biosimilar policy environment:
• Generally, healthcare systems should seek to encourage the use of the 'best value' biologic(s) for patients. Value should be defined not only by price but with the consideration of other factors including value-added services and supply.
  ○ There is a role for budget holders, pharmacists and physicians in the decision-making process, and decisions affecting availability/reimbursement/prescription of biologics should be made based on input from all of these stakeholders.
  ○ Prescribing physicians should have the ultimate decision to prescribe the 'best value' and most appropriate biologic for their individual patient.
  ○ If this selection is not in line with the multidisciplinary team's evaluation of the 'best value' biologic(s) then physicians should be asked to provide a legitimate reason.
• Ultimately, decisions affecting prescription of biologics need to be informed by appropriate and effective education and understanding of the advantages of biosimilars for the healthcare system as a whole as well as for individual patients.

- Prescribing incentives, where used, should encourage use of the 'best value' and be aligned across all key stakeholders (e.g. budget holders, pharmacists and physicians).
  - Indirect incentives (e.g. gain sharing) can provide a more effective and holistic solution to ensure physicians, patients and healthcare systems more broadly all benefit from prescription of 'best value' biologics, as the efficacy of direct benefits (e.g. financial) might be compromised if transparency is not maintained.
- Prescribing by active compound (INN prescribing) can reduce originator bias by equalising perception across all biologics of the same INN (originator and biosimilar). However, the nomenclature employed must allow for a correct differentiation of molecules (e.g. batch number, unique identifiers) to keep accurate monitoring and tracing upon switching in order to maintain a sustainable pharmacovigilance system (if other provisions do not establish this already).

Best practice examples

- In the UK, non-mandatory prescribing quotas still serve as an incentive for healthcare professionals. Moreover, gain-sharing mechanisms implemented at some local Clinical Commissioning Groups (CCGs) have ensured that savings driven by biosimilars are reinvested in healthcare systems, improving their perception.

Country characteristics

Good understanding of biosimilar value among key stakeholders	Less consensus of biosimilar value among key stakeholders
• Where there is widespread support for the use of best value biologics, the need for long-term direct incentives should be assessed; with appropriate education, healthcare systems should indirectly encourage prescription of best value products, reducing the need for formal incentives. • Indirect incentives (e.g. gain sharing) can provide a continuous encouragement for physicians and pharmacists to realise the value in biosimilar uptake and use.	• Incentives for physicians can guarantee a first push to initiate biosimilar uptake. As active and repeated educational efforts start showing results on biosimilar acceptance, these incentives can be withdrawn slowly, never abruptly. This should always account for the country context and other policies in place, and under no circumstances should incentives be turned into penalties.
BEL, DEU, ESP, FRA, GBR, ITA, NLD, NOR, AUS, BRA, CAN	JPN, BRA, CHE, MEX, SAU, UAE, USA

Biosimilar archetypes

	Chronic patients are subject to longer treatment duration and can therefore feel more attached to their 'brand'. Policies could consider patient incentives to encourage uptake (e.g. reduced patient co-payment). Additionally, active patient education can mitigate fear of switching to biosimilars.		N/A		Biosimilar acceptance in RD patients could be promoted by involving patient advocacy groups (PAGs) in policy decision-making. Further, RD biosimilars could leverage experience generated in other countries to instil confidence over time.

5.8. Dispensing

Dispensing decisions should ensure that patients receive the best outcomes while the healthcare system is able to provide the best value products. Evidence-based decisions should be made based on multidisciplinary perspectives and previous experience within the therapy area. Where pharmacists receive financial dispensing incentives, it is important that these do not discriminate against biosimilars (**Table 39**).

Table 39: Key recommendations for dispensing

Dispensing
Key recommendations

For an ideal sustainable long-term biosimilar policy environment:

- Treatment substitution should be a decision integrating the perspectives of all relevant stakeholders to ensure full alignment throughout the healthcare system. Therefore, physicians, budget holders and/or pharmacists and patients should have some role in product substitution decision-making to ensure the best outcomes for the patients and best value for the healthcare system.
- Decisions on the best product to dispense should be made on what is best for the patient and the health economy.
    - There should be understanding and consideration that there is not a 'one size fits all' approach that is suitable for all biosimilars.
    - Validated information should underpin decisions made.
    - Previous successes and challenges with biosimilars both within and outside of the therapy areas should be used by multidisciplinary teams to inform decision-making.
    - There should be international efforts to share experience with other countries on the safety and value of substitution for individual biosimilar products, to feed into local/regional/national decision-making
- Financial incentives for pharmacists should not penalise prescription of biosimilars (e.g. through lower margins for lower-cost products) and ideally should be aligned to the incentives in place for prescribing physicians.

Best practice examples

- In France, current dispensing regulations ensure that there is consistent communication between pharmacists and physicians through tracing digital systems to keep track of patients' treatments and any switch on these (e.g. Dossier Pharmaceutique, Mon Espace Santé). Moreover, treatment decisions in the inpatient setting are made with multidisciplinary input, accounting for both pharmacists' and physicians' opinions to ensure that the best decisions are made for patients.

Country characteristics

Biosimilars dispensed in outpatient setting

- Due to fewer opportunities and higher barriers for multidisciplinary decision-making, communication between physicians and pharmacists needs to be considered carefully to ensure alignment in guidance for prescribing and dispensing practices.
- Substitution practices should be implemented with measures to minimise friction between different opinions, for example notification of prescribing physicians.
    - Systems that avoid multiple switching of patients' treatments where not clinically supported should be implemented (e.g. electronic systems to notify dispensing pharmacists of previous treatment switches, booklets / prescription passports recording dispensing history).
- Consideration of reduced patient co-payments as a third layer of incentives can play a role in some countries.
    - Pharmacists should have a greater responsibility and confidence to act as a key point of contact for patients, ensure proper education and offer further guidance in their treatment.

AUS	BEL	BRA	CAN	CHE	DEU	ESP	FRA

ITA	JPN	NLD	NOR	MEX	SAU	UAE	USA	GBR
Biosimilar archetypes								
	Chronic treatments can be more frequently dispensed in the outpatient setting, and therefore good communication between physicians and pharmacists is especially relevant.		Oncology treatments in the inpatient setting require multidisciplinary decisions from a variety of experts to ensure optimal patient outcomes.		N/A			

5.9. Monitoring

Pharmacovigilance policies should not apply more stringent standards to biosimilars compared to originator biologics, unless there are other policies which limit the extent of biosimilar traceability. From a supply perspective, increased transparency into biosimilar supply and demand can ensure that product shortages are avoided (**Table 40**).

Table 40: Key recommendations for monitoring

Monitoring *Key recommendations*

For an ideal sustainable long-term biosimilar policy environment:
• Biosimilars should be subjected to the same pharmacovigilance standards as other biologic medicines.
  ○ To ensure patient safety, national pharmacovigilance systems need to be developed to ensure that monitoring can be conducted on a national scale.
• Nationally, stakeholder-led monitoring should be encouraged, with physicians, pharmacists and patients being empowered and educated to report AEs through a simple process.
• Measures to maximise traceability should be implemented to facilitate easy identification of brands and batch numbers on prescriptions / dispensing receipts:
  ○ Electronic systems to record individual patient prescriptions and the product used to fill each prescription
  ○ Notification systems to ensure that any changes to prescription are shared with prescribing physicians for approval/notification
  ○ Automated systems to facilitate easy identification of patients who have been dispensed medicines flagged for recall or additional safety follow-up
• While pharmacovigilance systems are being established, the following measures which can decrease traceability should be avoided:
  ○ Automatic substitution at the pharmacy level
  ○ INN prescribing (without the brand name or unique biosimilar identifier)
• In addition, usage and supply monitoring systems should be considered during contract negotiation and enforcement as a method to reduce risk of supply shortages.
  ○ Manufacturers and budget holders/procurement agencies should work collaboratively to share information regarding expected supply and demand.

Best practice examples

• In KSA, the Saudi Ministry of National Guard Health Affairs (MNGHA) has proposed a naming system for biosimilars combining the commercial name and the INN of the biosimilar, to allow proper monitoring after launch of biosimilar drugs. Physicians also need to actively engage in pharmacovigilance efforts and report to the Saudi food and drug authority about any adverse events.[174]					
Biosimilar archetypes					
	N/A		Robust pharmacovigilance can be more relevant for treatments which are used in acute settings, since AEs are more likely to emerge over longer chronic regimes.		Smaller patient volumes in rare diseases may necessitate greater pharmacovigilance and monitoring efforts in order to detect relevant AEs.

5.10. Overarching learnings

The implementation of sustainable policies is very specific to each country situation. However, across the nine therapy areas, there are some overarching learnings that can be drawn out:

- The introduction of biosimilar policy should support the goal of sustainability, ensuring cross-stakeholder perspectives are captured so that optimal value can be derived from the innovation of biosimilars.
- As a country's biosimilar landscape matures over time and stakeholder experience increases, there is a need to periodically evaluate and update policies to ensure sustainability is maintained.
- Policies are less effective when implemented in isolation; hence, implementation should consider the existing policy environment and where synergies can be leveraged across policy areas.
- Similarly, policies should adapt for variations resulting from differences between biosimilar archetypes.
- Cultivation of a sustainable global biosimilar landscape requires sharing of learning and best practices across countries, supporting accelerated development of countries which have less mature biosimilar landscapes.

Appendix 1

Table 41: Key literature sources defining sustainability for biosimilars

Publication	Full Title	Geographic Scope	Summary of key biosimilar sustainability findings
Vulto et al. (2020)	Sustainability of Biosimilars in Europe: A Delphi Panel Consensus with Systematic Literature Review	Europe	• A sustainable biosimilar market benefits all stakeholders over a long-term period. • Failure to focus on biosimilar sustainability can adversely affect biosimilar development and lead to increased costs and fewer incentives for innovation.
Pugatch Consilium (2019)	Towards a sustainable European market for off-patent biologics	Europe	• Biosimilar sustainability should benefit all stakeholders and is broadly agreed. • Policy environment across pricing, procurement and physician autonomy / patient choice is diversified but lacks long-term vision of sustainability. • Within these areas, there is a clear roadmap for European policy to ensure sustainability.
IQVIA Institute (2018)	Advancing Biosimilar Sustainability in Europe	Europe	• Sustainable biosimilar policies were analysed affecting five key elements: access, regulatory / clinical guidelines / product / incentives / competitive pressure. • A sustainability assessment highlights key areas at risk of failing to achieve long-term sustainability and some potential future solutions.
GfK Country Access (2014)	Factors Supporting a Sustainable European Biosimilar Medicines Country	Europe	• Four elements considered holistically can ensure a sustainable policy framework in Europe: education and understanding, experience and use, sustainable pricing and rational decision-making.
Other sources considered			
Simoens et al. (2018)	How to realize the potential of off-patent biologicals and biosimilars in Europe? Guidance to policymakers		
Kumar, A. (2018)	A Common Sense Approach To Sustainability In The Biosimilar Business		
Vulto, A. et al. (2019)	Sustainable biosimilar procurement in Europe: a review of current policies and their potential impact		
Ven den Hiven, A (2017)	Biosimilar medicines: Increasing access to modern essential medicines while supporting sustainability of healthcare systems		
Medicines for Europe (2021)	Filling the Gap: How off-patent medicines can improve the equity and quality of cancer care		
Simoens, S. and Vulto, A. G. (2021)	A health economic guide to country access of biosimilars		
Dutta et al. (2020)	Identifying Key Benefits in European Off-Patent Biologics and Biosimilar Countries: It is Not Only About Price!		
Allens & Linklaters LLP	Biologic medicines and biosimilars Protecting innovation without patents – data exclusivity and country exclusivity		
Allens & Linklaters LLP	Biologic medicines and biosimilars: Protecting investment in biologic medicines – biological medicines, biosimilars and the challenges they pose		

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AAM (2021)	Roadmaps for Ensuring Patient Access to Generic and Biosimilar Medicines: Securing Sustainable Countries
Barbier et al (2021)	Off-Patent Biologicals and Biosimilars Tendering in Europe—A Proposal towards More Sustainable Practices
IGBA (2020)	Developing a Regulatory Policy Framework Supporting Biosimilar Competition: The Opportunity for Tailored Clinical Biosimilar Development
IQVIA (2020)	The Impact of Biosimilar Competition in Europe: a review of current policies and their potential impact

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