Unlocking the Potential of Biosimilars

A Roadmap for Biosimilar Policy Sustainability

Biosimilar Policy Landscape & Sustainability Assessment

Netherlands

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Introduction

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

Methodology

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

Table 1 - Policy area assessment framework

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

Source: CRA

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

Table 2 – 5-point 'star rating' scale

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

Source: CRA

Summary

	Manufacturing and R&D	No specific manufacturing policies for biosimilar products have been identified in the Netherlands	★★★★★	Biosimilars are held to the same manufacturing standards as originator products therefore quality is maintained. Manufacturing can begin before originator LoE facilitating supply at launch while still observing the full exclusivity period of the originator product.
	Regulatory Approval	Following EMA's regulation	★★★★☆	Current evidence requirements are slightly streamlined and therefore can result in slightly faster access to biosimilars. However, recent research indicates that comparative clinical studies are not required for all biosimilar products and reducing the need for this evidence and/or implementing formally accelerated timelines could offer further regulatory efficiencies.
	Health Technology Assessment	No HTA required for biosimilars by ZIN	★★★★★	Lack of HTA requirements accelerates biosimilars access and avoids potential delays to access
	Pricing & Reimbursement	External fixed reference pricing from countries of the same cluster. Biosimilars officially allowed to launch at originator's price, but undergo discounts to avoid co-payments	★★☆☆☆	Reference pricing allows biosimilars to launch at originator's price, which can improve their value perception. However, subsequent contracting practices can undermine the sustainability of these policies and result in final, significant, and unsustainable price erosions
	Contracting	Tendering procedures for **inpatient products** in the country are run at the hospital level and only allow a single winner. Tenders are awarded predominantly based on price.	★★★☆☆	High payer influence on tendering results in big weight of price on awarding criteria, which might lead to unsustainable discounts on the long-term. **Inpatient tenders**, although only allowing for one winner, permit fair levels of market share given the varied participation and amount of organising hospitals. However, allowing of multiple winners on **outpatient tendering procedures** boost competition and provide better conditions for supply
		In the **outpatient sector**, tenders are run by health insurance providers and allow for multiple winners. Tenders are awarded predominantly based on price.	★★★☆☆	

	**Biosimilar Education & Understanding**	Health authorities' efforts to organise events (e.g., conferences) have driven improvement in biosimilar education	★★★★★	Initiatives to expand awareness around biosimilars through educational campaigns have resulted in an access increase and driven cost savings for insurance providers, benefiting multiple stakeholders
	**Prescribing**	Biosimilar prescription recommended by authorities and enforced by health insurances	★★★★☆	Payer pressure has positively increased competition and resulted in broad biosimilar prescription, driving cost savings. However, official policies to regulate this would improve physicians' flexibility without affecting biosimilars benefits
	**Dispensing**	Automatic substitution allowed for naïve patients. Fixed clawback of 6.82% of the total price is given for each biosimilar prescription	★★★★☆	Permission of substitution for naïve patients increases biosimilars' uptake without eroding originators' current market share. However, despite the implementation of the claw-back system, discounts from originators' manufacturers could still negate competition to a certain extent
	**Monitoring**	Following EMA's guidelines. HCP involvement in monitoring is required when treatment switching decisions are made	★★★★☆	Although EMA sets equal guidelines for risk management assessment of biosimilars and originators, HCP involvement in pharmacovigilance is encouraged in the country upon switching, which can help improve biosimilars' perception and access

Key Successes, Areas for Improvement & Risk Areas

Key Biosimilar Policy Successes
▲ HCP prescribing power is contained up to a certain degree by health insurance providers, which has enhanced biosimilars uptake ▲ Health education has proved to be optimal, also on the patient level
Key Biosimilar Policy Areas for Improvement
► High pressure exerted by insurance companies on tendering procedures can drive price erosion if uncontrolled. However, the containment of this pressure is observed as a difficult goal to achieve, given their influence in the current healthcare system
Key Biosimilar Policy Risks
▼ The positioning of patients as the main concern in the healthcare system has provided insurance companies with a rationale to exert extra pressure. This can provide a negative environment for manufacturing stakeholders, who often need to undergo unfair price discounts in order to compete, potentially driving long-term erosion
Key Biosimilar Policy Priorities to Achieve Long-Term Sustainability in the Netherlands
1. TBD The need to balance competition and price erosion with sustainability in the long run. The need to maintain multiple manufacturers on the market. 2. The need to include criteria other than price in tendering.

Policy Landscape Assessment

Manufacturing and R&D

No specific manufacturing policies for biosimilar products have been identified in the Netherlands.

European Good Manufacturing Practices

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

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

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

Regulatory Approval

Streamlined evidence requirements

Approval of biosimilars in the Netherlands follow EMA's guidelines. Therefore, efficacy, safety and quality of the product are assessed by the European Assessment Committee for Medicinal Products for Human Use (CHMP).[vii]

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

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

Immunogenicity data needs to be collected for one year before the CHMP allows marketing authorisation, and maintained later on for long-term pharmacovigilance purposes.[xiii] Immunogenicity factors are listed in the guidelines (e.g., anti-drug antibodies (ADAs)) but risk assessments are encouraged to be developed on a product-specific basis, as immunogenicity is hard to foresee.[xiv] **Extrapolation of indications is permitted by the EMA once biosimilarity has been demonstrated for at least one, when the scientific justification is granted**.[xv]

Health Technology Assessment

No biosimilar HTA requirements

ZIN does not require HTA to be conducted for biosimilar products since they are regarded as having no additional therapeutic value to the originator based on their non-inferiority status. For this reason, an economic evaluation via HTA is not required.[xvi]

Pricing & Reimbursement

Mandated Biosimilar Discounts

Pricing and reimbursement are applied as a single process.[xvii] **Biosimilars are not subject to any mandated discounts from their reference product's price and officially, biosimilars can launch with the same price as the originator**.[xviii]

Reference Pricing

However, an international reference pricing system is used in the Netherlands. Biologic products are organised in clusters, generally by therapeutic area and/or active ingredient, and the price of all products in the cluster is set at or below the average price of all products in the same cluster. The Ministry of Health (MoH) determines the maximum price possible for each therapeutic group, which is calculated as an average of the prices in four reference countries – Belgium, France, Norway, and UK.[xix] Further discounts are applied after contracting procedures.

Full coverage vs. partial coverage

The reimbursement level by third party payers is set based on the average price of the cluster. The differential between the reimbursed price and product price must be covered by a patient co-payment. As a result, biosimilars tend to have a price equal or below the products in the cluster and undergo price reductions to avoid high patient co-payments**.**[xx]

Contracting

Scope of contracts

Tendering procedures in the Netherlands vary for **inpatient products**, where tenders are run at the hospital level,[xxi] and the **outpatient sector**, where tenders are run by health insurance providers.[xxii] There are 4 different health insurance companies in the country, and the products covered by them are decided by the Ministry of Health.

Inpatient hospital tenders

Single-winner contracts

On the hospital level, only one winner is allowed.[xxiii]

Contract decision criteria

Hospitals fully award their contracts based on price.[xxiv] The tenders are influenced by health insurance providers, who pressure hospitals to obtain high discounts. However, supply is always taken into account and ensured.

Contract length

In the case of hospital tenders, **the duration can vary between 12 and 24 months**.[xxv]

Outpatient health-insurance tender

Multi-winner contracts

Tender contracts for outpatient biosimilars allow for **more than one winner**.

Contract decision criteria

Tenders for health insurance providers are not only awarded **based on price, but also on the capability of the winner to supply the biosimilar drug** (e.g. weekly updates on availability status, delivery information published on the supplier webpage).[xxvi]

Contract length

The contract duration for tendering procedures varies from one health insurance company to the other. **Ranges from a minimum of six months to a maximum of two years have been reported**.[xxvii]

Biosimilar Education & Understanding

HCP educational programs

The **Initiative Group for Biosimilars in the Netherlands** comprises of representatives from health insurance institutions, healthcare professionals and scientific representatives. This group aims **at raising awareness and bringing verified information regarding biosimilars in the country**. This group has its own webpage and also contributes to educational events such as conferences, clinical guidelines, and publications.[xxviii] Health authorities also get involved in the education of all stakeholders and organise conferences to improve the uptake and perception of biosimilars.[xxix]

In 2012, a number of teaching hospitals initiated the “learning healthcare system paradigm” for oncology patients. This initiative allows for the constant recording and update of health technology and drugs used for treating patients, including biosimilars. As a result, the database allows HCPs to get insights on biosimilar treatment switching percentages, rates and the statistics for these. This led to the realisation of low switching percentages due to sub-optimal efficacy recorded of biosimilars recorded.[xxx]

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

Patient educational programs

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

Prescribing

Clinical guidelines and prescriber-initiated switching

Biosimilar prescription instead of the originator when available is often enforced by health insurance for reimbursement purposes.[xxxv] Further to this, **prescribers are encouraged to switch patients from originator biologics to biosimilars, although close monitoring of the patient needs to be developed after the decision**. Moreover, The Dutch Medicines Evaluation Board (MEB) emphasises the importance of close cooperation between HCPs and pharmacists when switching treatment options. This MEB recommendation was made in 2015, when they updated their position towards biosimilars, favouring their utilisation after the revision of published data.[xxxvi] In addition to close co-operation between HCPs and pharmacists, patients must be kept informed when switching decisions are made by their doctors, and all changes need to be properly reported in the patient's files to allow traceability.[xxxvii]

Dispensing

Regressive Retailer Mark-Ups

Manufacturer discounts for pharmacies are permitted in the Netherlands and no fixed mark-up is established for biosimilars. However, as a measure to promote biosimilar uptake, **dispensing fees are variable and pharmacies receive a claw-back of up to 6.82% from the health insurance providers (sickness fund)**, setting a maximum of 6.80 euros for each prescription.[xxxviii]

Automatic substitution

In the Netherlands, automatic substitution at the pharmacy level is allowed for naïve patients, although it is prohibited for those patients who have already been initiated on a treatment (originator or biosimilar). Physicians must be notified in case of substitution and can also specify their decision when prescribing.[xxxix]

Monitoring

Pharmacovigilance measures

Biosimilar pharmacovigilance requirements are no different from innovative biologics.

The Netherlands Pharmacovigilance Centre is responsible for biologics and biosimilar monitoring in the country, and the Netherlands Health and Youth Care Inspectorate (IGJ) also intervenes and periodically inspects manufacturing sites. According to these bodies, it is the responsibility of the manufacturing entity to develop a system for the monitoring of drugs after marketing approval. They indicate that the system in place needs to enhance traceability of the product.[xl]

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

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