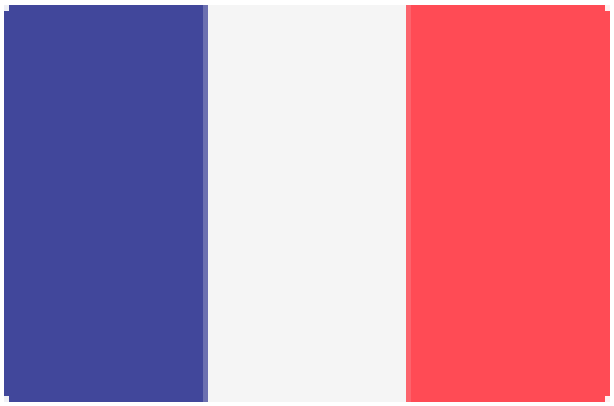
Unlocking the Potential of Biosimilars

A Roadmap for Biosimilar Policy Sustainability

Biosimilar Policy Landscape & Sustainability Assessment

France



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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 biosimilar-specific manufacturing policies in France or at the EMA-level were identified. Although, Good Manufacturing Practice (GMP) legislation is in place to govern biosimilar manufacture with some additional conditions versus small molecule manufacturing.	★★★★★	Biosimilars are held to the same manufacturing standards as other products therefore quality is maintained in order to build trust among health professionals (physicians, pharmacists). Manufacturing can begin before originator LoE facilitating competition, supply at launch and competition but local manufacturing incentives to promote biosimilar competition & innovation are limited or not yet implemented
	**Regulatory Approval**	France follows the regulation (EC) No 726/2004 for centralised marketing authorization from the European Parliament, streamlining evidence requirements. Indication extrapolation can be possible following regulatory approval.	★★★★☆	Current evidence requirements are slightly streamlined and therefore can result in slightly faster access to biosimilars. Additional national policies could support further acceleration
	**Health Technology Assessment**	The CT conducts rapid HTA reviews on behalf of HAS for all biosimilars: they automatically grant biosimilars with an ASMR V and remove the need for an economic assessments to accelerate the review. However, while this process is streamlined still results in a short period (avg. 68 days) of time to process the decision officially.	★★★☆☆	Rapid HTAs support earlier patient access, decreasing the opportunity for bureaucratic delays. Given biosimilars receive an automatic ASMR rating, removing the requirement for biosimilar HTA would accelerate biosimilar access to the market.
	**Pricing & Reimbursement**	Mandatory list price discounts for originators and biosimilars at biosimilar launch • Retail: originator (20% discount) & Bx (40% discount) Hospital: originator & biosimilar (~30% discount)	★★★☆☆	Mandated originator and biosimilar discounts can improve business predictability while driving cost savings. However, they have the potential to encourage unsustainable price erosion given further price reductions in tenders, removing incentives for future innovation
	**Contracting**	Single-winner tenders conducted mostly at hospital (but also regional) level, generally lasting 36 months (re-open following the initial biosimilar launch) and primarily being driven by price but also other criteria	★★☆☆☆	Tenders that allow for single winners and governed mainly by price can lead to significant price erosion, especially given that list pricing is already discounted at launch at the national level

	**Biosimilar Education & Understanding**	Educational resources created for HCPs/pharmacists, alongside tools, such as the biosimilar register, which lists biosimilar alternatives to reference products. EMA materials have also been created in 23 languages, including patient-specific manuals.	★★★★☆	Nationally, there are a variety of educational resources for different stakeholders. Although additional government support would be beneficial, current resources improve value perception, biosimilar uptake and overall access. Specifically, the relevance of educational materials would be improved though greater multidisciplinary input to material development
	**Prescribing**	Governmental recommendations for biosimilar initiation and switching, alongside some prescription quotas and gain sharing policies (in hospitals and for some outpatient products)	★★★★☆*	Financial incentives are supportive of cost savings driven by biosimilar uptake and have managed a good uptake of biosimilars in the country, improving patient access. However, more explicit guidance for prescribers to highlight the benefits for biosimilars would promote their prescribing from the ground up.
	**Dispensing**	Pharmacy-level automatic substitution will be introduced in 2022 (interchangeable list of biosimilars is not yet published). Regressive pharmacy discounts do provide incentives for pharmacists to dispense biosimilars and originator discounts are limited to prevent significant erosion	★★★★★	Physicians are key-decision makers, enabling clinical value to drive prescribing decisions. Financial incentives at pharmacy level promote biosimilar dispensing where medically allowed, increasing uptake and capturing cost savings, while limits on originator discounting prevent uncompetitive price reductions. Introduction of automatic substitution for some biosimilars might reduce physicians' authority in determining patients' treatment, although
	**Monitoring**	No biosimilar-specific policies identified, although willingness to improve the traceability of biosimilar medicines has been proposed in the 2018 French Social Security Financing law	★★★★☆	EMA's guidelines for risk management assessment of biosimilars and originators can help on broadening biosimilars' access and enhancing their value understanding, but HCP involvement in pharmacovigilance upon switching must be ensured to safeguard this

Key Successes, Areas for Improvement & Risk Areas

Key Biosimilar Policy Successes

- ▲ Accelerated HTA process through rapid reviews
- ▲ Tenders are re-opened following the launch of the first biosimilar
- ▲ Education resources are created for HCPs/pharmacists, including resources to support awareness of treatment switching options; these are provided in a variety of languages
- ▲ Recommendations for biosimilar initiation and switching, alongside prescription quotas and gain sharing policies
- ▲ Regressive pharmacy discounts incentivise dispensing of cheaper products
- ▲ Limits to originator discounting at the retail pharmacy level prevent anti-competitive offers of excessive discounting, facilitating biosimilar competition

Key Biosimilar Policy Areas for Improvement

- ► Mandatory list price discounts for both the originator and biosimilar, which vary between the retail (20% & 40%) and hospital (both 30%) setting
- ► Tenders are single-winner with a key focus on price

Key Biosimilar Policy Risks

- ▼ Mandatory list price discounts for originators and biosimilars have the potential to drive unsustainable price erosion
- ▼ Single winner tendering which reopen following the launch of new biosimilars can also support significant price erosion through successive tenders
- ▼ Future introduction of automatic substitution in pharmacies might distort fair competition between biosimilars, driving erosion of price benchmarks as a result of higher discounts arising from rebate negotiations at the pharmacy level

Key Biosimilar Policy Priorities to Achieve Long-Term Sustainability in Australia

1. Removal of HTA assessments at the national level which delay biosimilar launches and hence slow patient access
2. Mandatory discounts introduced through pricing and reimbursement policy should be optimised to mitigate the risk of unsustainable price erosion to occur
3. Improve procurement policy to consider more diverse award criteria in order to avoid single-winner, price-driven tenders which introduce further discounts, increasing the likelihood of unsustainable price erosion

Policy Landscape Assessment

Manufacturing and R&D

No national or European-level policies incentivising local manufacturing of biosimilars were identified however, Good Manufacturing Practice (GMP) legislation is in place to govern biosimilar manufacture with some additional conditions versus small molecule manufacturing.
The manufacture of biological medicines tends to be more complex than for chemically-derived molecules. For biological medicines, some of the GMP requirements have been adapted to take into account their specific nature (e.g., use of appropriate aseptic techniques, refrigeration and other storage conditions, stability, transport etc.).[vi]

Regulatory Approval

Streamlined evidence requirements

The centralised procedure for granting regulatory approval of biosimilars was first introduced by the EMA in 2004 (Regulation n. 726/2004).[vii, viii] 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.[ix]

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.[x,xi]

Immunogenicity data needs to be collected for one year before the CHMP allows marketing authorisation, and maintained later on for long-term pharmacovigilance purposes.[xii] 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.[xiii] **Extrapolation of indications is permitted by the EMA once biosimilarity has been demonstrated for at least one, when the scientific justification is granted**.[xiv]

Health Technology Assessment

Simplified HTA submission requirements

In France, the Commission de la Transparence (CT) conduct rapid HTA reviews on behalf of Haute Autorité de Santé (HAS). The assessment process is accelerated by removing cost-effectiveness and economic modelling, as well as critical appraisals of the quality of evidence and considerations of ethical implications.[xv] Furthermore, biosimilars are given the same Service Medical Rendu (SMR) level as the originator and an Amélioration du Service Medical Rendu (ASMR) rating of V by default. An analysis of HAS biosimilar HTAs up until 2018 found that of 31 assessments in total, all of these were rapid HTA

reviews.[xvi] Rapid HTAs are still considered as a burden, as they can still take up to 3 months (average was calculated to be 68 days), what may result in further delays on price negotiations with the Comité Economique des Produits de Santé (CEPS).

Pricing & Reimbursement

At Launch – Mandated Fixed Discounts for Biosimilars and Originators

Prices of biosimilars are negotiated between the pharmaceutical companies and the CEPS. In March 2021, a new 3-year pricing framework agreement was co-signed by the CEPS and the French pharmaceutical industry association (Leem) in the presence of the French Ministry of Health. Article 25 of this framework outlines mandatory list price discounts for the originator and biosimilar, at the point of biosimilar launch.

In the retail pharmacy ("pharmacies de ville") market, the originator must discount by 20% and the biosimilar must discount by 40% (from the originator's initial list price). Variable discounts can be seen depending on the penetrations of biosimilars and 5 years after the first biosimilar launches, CEPS is expected to initiate price convergence.

In the hospital pharmacy market, both the originator and the biosimilar must discount by 10% upon registration of the biosimilar on the lists provided for in the social security code ("liste en sus" and "liste retrocession").[xvii] This discount can be increased to 30% depending on the hospital purchase prices, or it can be increased above 30% if the purchase price is less than 50% of the CEPS tariff. Recent discussion regarding automatic substitution in the country would potentially modify the pricing landscape, as bigger discounts might arise from rebate negotiations in pharmacies.

Contracting

Tendering Practices

- ***Number of granted winners***

Tenders are conducted at the hospital, and regional level. Importantly, tenders only have one winner, in order to reduce the storage costs of multiple products but also to reduce the risk of dispensing errors.

- ***Awarding criteria***

Price is the primary focus of tenders, but other factors are considered. These include: customer service, patient support, local manufacture, the range of indications, ability to supply, environmental aspects, condition of payment, formulation, aggregation, packaging and corporate responsibility.

- ***Contract length***

On average, contracts last 36 months, but the tender process is re-opened following the entry of a new biosimilar.

Biosimilar Education & Understanding

HCP-targeted educational programs

In 2017, the National Agency for Medicines and Health Products Safety released the French biosimilar register (liste de référence des groupes biologiques similaires). This register is aimed at increasing physician awareness of the available biosimilar versions of reference biologics. Additional information on each product (e.g., dosage, pharmaceutical form, therapeutic indications, marketing authorization holder) is also available.[xviii]

The Agence Nationale du Développement Professionnel Continu (ANDPC) leads HCP-targeted educational programs in France and provide references to other educational resources.[xix] These are primarily for pharmacists but are also relevant for other healthcare professionals.[xx] HCP input is collected though Collèges nationaux professionels (CNPs) which informs the priorities of educational programmes.

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).[xxi, xxii]

Previously, multidisciplinary efforts have been made – e.g. HAS initiated work on this in 2017 – although, additional work is required to maximise the impact and relevance of this input across stakeholder groups.[xxiii]

Patient-targeted educational programs

In addition to the online documents available in the EMA's webpage, other patient-friendly resources are available, for example, an animated video was created, also in a wide scope of languages, clarifying key factors for these medicines for patients.[xxiv] The European Commission has also created manuals to raise patient awareness around biosimilars.[xxv] Existing materials provided to patients often have received PAG approval and are also hosted on their websites, complementing dissemination in hospitals and pharmacies.

Prescribing

Clinical recommendations for prescriber-initiated prescription of biosimilars

A ministerial directive issued in August 2017 highlighted that, during the course of treatment, an originator biologic can be switched (by the physician) with a biosimilar at any time. Furthermore, it outlined (non-binding) objectives related to increasing switching (in originator treated patients).[xxvi] However, better recommendations and guidance on why physicians should do this could improve their understanding on biosimilar benefits.

Prescription quotas for volume of biosimilar prescription

Biosimilar prescription quotas are used infrequently in France, although the aforementioned ministerial directive (August 2017) did also propose a goal (non-binding) of 70% biosimilar prescribing (for naïve patients).[xxvii]

In 2016, physicians working in ambulatory care were encouraged (not mandatory) to prescribe at least 20% of patients with insulin glargine biosimilars. Those who met this objective were awarded performance-based capitation payments.[xxviii] Such incentives still apply nowadays and have proved to be efficient.

Financial incentives linked to biosimilar prescribing

In 2017, agreements made between hospitals and the branch of Social Security that pays medical costs were implemented for three molecules: adalimumab, insulin glargine, and etanercept. Under these

arrangements, hospitals receive 20-30% of the savings from reference product's prices for each biosimilar prescription.[xxix] Although these agreements are not directly with physicians, they influence their prescribing behaviour. Early results demonstrate a higher initiation rate on biosimilars for adalimumab and insulin glargine, and a growth in the penetration rate, compared to control groups that did not partake in the gainsharing experiment.[xxx]

Performance contracts may apply at the hospital level, where physicians are given points when increasing their prescribing of biosimilar, also getting access to gain sharing schemes, as recently proposed in Article 51.

Conversely, although no penalties officially apply in the country, hospitals with biosimilar prescription quotas below the average might be pinned down by the HAS and encouraged to change their prescribing attitudes.

In January 2022, agreements were made made between physicians and the branch of Social Security that reimburses medical costs were implemented for five molecules in the outpatient setting: etanercept, adalimumab, follitropine alpha, enoxaparin, teriparatide, insulin aspart.[xxxi] Under these arrangements, physicians will receive 30% of the savings (from the originator's price) for each biosimilar prescription in 2022. This will decrease to 20% in 2023 and 10% in 2024, with a maximum of 7000€ for all molecules combined.

Dispensing

Automatic Substitution

Legislation introduced in 2014 and 2017 (Article 96 of the 2017 French Social Security Financing law) authorised pharmacist substitution (under certain conditions) by law, although this was never ratified by an implementation decree, hence it never came into force.[xxxii] In 2020, an update to the Social Security Financing law abolished the potential for substitution due to concerns regarding traceability and safety of such use of biosimilars.[xxxiii] Despite this, as per Article 42 of the same law, a working group will be established by the French government to determine the potential for interchangeability between biologics.[xxxiv] More recently, discussions have focussed on Article 64 of the 2022 Social Security Financing law which will introduce interchangeability between biosimilars and their originator and would therefore allow automatic substitution of biosimilars. Automatic substitution came into effect in January 2022, but the list of interchangeable biosimilars has not been published yet (expected in mid-2022 and to initially contain pegfilgrastim and somatropin). Automatic substitution would be restricted to retail pharmacies for patients naïve to that specific treatment. Furthermore, chronic diseases may be excluded, only certain ANSM-defined biosimilar groups might be substituted and importantly, it would be contingent on physician approval, with justification required to veto.

Additional policies complementary to substitution that have been proposed and would imply better traceability are the pharmaceutical files (Dossier Pharmaceutique - DP) and the shared medical files (Mon Espace Santé). The first one, already available in the country, is a personal record of individual patient's treatments, including the brand name, that can be acquired at the pharmacy. The latter started in February 2022 and can include the medical file as well, providing better communication between HCPs and pharmacists and avoid untimely switches for patients.

Interestingly in some hospitals, the penetration of injectable oncology biosimilars can approach 100%, since cancer committee consultations between pharmacists and physicians have approved automatic substitution of injectable originators.

Regressive Retailer Mark-Ups

At the retail pharmacy level, there is a regressive mark-up system (26.1% – 6% on the MSP), where pharmacies can charge larger percentage mark-ups on cheaper drugs. Thus, there is an incentive for pharmacists to dispense lower cost drugs.[xxxv]

Additionally, there are restrictions on the maximum level of discounts (2.5%) that manufacturers of originators are able to offer retail pharmacies, enabling biosimilar manufacturers to provide larger and more attractive discounts.[xxxvi]

Monitoring

Post-commercialisation pharmacovigilance measures

Although no specific policies have been identified which differentiate biosimilar monitoring from other pharmacovigilance efforts, the 2018 French Social Security Financing law highlighted a need to facilitate the traceability of biosimilar medicines. This need was emphasised within the context of a change to a drug during the course of treatment.[xxxvii]

Where required, traceability should be ensured by the dispensing pharmacist who should note the name of the dispensed medicinal product and the batch number dispensed. This practice is technically required under French law, but it not

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".[xxxviii, xxxix]

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