Unlocking the Potential of Biosimilars

A Roadmap for Biosimilar Policy Sustainability

Biosimilar Policy Landscape & Sustainability Assessment

Italy

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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: recent into 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] Within country biosimilar utilization can also vary significantly. 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 associated with biosimilar use.[iv] The variation in biosimilar success is likely to be largely due to a country's policy environment. 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. These 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 operating 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 Roadmap for Biosimilar Policy Sustainability'.

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	European manufacturing waivers are granted to biosimilars ahead of originator LoE facilitating efficient access at launch. GMP standards remain the same across all biologic prices	★★★★★	Biosimilars are held to the same manufacturing standards as other products therefore quality is maintained. Manufacturing can begin before originator LoE facilitating competition, supply at launch. Given the fast pace and innovation observed in the originators field, establishing equal manufacturing measures can support biosimilar competition.
	**Regulatory Approval**	Streamlined evidence requirements establishing biocomparability assay following EMA's guidelines	★★★★☆	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**	An HTA analysis is not required. In any case, economic assessments of regional HTAs can be used to inform decision-makers on procurement matters, so as to correctly value the economic-organizational impact	★★★★★	Specific economic assessments through regional streamlined HTAs can still improve biosimilars' perception and understand of their value
	**Pricing & Reimbursement**	Minimum 20% price discounts for biosimilars to be reimbursed. Further discounts applied if volume thresholds are reached	★★☆☆☆	Mandatory discounts for biosimilars can improve the predictability of spending and possible savings. Furthermore, predicting possible savings in advance also makes it possible to establish which other additional funds will be available to finance the innovations. However, list prices are subject to significant additional discounts during procurement procedures which can lead to unsustainable price reduction as no volume guarantees or maximum discount levels are granted
	**Contracting**	Tendering procedures are organised on the regional level and they can allow for multiple winners. Contracts have a 24-month duration but are reopened following launch of a new biosimilar. Current law promotes the use of HTA and cost effectiveness and price-quality	★★★☆☆	Multi-winner tenders promote competition within the market. Moreover, reopening of tenders upon new entry does not close the market for significant periods of time although can increase the risk of frequent price revisions and a 'race-to-the-bottom'. Tender award solely on price can be

		considerations however, regions tend to award tenders solely on price despite the law.		unsustainable in the long term, not allowing for differentiation in terms of quality, supply, reputation, and additional patient support services and not allowing for sufficient clinical input/buy-in to ultimate prescribing options.
	**Biosimilar Education & Understanding**	Efforts to promote education from Egualia (formerly AssoGenerici) association	★★★★★	Educational programs are in place across regions, which improves value perception and therefore biosimilar uptake. However, increased government support to align educational campaigns nationally could contribute to higher rates of biosimilar uptake.
	**Prescribing**	Switching is responsibility of the physician. Prescribing lists bound to tendering procedures and biosimilar prescribing quotas varying across regions	★★★★☆	In the context of multiple winner tenders, binding of prescribing lists to tenders has less impact on physician autonomy and maintains some flexibility for prescribers. Non-mandatory switching policies are viewed more positively by physicians but can result in unequal access across regions; especially where incentives for prescribers (direct or indirect) are not always applied.
	**Dispensing**	Prohibited automatic substitution. Certain patient co-payments applying for outpatient biosimilars, although these represent a small percentage compared to inpatient products	★★★☆☆	Automatic substitution is not permitted. However, there is room to introduce policies to incentivise biosimilar dispensing and increase pharmacist input to decision making (e.g. during tender award processes) to result in a more competitive environment, leading to greater cost savings.
	**Monitoring**	Development of a risk management plan after market authorisation following EMA's guidelines	★★★★☆	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
▲ Inclusion of HCPs and pharmacists' considerations into policy makers decisions has resulted to an increase in biosimilar uptake in the past 5 years
Key Biosimilar Policy Areas for Improvement
► Tenders considering additional value when awarding were already implemented with positives outcomes in the country – i.e., tenders for the HPV vaccine favoured differences in genotype variants ► Health education and awareness around biosimilars must be improved in the country, especially regarding patients
Key Biosimilar Policy Risks
▼ Tendering procedures fully awarded on price result in continuous and unsustainable price erosion for biosimilars. Furthermore, the procurement law unequivocally stresses that the logic of price must be overcome in favour of an HTA approach (e.g., cost-effectiveness, price quality).
Key Biosimilar Policy Priorities to Achieve Long-Term Sustainability in Italy
1. Ensuring that requirements for tender awarding gathered in the budgetary law are well followed by regional authorities 2. Ensuring that pricing guidelines and contracting practices are aligned to avoid unnecessary price reductions for biosimilars through subsequent procedures

Policy Landscape Assessment

Manufacturing and R&D

Manufacturing Exemption Waiver

The manufacturing of biosimilars (and generics) can begin prior to the expiry of the originator's patent exclusivity in a similar manner to that permitted by EU legislation.

No further specific Manufacturing and R&D policies were identified for biosimilars in Italy.

Regulatory Approval

Streamlined evidence requirements

As a member of the European Union (EU), Italy follows the guidelines to establish biocomparability dictated by the European's Medicines Agency (EMA). Such regulation has been added to the Italian law via the Decree n.219 of April 2006.[v] The Italian Drugs Agency (AIFA) must grant marketing authorization within 60 days from EMA's approval.[vi]

Health Technology Assessment

No biosimilar HTA requirements

In Italy, biosimilars do not officially need to go through full-length HTA processes, but the outcome of certain simplified analysis (e.g., organizational impact) can be used in subsequent contracting practices to negotiate tender awards, as included in the Italian budgetary law. However, such practices are not fully monitored in real practice, and therefore more unsustainable criteria can apply in tenders (e.g., price playing the main role).

Pricing & Reimbursement

Reference pricing

Pricing and reimbursement are closely related, as both are coordinated by AIFA. Pharmaceutical companies need to undergo price negotiations for innovative biologics with the institution based on criteria like the therapeutic value and innovation, pharmacovigilance data, price in other EU markets, price of other products within the same therapeutic area and forecasting of potential patients. These negotiations set the pharmacy retail price and the maximum sale price for the National Healthcare Service ("SSN"). However, pharmaceutical companies must undergo further discounts at the hospital level.

Biosimilars can theoretically be included in the same class as their originator - from those considered essential drugs (class A) to drugs which require a hospital setting and specialist care (class H). However, biosimilars are normally regarded by AIFA from a non-inferiority perspective, not necessarily providing extra therapeutic added value. Therefore, AIFA requires manufacturers to provide additional convenience through their price, this means, via price reductions.[vii] Pricing guidelines for biosimilars were recently updated in 2021. These updates mainly allow more streamlined price and reimbursement negotiations (lower supervision of AIFA) for those biosimilars included in class A or H, as long as they follow the mandated price reductions.[viii]

Mandated fixed discounts

Biosimilars must undergo at least a 20% price reduction from their originator after their negotiation with AIFA.[ix] However, final net prices arise from subsequent contracting procedures, which result in higher discounts applied for the final retail price.

Progressive price discounts

AIFA's pricing guidelines latest updates also take into consideration projected sales volumes.[x] In the case of biosimilars, further price reductions ranging from 15% to 22% are applied if the agreed volume threshold is reached.[xi]

Scope of contracts

Rules for the design of public tenders are gathered in the Draft Budgetary Law of 2017.[xii] In Italy tendering procedures are organised for the supply of inpatient biosimilars on the regional level, including the 20 different regions.[xiii] Outpatient care is not included in tendering systems.[xiv]

Single-winner contracts

Tendering procedures in Italy allow a single winner when less than three competitors participate for a biologic substance.[xv] The awarding rules are gathered in a framework agreement (accordo quadro), where it is established that the first winner will be granted a 50% share, with the rest divided between the other winners.

Multi-winner contracts

When the tender includes the participation of more than three competitors, then it must be awarded to several participants.[xvi]

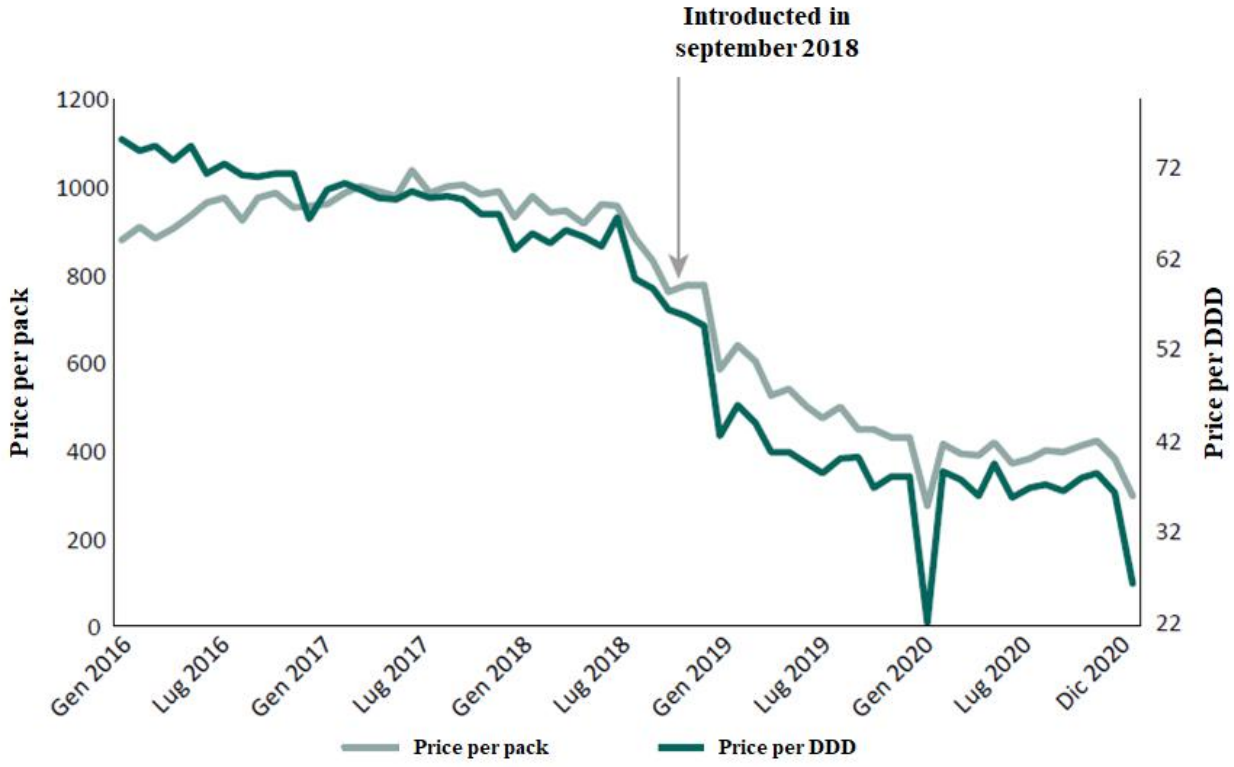
Contract decision criteria

Despite the new procurement code requiring to structure tenders on other criteria beyond price, this is normally not followed and price still governs awarding criteria.[xvii] Tenders, in any case, must follow a quality-price ratio (most economically advantageous offer). Although this second approach is included in the law, tendering procedures are normally governed exclusively by price. Basing tender awards solely on price can provide an even more risky environment when volume expectations are not monitored / transparently shared, as the price-volume relationship can be more pronouncedly compromised.

Based on the currently implemented procurement system, which considers exclusively the lowest price values offered in tenders biosimilars' price tends to be extensively reduced. Data published by the Italian Medicines Agency (AIFA) have shown a decrease of 91.1% and 68.2% for prices concerning DDD[1] and pack respectively (

Figure 1), in approximately 24 months since the introduction of the biosimilar trastuzumab (September 2018).[xviii]

Figure 1 - Mean price registered for trastuzumab in the period 2016-2020. Adapted from the Italian Medicines Agency publication

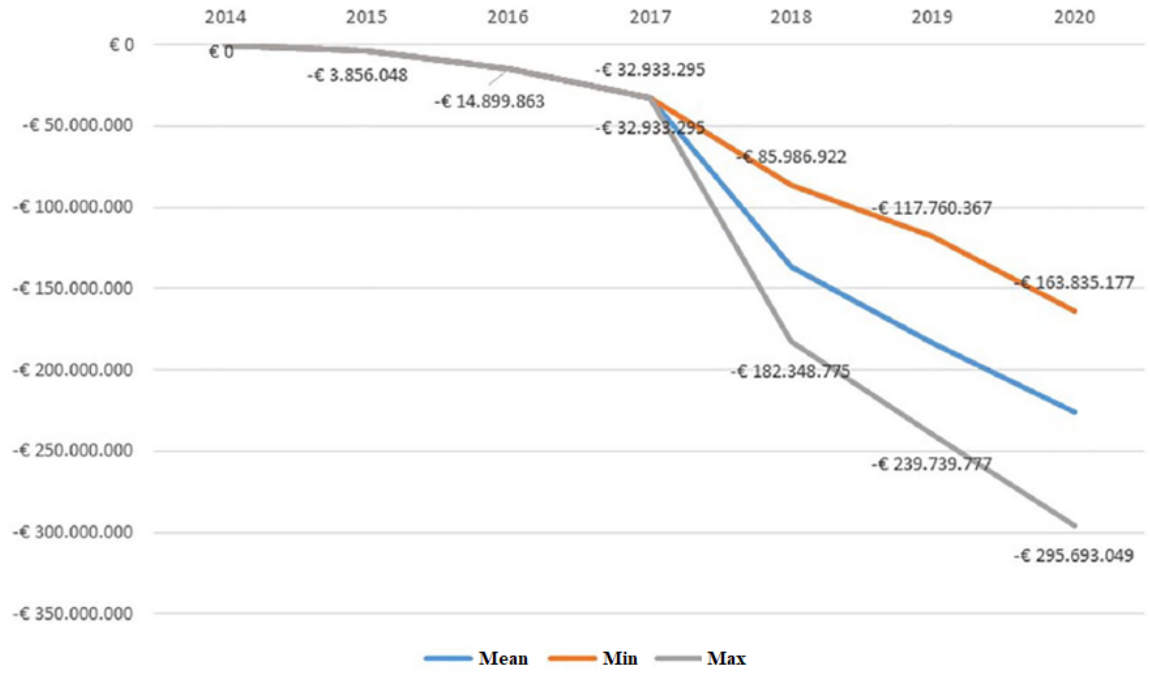


Source: Italian Medicines Agency (AIFA) [xix]

In a study conducted by a group of university centers, research institutes and public health authorities, the economic impact of biosimilars on the public health expenditure in Italy was assessed.[xx] Considering utilization data (consumption per standard unit and equivalent patients), it was estimated the monthly expenditure for some of the biological drugs (i.e., infliximab, etanercept, adalimumab, insulin glargine, trastuzumab, rituximab, bevacizumab, and insulin aspart) currently available in Italy that either have had or are about to have patent expiry within the analysis period (2014-2020). Results were represented as the difference between the estimated expenditure in the absence of biosimilars and the estimated expenditure with biosimilars based on a real or an assumed frequency of their utilization. Biosimilar introduction generates savings between € 3.8 million in 2015 and € 32.9 million in 2017 in comparison with a scenario in which their utilization was not taken into consideration (Figure 2).

[1] DDD – Defined Daily Dose

Figure 2 - Impact of biosimilars on pharmaceutical expenditure estimated in the period 2014-2020

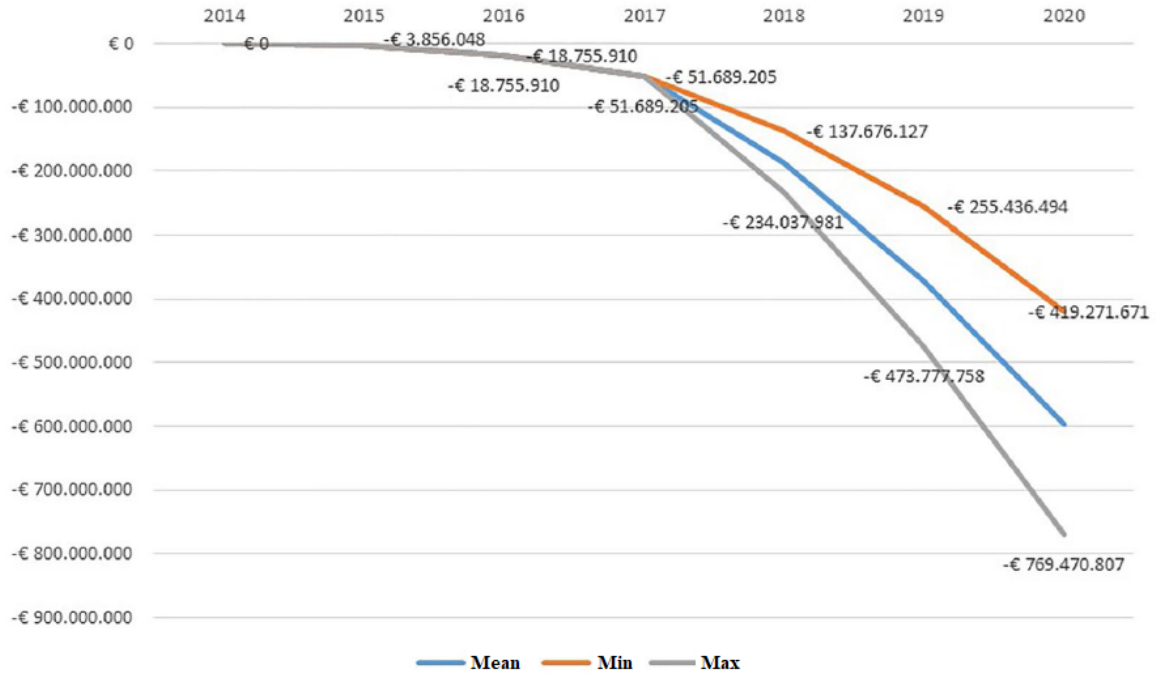


Source: Adapted from Mennini et al. [xxi]

Assuming an increasing frequency of biosimilars utilization between 2018 and 2020 (Figure 3), the scenario analyses predict a cumulative cost reduction corresponding to a range between € 419-769 million (€ 597 million on average).[xxii] These significant expenses decrease can be channeled to support the financing of a National Health Service (NHS) focused on technological innovation.

Whether a tender system for the procurement of a drug is structured to assess and reward the appraisal of a single criterion (i.e., price), it cannot capture any potential qualitative difference that may exist between the tenderers. Naturally, differences do not necessarily have to be correlated with the goods being tendered for. When offered prices show the propensity to erode or even minimise the economic margin, the profitability of a company is undermined and its interest in competing to meet supply needs is lost. According to the health authority evaluations, devastating price reductions for biosimilars have been already registered (range between 65% and 85% compared with initial value of the mean DDD cost per month)[xxiii] and the persistence of this condition can have only and equally damaging consequence in the short-medium term: the progressive distortion of the market with a return to a monopolistic or pseudo-monopolistic regime, lessening of competitiveness and likely decline of employment rate.

Figure 3 - Cumulative cost reductions associated with the utilization of biosimilars in the period 2014-2020



Source: Adapted from Mennini et al.[xxiv]

On the other hand, there is another procedure for accomplishing drug procurement tenders in Italy, as ratified by the Public Contracts Authority and the Anti-Corruption Authority (ANAC): the standard of the most economically advantageous offer (Offerta Economicamente Più Vantaggiosa - OEPV).[xxv, xxvi] In this case, the award of the tender is based on the combined evaluation of quality parameters (such as technical and qualitative differentiation, functional characteristics, delivery dates, provisioning certainty, and so on) with the price of the offer. Price-quality ratio-based tenders are already widely used for the supply of vaccines. The implementation of this specific procedure for vaccines was officially recommended in 2008 by the former Guarantor Authority for the Supervision of Public Contracts, now ANAC.[xxvii] The competent authority reported an opinion regarding tender procedures for HPV vaccines declaring: «considering that the drug market is controlled, the price cannot be the only criterion to compare products because it is set by the regulatory authority from the beginning». Moreover, «the assignment of a contract must be operated through the implementation of objective criteria that respect the principles of transparency, non-discrimination and equality, ensuring the evaluation of offers in a competitive context», in other words an OEPV criterion. As far as the provision of vaccines is concerned, the authority strongly suggested that the decision-making process should be based on both quality and price (cost-effectiveness), since basing decisions exclusively on price does not allow the identification of the truly best offer.[xxviii] To some extent, each NHS is characterized by limited resources; hence, to maximize the net benefit in terms of public health, it is essential to allocate funds in the best effective way considering the various available options, while respecting the principles of equity and solidarity. Like this, the solid economic value of competitiveness is preserved, and a potential market distortion should be prevented, ensuring an improvement of goods procurement and consequently a greater sustainability for the NHS.

Contract length

Contracts are maintained for 24 months and need to be reopened within 60 days after market entry of biosimilars.[xxix]

Biosimilar Education & Understanding

HCP educational programs

The Italian Association for Generics (Egualia, formerly AssoGenerici)[xxx] has made effort to promote the education of biosimilars in the country, including the publishment of papers.[xxxi] In the past 5 years, integration of both physicians and pharmacists into decision making has resulted in an increased uptake of biosimilars.

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).[xxxii, xxxiii]

Patient educational programs

Dedicated efforts to bring awareness to patients around biosimilars are scarce, which has an impact on their uptake. Patient advocacy groups (PAGs) have gained importance in the past years with an increased awareness around biosimilars.

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.[xxxiv] The European Commission has also created manuals to raise patient awareness around biosimilars.[xxxv]

Prescribing

Clinical guidelines and prescriber-initiated switching

Switching between reference biologics and their biosimilars, as well as between biosimilars, is not mandated in Italy, but can be decided by the physician.[xxxvi] Prescribing options are directly related to tendering procedures, as only biosimilars included in tenders can be prescribed. Moreover, the reasoning behind multi-winner tenders aims at providing enough variety and supply for both physicians and patients to decide their choice of treatment.[xxxvii]

Prescription quotas

Prescription quotas are applied in Italy depending on the region (Tuscany, Campania, Veneto, Umbria and Sicily). [xxxviii] Although penalties have been reported when quotas are not met, monitoring is difficult, as this is not nationally controlled.[xxxix,]

Dispensing

Automatic substitution

Automatic substitution is prohibited in Italy. Biosimilars are not considered equivalent to their originators and, therefore, are not included in the 'transparency list' for automatic substitution.[xl] They cannot be substituted without physician consultation.[xli]

Reduced patient co-payments

For outpatient small molecule drugs reimbursed by the NHS (class A) with the same composition and packaging, the reference price covered will be the lowest price of the generic drug available in the regional distribution cycle. The difference will be co-paid by the patient. **Even though this policy has helped improve generics' uptake, its implementation would have low value for biosimilars**, as 95% of the volumes are used for inpatient care, where no co-payments apply.

Monitoring

Pharmacovigilance measures

No specific pharmacovigilance requirements were identified for biosimilars.

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".[xlii, xliii]

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