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Healthy Policy Analysis

Savings From Biosimilars Use in the Italian National Health Service

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ABSTRACT

Objectives: There is a paucity of evidence around the true economic value of biosimilars, especially in the long term. The aim of this study was to estimate the biosimilars uptake, cost trends of off-patent biologics and savings generated through the use of biosimilars in the Italian National Health Service in the 2013 to 2022 period.

Methods: We identified all biologics (ie, reference products) and related biosimilars that were approved in Europe and marketed in Italy until December 2022. The savings were estimated by multiplying sales volume for biosimilars by the difference between the reference product and biosimilars cost in each year.

Results: A total of 12 off-patent biologic medicines were included in the analysis, and in 2022, the mean uptake was 80%. It showed a descending trend of reference product and biosimilar cost, although, by maintaining a relevant difference. Italian National Health Service saved a total of 3.09 billion euros through the use of biosimilars, increasing over the study time period from 37.7 million euros to 762.6 million euros, representing 5% of overall pharmaceutical spending of public health facilities in 2022. The loss of savings due to the use of on-patent active ingredients, belonging to the same anatomical therapeutic chemical, was 1 billion euros.

Conclusions: The study confirmed a high biosimilar uptake in Italy and a decreasing trend in the mean cost per defined daily dose in the 2013 to 2022 period. Biosimilars led to important savings; however, major savings are obtainable by increasing the biosimilar uptake and preferring off-patent biologicals to on-patent medicines belonging to the same IV-level anatomical therapeutic chemical, when appropriate.

Keywords: biologics, biosimilars, cost savings.

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Introduction

Biosimilars represent biological medicines similar to a reference originator that has already been authorized in the European Union and whose patent coverage has expired.[1] A biosimilar is highly similar to reference biological medicine in terms of structure, biological activity, efficacy, safety, and immunogenicity profile.[1] Biological medicines are often produced using cutting-edge technology, the production process plays a significant role in the functionality, and the biological drug is considered a part of the process.[2]

Biological medicines are treatment options for patients with chronic and often disabling conditions, such as diabetes, autoimmune disease, and cancers. They account for an important part of pharmaceutical spending in Europe, about 80 billion euros, corresponding to a share of 35%, and have experienced a compounded average growth rate (CAGR) of 11.3% over the past 5 years, which is twice that of the global market (CAGR 6.3%).[3] In 2022, the European Union's biosimilars market is worth 9 billion euros, representing about 11% of biologics.[4] The first biosimilar was approved in European Union in 2006, being the biosimilar of somatropin. Up to 2022, European Medicines Agency has authorized biosimilars for 18 active substances, leading to several advantages for patients, payers, and the healthcare system. In fact, biosimilars can promote access to medicines for more patients thanks to savings generated for healthcare system.[5-7] Nevertheless, published studies have reported that there are varying policies and biosimilar uptake levels in European countries, resulting in different savings amount for healthcare systems.[8-10] According to the Italian National Report on Medicines Use in Italy, in 2023 the European biosimilars uptake in terms of volumes sold varied between 66.9% for Italy and 6.8% for Belgium.[9] In Italy, biosimilars have been historically considered an opportunity to guarantee access and sustainability at the same time and were continuously examined over time by the scientific community.[11-13] The Italian Medicine Agency published a position article, highlighting the role of biosimilars and clarifying issues related to the prescribing and switching.[14] However, automatic substitution between a reference biological drug and its biosimilar or between biosimilars is not permitted; therefore, the substitution by the pharmacist should

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only take place after consultation with the prescribing physician. A price linkage system is in place in Italy: biosimilars are given a price reduction between 30% and 75% compared with the price of the reference product before patent expiry. The exact discount depends on reference product annual pharmaceutical expenditure in the previous 3 years and on hospital or retail distribution of the reference medicine.[15] Companies that present the pricing dossier according to these discounts can have access to a simplified procedure for pricing and reimbursement, set up in October 2020 by Italian Medicines Agency to speed up the availability and the market competition.[16] Tendering, conducted at the local level, is used to procure biosimilars by public health facilities, which leads to lower prices compared with what is negotiated at centralized level as an effect of competition.[17] Finally, a dedicated monitoring infrastructure has been introduced since 2019, which is updated monthly and is devoted to regional health facilities to help in planning procurement and benchmarking.[18]

Several studies aimed to forecast expected savings from biosimilars in European and extra-European countries[19-22]; however, there are few data about real/observed savings obtained with biosimilars introduction, often limited to specific therapeutic areas or single active ingredients.[23-27] Moreover, several studies investigated biosimilars penetration and price dynamics after the patent expiration.[10,28-31] A recent extensive study conducted in France showed that biosimilars provided 2.4 billion euro savings between 2012 and 2022.[3]

There is a paucity of evidence around the true economic value of biosimilars, especially in the long term[32] because of the lack of long-term data on essential parameters, such as biosimilars penetration and prices. To our knowledge, there are no published studies attempting to estimate the savings coming from the use of all biosimilars marketed in Italy. One study assessed the awarded prices and thus the real level of competition in the Italian regional tenders[17] related to somatropin, epoetin, and filgrastim.

The aim of this study was to calculate the biosimilars uptake, cost trends of off-patent biologics, and savings generated through the use of biosimilars in the Italian National Health Service (INHS) over a 10-year period (2013-2022). Considering that, for some therapeutic categories, on-patent active ingredients sharing similar indication are available, we estimated the related loss of savings (LoS).

Methods

Data Sources and Cohort Selection

All biologics (ie, reference products) and related biosimilars approved in Europe and marketed in Italy until December 2022 were included in the study and were analyzed in the period between 2013 and 2022.

The list of biosimilars and their reference products was retrieved from European Medicines Agency website.[33] Expenditure and volumes of packages sold during the study period were extracted from the Medicines Utilization Monitoring Centre (Osservatorio Nazionale sull'impiego dei Medicinali, OsMed) administrative database "Traceability of medicines" dedicated to medicines directly purchased by public health facilities and reimbursed by the INHS. For each year, molecules that had both a reference product and at least 1 biosimilar available in Italy (more than 1 pack sold) were included in the analysis.

Because, in Italy, the tendering mechanism is applied only to medicines used by public health facilities (ie, tenders are not adopted for medicines dispensed by the community pharmacies), only molecules with more than 60% share of public health facilities spending were considered. The share of public health facilities was calculated against the total public spending given by both community pharmacies and public health facilities sales.

Drugs were analyzed first on a package level. Afterward, data were aggregated at ATC 5th level, which defines the active ingredient.

For infliximab, rituximab, and trastuzumab, only intravenous formulations were considered because subcutaneous formulations do not have the corresponding biosimilar.

Data Analysis

Uptake and cost per defined daily dose (DDD)

For each year and for each active ingredient, we calculated the reference product and biosimilar uptake as the units sold either by biosimilars or by the reference product divided by the sum of the total units of the active ingredient (including reference product and biosimilars).

The mean cost per DDD was calculated by dividing the monthly expenditure of each active ingredient, either reference product or biosimilars, by the total number of DDDs dispensed in the same period.

The doses included in each package were determined through the DDD established by the World Health Organization Collaborating Centre for Drug Statistics Methodology on the basis of the assumed average maintenance dose per day of the medicine, used for its main indication by adults.[34]

The relation analysis between the biosimilars uptake and the mean cost per DDD

The relation analysis between the biosimilars uptake and the mean cost per DDD of the active ingredient (including both the reference product and the biosimilars) was performed through a Pearson correlation. Both biosimilars uptake and the mean cost per DDD were considered in the calculations as monthly values over the years 2013 to 2022. A Pearson correlation coefficient was calculated for each active ingredient. For each coefficient, the observation units were the monthly mean cost per DDD and the monthly biosimilar uptake.

Savings

Savings (S) generated through the use of biosimilars in the i-th year included in the analysis were estimated by multiplying sales volume for biosimilars (Q_{bi}) by the difference between the reference product (C_{RFi}) and biosimilars (C_{bi}) cost as follows:

$$Si = Q_b i \times (C_{RFi-} C_{bi})$$

These annual values were then summed up to obtain whole period savings.

In a sensitivity analysis, we attempted to simulate increased savings by raising the biosimilars uptake by 10% or 20% compared with that observed in each year of the study period.

LoS

We estimated the LoS due to the use of on-patent active ingredients instead of those having expired patent and similar indications. Indeed, for each biologic included in the analysis, we identified on-patent active ingredients belonging to the same IV ATC level and denominated them as "others." We estimated the LoS by multiplying sales volume (Q) of "others" by the difference between the others (C_{others}) and off-patent biological (C_{OP}) cost in the i-th year included in the analysis, as follows.

$$LoSi = Q_{others\ I} \times (C_{others\ i} - C_{OB\ i})$$

We conducted a secondary analysis on the LoS, in which sales volume (Q) of "others" was multiplied by the difference between

the others (C_{others}) and biosimilars (C_B) cost in the i-th year included in the analysis.

Results

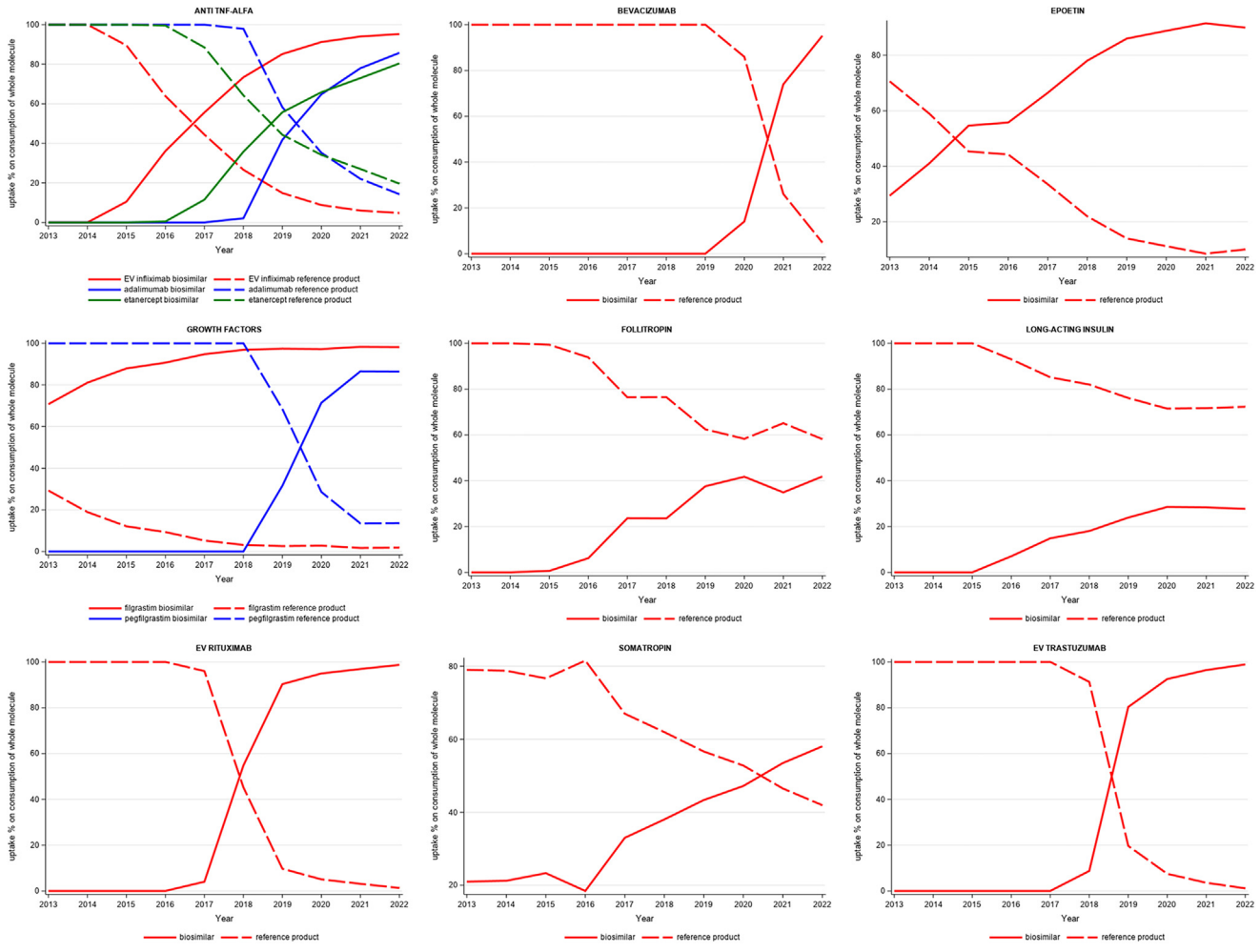
Overall, 16 active ingredients were identified for which at least 1 biosimilar was authorized in Europe up to December 2022. One active ingredient was excluded, ranibizumab because no biosimilar was marketed in Italy up to December 2022. Three active ingredients were excluded given that they had a share of public health facilities spending less than 60% (ie, low-molecular-weight heparin, fast-acting insulin, and teriparatide).

Thus, a total of 12 active ingredients, considered as off-patent biologic medicines, were included in the analysis: adalimumab, etanercept, infliximab, bevacizumab, epoetin, filgrastim, pegfilgrastim, follitropin insulin glargine, rituximab, somatropin, and trastuzumab. The most frequent first ATC level observed was L (antineoplastic and immunomodulating agents; 66.6%), followed by A (alimentary tract and metabolism), B (blood and blood forming organs), G (genito urinary system and sex hormones), and H (systemic hormonal preparations, excl. sex hormones and insulins; 8.4% for each one) (see Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2025.101142). For the majority of active ingredients (10 out of 12), the first biosimilar entered the market during the study period; only epoetin and filgrastim's patent expired before 2013.

Biosimilars Annual Uptake

Biosimilars reached high uptake values in the majority of included active ingredients during the study period (Fig. 1). Overall, in 2022, an 80% mean biosimilar uptake was reached when considering all active ingredients. In particular, for bevacizumab, infliximab, rituximab, trastuzumab, and filgrastim, biosimilars uptake exceeded 95% in 2022 (95%, 95%, 98%, 98%, and 98%, respectively). The biosimilars uptake was between 80% and 90% for etanercept (80%), adalimumab (85%), pegfilgrastim (86%), and epoetin (90%). For somatropin and follitropin, biosimilars and reference products had a similar uptake (58% and 42%, respectively), and the share of biosimilars was under 40% only for insulin glargine (Fig. 1, Appendix Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2025.101142). For all of the

Figure 1. Reference product and biosimilars uptake (%) by active ingredient (n = 12) in the 2013 to 2022 period.



off-patent biologics, the use of biosimilars increased over time, and concomitantly, the use of the reference product declined. For all biologics for which the patents expired during the study period (n = 7), with the exception of insulin glargine and follitropin, the biosimilar reached an uptake greater than 50% before the third year since market entry.

The Mean Cost Per DDD Trend

The mean cost per DDD trend was analyzed for all biologics included in the analysis in the 2013 to 2022 period, separately for reference product, biosimilars, and the entire molecule (Fig. 2, Appendix Table 3 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2025.101142). These estimates showed a descending trend for both the reference product and biosimilars cost as effect of tendering mechanism. The active ingredients that showed the highest reduction in the cost per DDD during the study period were adalimumab and trastuzumab (CAGR 2013-2022 −18% and −19%, respectively) because of the patent expiration during the study period. In 2022, for the majority of active ingredients (9 of 12), the mean difference between the reference product and biosimilar cost was higher than 100%, ranging between 359% and 13% (see Appendix Table 3 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2025.101142). Furthermore, the difference increased over time for all biologics, with the exception of follitropin and insulin glargine, because of the higher cost reduction for biosimilars. For active ingredients of which biosimilars entered the market during the study period, a significant reduction of biologics cost was observed, including the reference product. The active ingredient cost in the third year of biosimilar marketing was lower almost of 50% compared with the cost of the reference product in the year before the introduction of the biosimilar (see Appendix Table 3 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2025.101142). After an initial high reduction due to the market entry of the biosimilar, in the subsequent years, the mean cost per DDD continued to decrease although at lower rates (Fig. 2). For active ingredients of which the patent expiration occurred before 2013, the mean cost per DDD decreased as well (CAGR 2022-2013 going from −14% to −3%). It was the case of epoetin which, although the first biosimilar was marketed in Italy in 2007, observed a cost reduction by 65% in 2013-2022, led by the cost decrease for both biosimilars and reference product (see Appendix Table 3 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2025.101142).

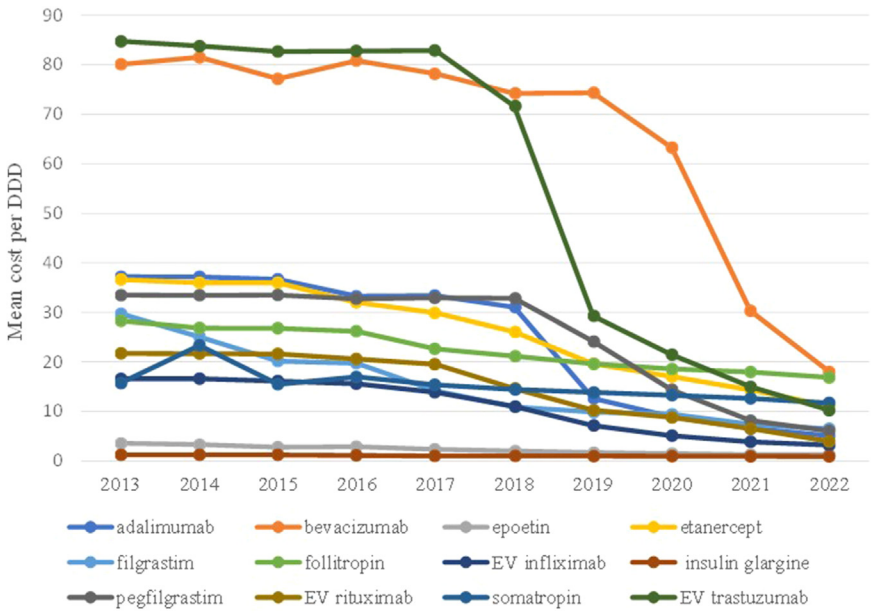
Correlation Between the Mean Cost Per DDD and Biosimilar Uptake

When analyzing the crude relation between biosimilars uptake and the mean cost per DDD of the active ingredient, a statistically significant negative correlation was also obtained, meaning that the increasing use of biosimilar led to a decreasing of molecule DDD average cost, without controlling for other time effects, as shown by the correlation coefficient reported in Figure 3. Value of the correlation coefficient near to −1 means an inverse relation for the majority of medicines evaluated (11 of 12), except for somatropin, for which the relation is weaker, probably because of a less biosimilar uptake.

The Actual Savings Resulting From the Biosimilars Use

We estimated that in the period between 2013 and 2022, for all off-patent biologics included in the analysis, the INHS saved 3.09 billion euros because of the use of biosimilars (Table 1). Savings have increased over the study time period from 37.7 million euros in 2013 to 762.6 million euros in 2022 (CAGR 2013-2022, 35.1%), representing 5% in 2022 of the overall pharmaceutical spending of public health facilities. Higher increases in overall savings were observed since 2018, also as a consequence of patent expiration of highly spending active ingredients (eg, trastuzumab and adalimumab). Savings varied from 679 million euros for epoetin to 10 million euros for follitropin (IQR 329.1 million euros). For each medicine, savings had grown over the time because of the increasing use of biosimilars and the cost reduction (Table 1,

Figure 2. Mean cost per DDD by active ingredient in the 2013 to 2022 period.



DDD indicates defined daily dose.

Appendix Fig. 1 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2025.101142).

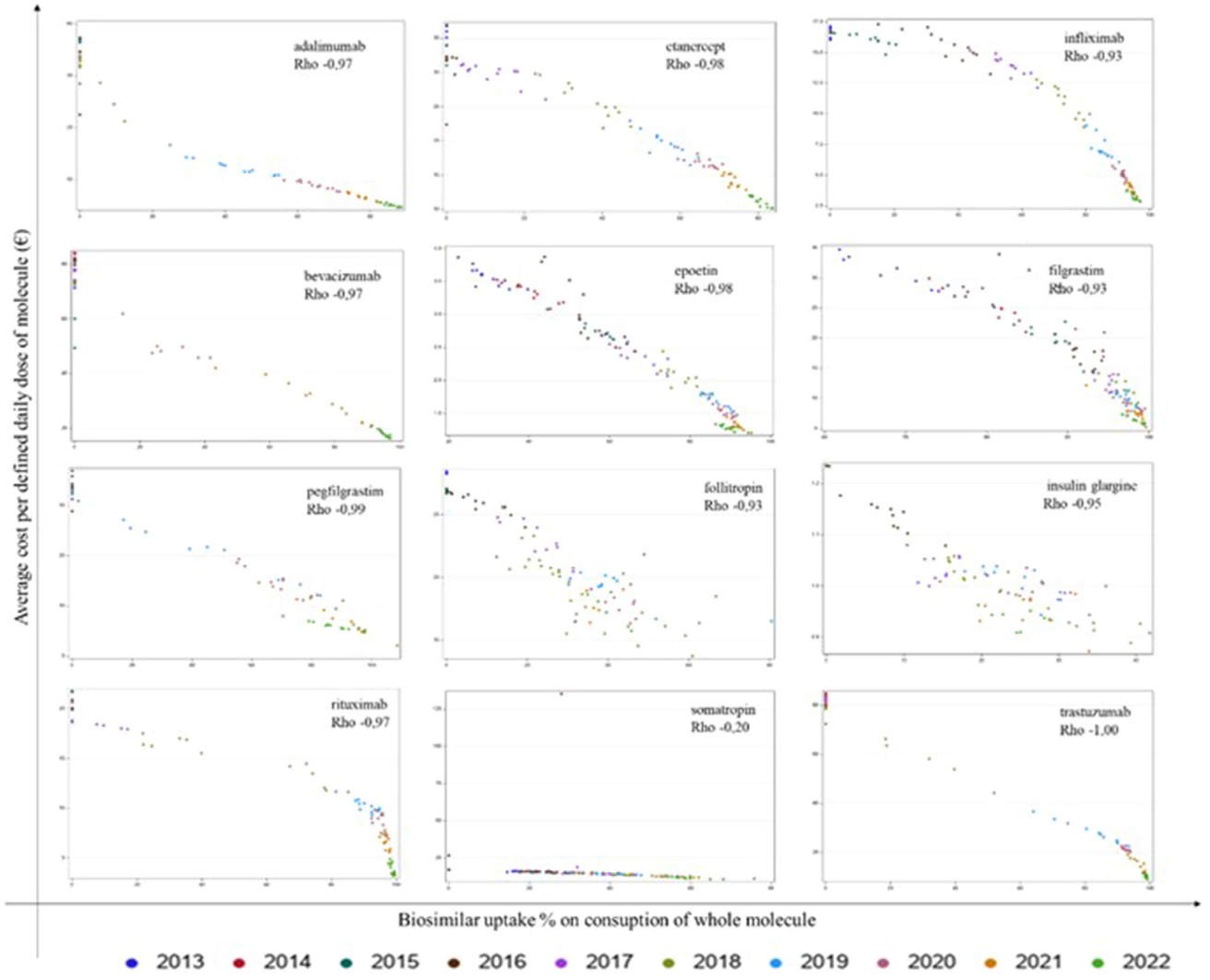
We identified 6 "Others" categories (see Appendix Table 4 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2025.101142) and 18 related on-patent active ingredients. We estimated a LoS due to the use of on-patent active ingredients belonging to the same IV ATC, being 1 billion euros (Table 2). In the secondary analysis in which we analyzed the LoS with respect to the cost of the biosimilar, we estimated a LoS of 1.7 billion euros (see Appendix Table 5 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2025.101142).

The sensitivity analysis, which simulated additional savings by increasing the uptake of biosimilars by 10% and 20% each year, showed a moderate increase in savings of up to 3.3 billion euros and 3.5 billion euros, respectively. They represented an increase of 7.8% and 12.8% of the overall observed savings (see Appendix Tables 6 and 7 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2025.101142). For both scenarios, the greatest increase in savings was obtained for insulin glargine (+10.2%; +20.3%), somatropin (+10.1%; + 20.1%), follitropin (+9.9%; +19.9%), and etanercept (+10%; +20%), whereas the lowest increase in savings was for filgrastim (+4.48%; +5.67%).

Discussion

It is well recognized that biosimilars represent a real opportunity for national healthcare systems, ensuring important cost savings and guaranteeing the same efficacy, safety, and quality of biologics originators. Indeed, biosimilars also allow freeing up economic resources that can be used to treat a wider range of patients and addressing other aspects of patients care.[35,36] Our study found that, for all biosimilars taken together over the 10-year period, a total of 3.1 billion euros were saved by the INHS in relation to the observed cost of the reference product. The savings obtained in 2022 of 762.6 million euros corresponded to more than 5% of the overall pharmaceutical spending of public health facilities, confirming the biosimilars' important contribution to the sustainability of pharmaceutical systems. Savings were dependent on time of patent expiration, the difference between reference product and biosimilars cost, biosimilars penetration,

Figure 3. Correlation between biosimilar uptake and mean cost per DDD by active ingredient.



DDD indicates defined daily dose.

Table 1. Savings per year (2013-2022) in millions of euros for patent expired biologics, at the national level.

Active ingredient	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	Total for molecules
adalimumab	0.0	0.0	0.0	0.0	0.0	3.6	47.3	82.4	131.7	173.8	438.8
etanercept	0.0	0.0	0.0	0.2	5.1	22.0	47.2	62.0	77.3	92.7	306.5
infliximab	0.0	0.0	2.3	13.1	26.5	48.6	39.5	40.9	56.1	63.1	290.3
bevacizumab	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12.7	51.2	91.0	154.9
epoetin	16.5	22.6	35.8	32.7	68.9	89.8	102.0	104.9	100.6	105.1	679.0
filgrastim	18.6	27.4	32.9	32.4	50.8	59.4	68.4	71.0	63.0	65.4	489.2
pegfilgrastim	0.0	0.0	0.0	0.0	0.0	0.0	5.4	17.0	22.4	13.4	58.3
follitropin	0.0	0.0	0.0	0.3	1.0	1.0	2.2	1.7	2.0	1.9	10.1
insulin glargine	0.0	0.0	0.0	1.4	1.6	2.2	2.9	3.3	2.1	1.6	15.2
rituximab	0.0	0.0	0.0	0.0	2.2	23.1	38.4	46.7	47.5	48.4	206.3
somatropin	2.6	6.5	4.0	0.5	7.1	7.3	8.8	9.2	10.0	12.2	68.2
trastuzumab	0.0	0.0	0.0	0.0	0.0	7.0	75.7	104.1	99.5	93.9	380.2
Total	37.7	56.5	75.0	80.7	163.3	264.0	437.8	556.1	663.5	762.6	3097.0

and the overall units sold. Our findings suggested that a faster biosimilars market entry and a higher uptake result in overall lower costs. Indeed, in other contexts, such as the United States, limited biosimilars availability and low uptake have led to higher cost both for the reference product and biosimilars.[29-37] This is due to the ongoing patent litigation and to policies adopted by biologics manufacturers to delay availability of biosimilars, including patents thickets that extend the actual patent protection period much longer.[38,39] A second issue is related to confidential discounts applied by originators manufacturers to health plans and pharmacy benefit managers to maintain position in formularies. Therefore, future policies should address the patent thickets issue to reduce the exclusivity period and to encourage timely biosimilar market entry and the removal of confidential discounts after the biosimilar market entry.[39,40]

Similar results were obtained by a study conducted in France showing that biosimilar medicinal products provided 2.4-billion-euro savings between 2012 and 2022.[3] A further study was conducted in France, which estimated the savings obtained after the introduction on the market of anti-TNF biosimilars.[23] Savings were estimated calculating the product of sales volume multiplied by the difference between the price in force before the introduction of the first biosimilar and the actual final hospital purchase price of the drug. They estimated a savings amount of 820 million euros over 5 years. Differently, our study quantified savings in relation to the actual cost of the reference product in each year of the study period because the objective of our study was to assess the "real" savings obtained by the use of biosimilars instead of the reference products. Therefore, our savings estimation could result lower than considering the reference product cost before the patent expiration.

A study conducted in the Canadian context estimated cost savings obtained by the use of biosimilars of 3 active ingredients (filgrastim, infliximab, and insulin glargine) and the unrealized cost savings.[41] The savings accounted only to 4.2% of potential total savings because of the low uptake of biosimilars; this highlighted the importance to evaluate the penetration of biosimilars and not only the availability. Relevant savings coming from our study were also driven by the high biosimilar uptake in Italy for the majority of biologics, and it was also shown that biosimilars required less than 3 years to obtain the majority of the market shares. The high uptake has led, thanks to the effect of tendering mechanisms, to a relevant decrease of reference product and biosimilar cost, including in the case of biologics of which the patents expired before the study period. The difference between the reference product and biosimilar cost tended to be

Table 2. Loss of savings per year (2013-2022) for category "others," versus patent expired molecules, in millions of euros, at the national level.

Therapeutic category	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	Total for molecules
anti-TNF alfa	0.0	0.0	−2.2	7.8	10.4	20.4	57.5	56.1	53.4	62.7	266.0
epoetin	53.3	53.4	63.7	55.9	59.0	53.5	50.7	46.5	45.4	44.4	525.8
growth factors	13.7	11.1	8.9	6.6	7.3	5.9	5.9	5.4	6.5	5.6	77.0
follitropin	0.0	0.0	−10.0	−11.4	−6.3	−2.7	1.6	1.6	5.6	12.2	−9.6
long-acting insulin	0.0	0.0	0.0	12.3	13.7	20.5	25.4	31.0	38.2	38.7	179.8
somatropin	5.8	−21.5	8.0	−2.9	4.3	7.0	7.0	6.1	3.9	5.0	22.6
Total	72.8	43.0	68.4	68.3	88.4	104.5	148.0	146.7	153.0	168.6	1061.6

Note. Positive value: non saving; Negative value: saving.
TNF indicates tumor necrosis factor.

nonnegligible and increased during the study period for the majority of the biologics included. Differently, in Italy, when considering the generics market (intended as off-patent non-biologicals), the ex-originators tend to maintain high market shares after generics entry as well,[9] and the cost of unbranded and branded drugs, after the reduction of the first year, remained almost constant in the following years. Indeed, the effect of patent expiry was concentrated in the first year because of the generics market regulation.[42] Instead, in the biologicals market in Italy, it seems that the effects of competition are disclosed in the subsequent years as well, leading to a descending trend in costs of both biosimilars and reference products. More savings are expected in the next years as an effect of the increase in existing biosimilars uptake and price reduction and as a consequence of new biosimilars launch. Indeed, 110 biological medicines are anticipated to have their patent expire by the end of 2032. Nevertheless, some challenges in new biosimilars development and availability were highlighted with regard to low-sales products and because of the increasing complexity of new biologicals in comparison with early products in terms of manufacturing, clinical testing, and logistical complexity.[43]

Strengths and limitations

Our study, conducted by the use of comprehensive nationwide data, fully described the biosimilars market in Italy in a long observation period, from 2013 to 2022. Another strength referred to the data used to calculate the mean cost per DDD, corresponding to the actual cost paid by health facilities, which resulted by the tender mechanisms. All data presented could contribute to more reliable savings projections for the next biosimilars.

Nevertheless, our study presented some limitations. First limitation was related to the fact that biologics largely distributed by community pharmacies, such as low-molecular-weight heparin, fast-acting insulin, and teriparatide, for which public tenders are not applied, were not considered. Moreover, our study did not assess the impact of competition (eg, number of competitors) on prices and did not quantify the price reduction according to the time of first biosimilar market entry. All of these analyses were beyond the scope of this study and may be evaluated in future studies, including the crude negative correlation estimated between biosimilars uptake and the mean cost per DDD of the active ingredient, which may require multivariate regression techniques to control for other time effects.

Conclusions

This study confirmed a high biosimilar uptake in Italy and a decreasing trend in the mean cost per DDD in the 2013 to 2022 period, both for biosimilars and reference products. However, the difference between the biosimilar and reference product cost was maintained high. INHS saved 3.09 billion euros from the introduction of biosimilars over the 10-year period. Nevertheless, our study also identified the possibility for additional savings by increasing the biosimilar uptake and preferring off-patent biologicals to on-patent medicines belonging to the same IV-level ATC, when appropriate.

Author Disclosures

Author disclosure forms can be accessed below in the Supplemental Material section.

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the respective authors' organizations.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.vhri.2025.101142.

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