Incentives For Using Biosimilars In France And Europe

Analysis, assessment, and perspectives

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ISABELLE DURAND-ZALESKI

Professor of Public Health Medicine and Doctor of Economics.

Director of URCEco.

THIERRY THOMAS

University Professor-Hospital Practitioner, rheumatology specialist.

Head of department, CHU de Saint-Etienne [Saint-Etienne University Hospital]

Synopsis

With an annual growth twice as fast as that of the total market for medicinal products, biologics represent 35% of pharmaceutical spending in Europe. The use of biosimilars, manufactured using a biotechnological process similar to that of existing biologics and for which the patent is in the public domain, is an important source of savings for health systems, and is growing rapidly. In France, a study conducted by IQVIA showed that biosimilar medicinal products provided a €2.4 billion saving between 2012 and 2022. According to the income and expenses report by French national health insurance, €100 million, including 40 million in 2022 and 2023, could be saved each year if biosimilars could achieve an 80% rate of market penetration. This was the case in the hospital context in 2021, unlike in the outpatient setting, where these medicinal products constitute only 31% of sales volumes for biologics.

In France, it is the use of biosimilar medicinal products that generates the most savings (67%, according to the IQVIA study), and as a result, in order to accelerate their use, various incentives were introduced. The Article 51 test progamme in the hospital setting, in particular, has been recognized as a “success” by the strategic council for health innovation. Addendum 9 to the national contract between private physicians and health insurance also produced visible and encouraging results in the community setting.

Ireland, England, Germany and Spain have also deployed incentives to encourage the adoption of biosimilars and expand access to biologics. The calculation mechanisms and implementation of these measures vary, making it difficult to replicate them in other countries.

However, the adoption of biosimilars in these different countries, like the measures deployed in France, depends on incentives that are often based on the sharing of value between prescribers and health authorities, and makes it possible to generate savings for health systems.

Simplicity, legibility, and taking into account specific benefits for the hospital setting and community prescribers, as well as support from the authorities may be considered to be components favoring the success of the next incentives in achieving the 80% market penetration rate set by the national health strategy. The mechanisms of these measures will need to consider and adapt to the patient’s situation (are they treatment-naïve, or being treated?), the goal of the treatment (is it a one-time prescription, or is it the patient’s long-term treatment?), and the biosimilar’s previous results. The levers that may expedite the market penetration of biosimilars are clearly identified by experts: first of all, the influence of the hospital context on the outpatient setting, as well as enhanced communication regarding the bioequivalence of biosimilars, and publication of scientific studies based on real-life health data.

In the medium term, a growing proportion of medications will lose their exclusivity by 2027, and we do not plan to compete by developing biosimilars for each of these biologics. In the long term, the question of patient access to all biologics recently authorized in Europe arises if they are not included on national reimbursement lists.

In conclusion, both in France and in other European countries, the use of biosimilars naturally causes a prescription cost effectiveness challenge, and on one hand, access needs to be guaranteed; on the other hand, incentives must continue to be offered in order to motivate their prescription, in order to promote growth of their market penetration rate and prepare for the arrival of future biosimilars.

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Introduction

Biosimilars are drugs obtained by a biotechnological process similar to that of existing biologics, referred to as reference products, and for which the patent is in the public domain. Biologics are made from living cells, making them more complex and more expensive to produce than conventional drugs. Biosimilars, despite their complex (5-6 years) and expensive (€100-300 million) development process,[1] offer a less expensive alternative to reference biologics, while ensuring the same efficacy and safety for the patient.

In France and Europe, biosimilars play an important role in reducing health costs while maintaining quality of care. This economic concern is even more important given the current context (economic crisis, budgetary pressure, aging population, therapeutic innovation, etc.), that biologics and their biosimilars mainly target chronic conditions such as cancer, chronic inflammatory diseases, or autoimmune diseases. Therefore, in order to support the adoption of biosimilars, France and other European countries may, among other things, introduce prescription incentives.

"What are the different measures and how do they work? What impact did they have? What can they teach us about the future?"

This report was created in collaboration with:Prof. Isabelle Durand-Zaleski, Professor of Public Health Medicine and Doctor of Economics, and Prof. Thierry Thomas, University Professor-Hospital Practitioner, specialty rheumatology. This is based on a literature analysis completed by data generation from IQVIA databases. Prof. Pascal Paubel, Pharmacist, University Professor - Hospital Practitioner, Member of the Institut Droit et Santé [Institute of Law and Health] (Université de Paris [University of Paris]) was consulted for this work.

Place and benefits of biosimilars in Europe

BIOLOGICS: A CONSIDERABLE AND GROWING PART OF PHARMACEUTICAL EXPENSES

Biologics represent 35% of all pharmaceutical expenditure in Europe (catalogue price), with a compound annual growth rate (CAGR) of 11.3% over the past five years (2016 – 2022). This rate is nearly two times higher than the total medicinal product market in Europe, the CAGR of which reached 6.3%[2] over the same period.

Given the importance of biologics, the adoption of biosimilars and increased competition are increasingly critical success factors in the current economic context for European care systems.

In 2006, the European Union (EU) approved the first biosimilar (somatropin growth hormone). Since then, the EU has approved the largest number of biosimilars worldwide.[3] By the end of 2022, 19 reference biologics (see Figure 2) share the market with, on average, 3.8 biosimilars per proprietary medicinal product (adalimumab alone has 10 biosimilars approved in Europe).[4] In 2019, the European Medicines Agency (EMA) took a stance on the interchangeability of biosimilars by stating that it was under the jurisdiction of the member states of the EU, although any decision concerning the switch must involve an agreement between the prescriber and the patient.

Figure 1: Annual market growth rate of the drugs and biologics market in the European Union between 2016 and 2022

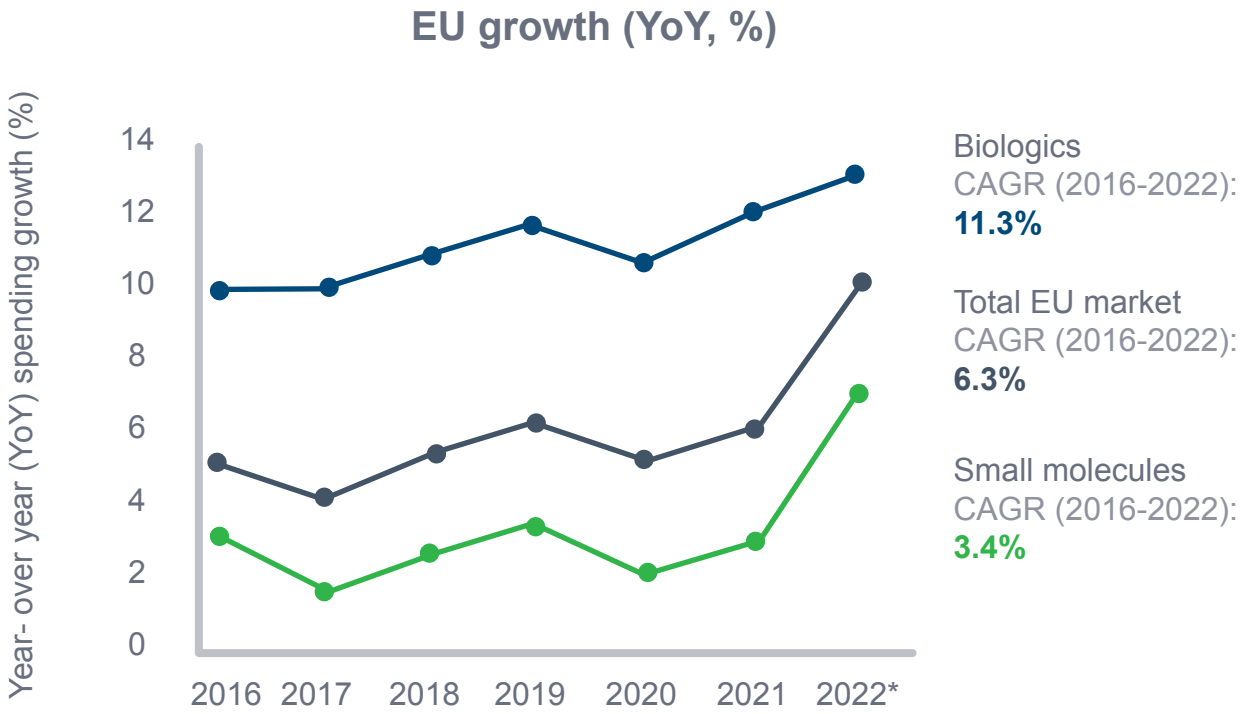
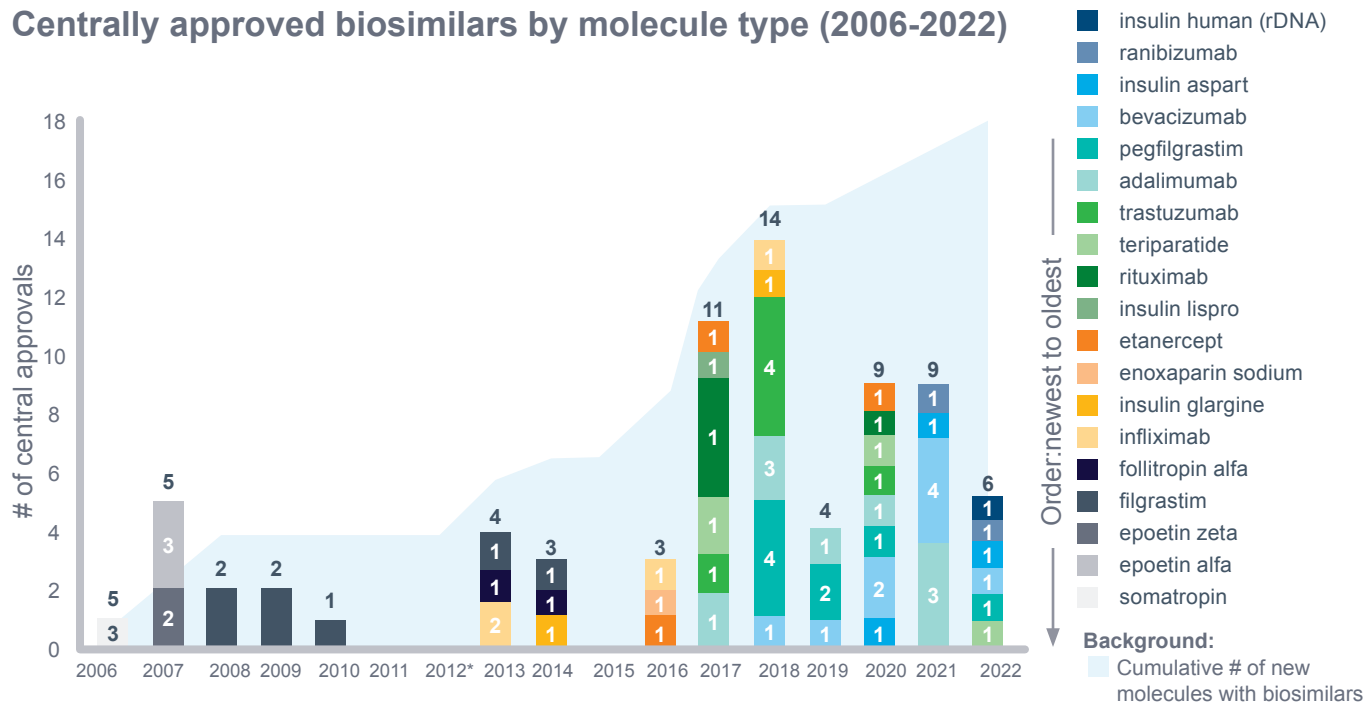


Figure 2: Number of biosimilars approved in Europe by molecule and by year



Source: IQVIA analysis of EMA list (last accessed November 2022)
The Impact of Biosimilar Competition in Europe 2022; Prepared for European Commission (DG SANTE) December 2022

BIOSIMILARS IN FRANCE, AN SAVINGS AND EFFICACY CHALLENGE

The prices of biosimilars are defined by the framework agreement established between the Leem [Les entreprises du médicament (Medication companies)] and the Centre for European Policy Studies (CEPS)[5] and are impacted by four price reduction mechanisms:

- The decrease in price of the reference drug on the arrival of biosimilars
- The difference in price between the reference drugs and biosimilars
- The subsequent price decreases over time
- The convergence of prices

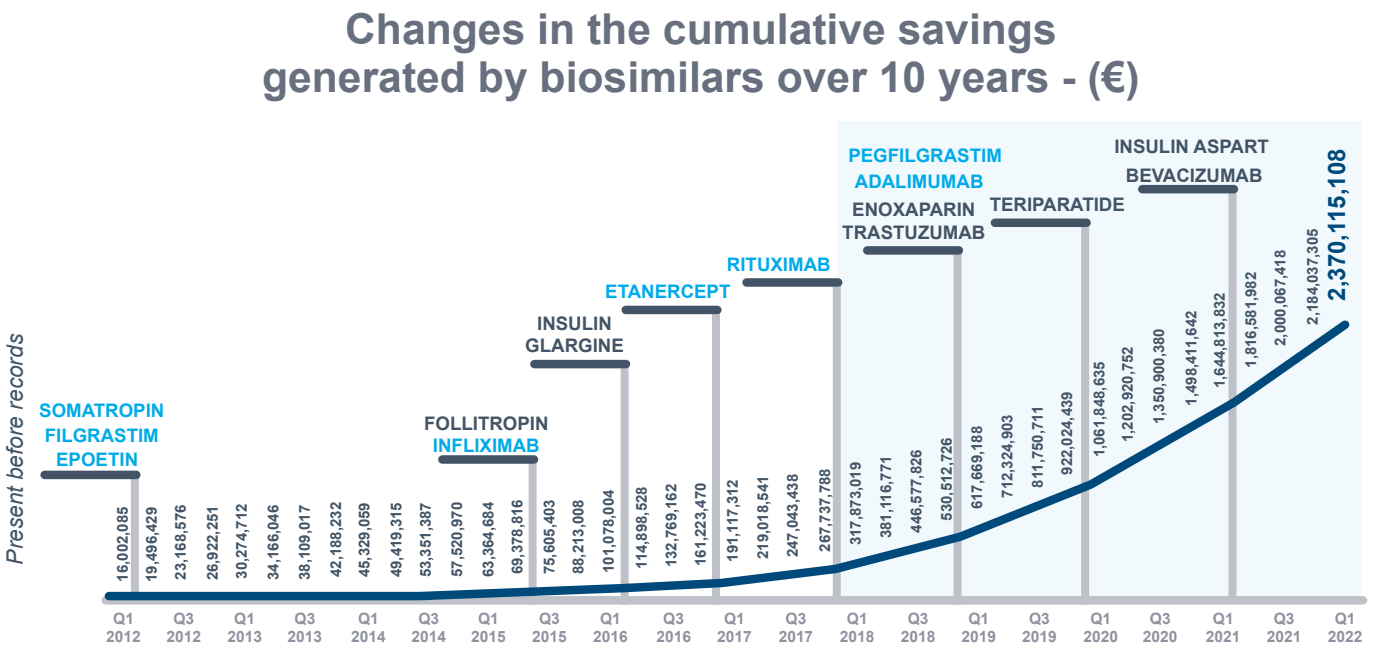
Moreover, market competition tends to broadly favor the reduction in established prices (including reference biologics).

In the income and expenses report (July 2022), the French national health insurance presents an accounting projection of the savings associated with achieving the target of 80% market penetration of biosimilars on the reference market by 2022, set by the National Health Strategy (SNS [Stratégie Nationale de Santé]). Considering the price of biosimilars, which are on average 15 to 30% lower than those of the reference drugs, the savings generated by the market penetration of biosimilars are therefore estimated to reach "€100 million, including €40 million seen in 2022 and 2023".[6]

This French national health insurance analysis can be supplemented with an estimation produced by IQVIA teams between 2012 and 2022, which shows that cumulative biosimilar savings are estimated at €2.4 billion (see IQVIA method of calculation in the Appendix).

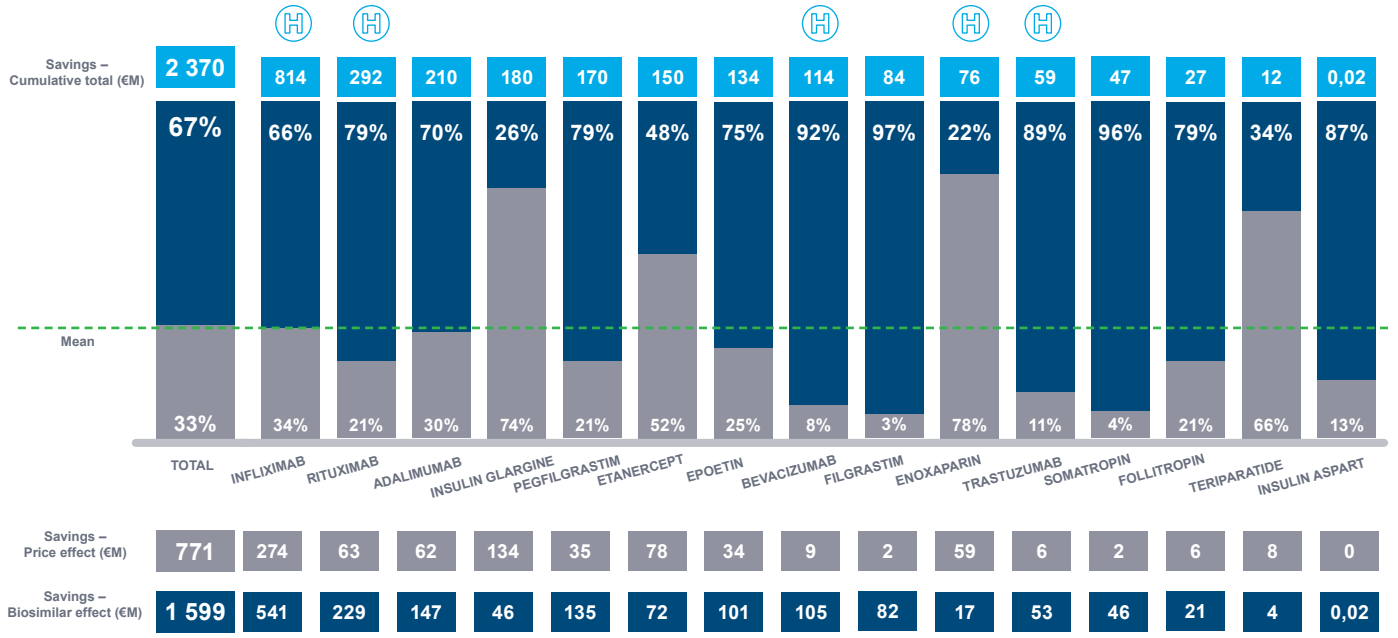
A sharp acceleration in these savings has been seen over the last five years due to the doubling of the number of reference biologics concerned by the launch of biosimilars (Figure 3).

Figure 3: Cumulative savings generated by biosimilars over 10 years in France



In France, savings are mostly generated via two mechanisms, the respective importance of which varies depending on the products: the use of biosimilars, resulting in 67% savings, and the price effect, producing 33% savings.

Figure 4: Split of the origin of the savings made between price effect and competition effect



In 2012, on a European scale, estimates suggest that savings could be approximately €12 billion to €34 billion by 2020. In 2022, cumulative cost savings on the catalog price resulting from the impact of the competition of biosimilars in Europe reached more than €30 billion.[7]

Beyond this savings issue, it is important to note that the diversification of production sources and the stimulation of competition contribute to securing supply chains by reducing the risk of supply disruptions and stock shortages.

Incentives to promote biosimilars

THE CASE OF FRANCE

In the hospital setting, market penetration of biosimilars was over 80% (in volume) in 2021.[8] This strong growth is supported by different incentives.

The Ecart Médicament Indemnisable [reimbursable drug differential] (EMI) is a device, not specific to biosimilars, the purpose of which is to encourage Hospitals Buyers to negotiate the lowest possible prices for medicinal products on the list of drugs and services reimbursed on top of inpatient care, while limiting over-reimbursement by health insurance. In this way, if an hospital is able to negotiate a price below the standard rate, 50% of the savings generated will be allocated back to it (sharing the savings between the French health insurance and the hospital).

However, the EMI is not a permanent solution, as the standard rates are routinely reduced by health authorities, particularly due to competition from biosimilars.

Furthermore, the EMI only applies to medicinal products on the list of drugs and services reimbursed on top of inpatient care, which are expensive and innovative drugs mainly used in hospitals. In addition, they are paid for directly by the social security budget.[9] It should be noted that biosimilar molecules will have to be removed from the list of drugs and services reimbursed on top of inpatient care due to a regular decrease in the standard rate (price 30% lower than the GHS rate), ultimately limiting the EMI's efficacy.

The Contrat d'Amélioration de la Qualité de l'Efficience des Soins [improvement in the quality and efficiency of care contract] (CAQES), created by the Social Security Funding Law of 2016, is a tripartite agreement between the Regional Health Agencies [Agences Régionales de Santé (ARS)], the French national health insurance system, and Hospitals. The purpose of the CAQES "is to improve the practices, the provision of care regulations, and the efficiency of French national health insurance spending".[10]

- As such, CAQES 2018-2022 proposed specific national indicators for biosimilars that experts interviewed deemed to be of benefit for their development with regards to purchasing, hospital prescriptions for drugs dispensed in a community pharmacy (PHMEV), or even information for patients. However, the COVID-19 health crisis has strongly impacted the implementation and monitoring of this tool

- The new CAQES 2022-2026 does not contain national indicators for biosimilars, but only regional indicators, which are now no longer applied by all ARSs. The experts consulted are disappointed by this trend and also note that the remuneration associated with the CAQES is paid to the hospitals and not to the prescribing departments, which may diminish its impact as an incentive

The test programme of the incentivization of hospital prescription of biosimilars dispensed in a community pharmacy (Article 51 implemented at 63 Hospitals) which ended in January 2023 consisted of paying a financial benefit of up to 30% of the savings gained to hospital departments by prescribing biosimilars rather than reference biologics. The primary objective of this test was to expand the prescription of biosimilars (etanercept, adalimumab, and insulin glargine) and to increase their prescription rate by at least 15% in the hospitals participating in the test.

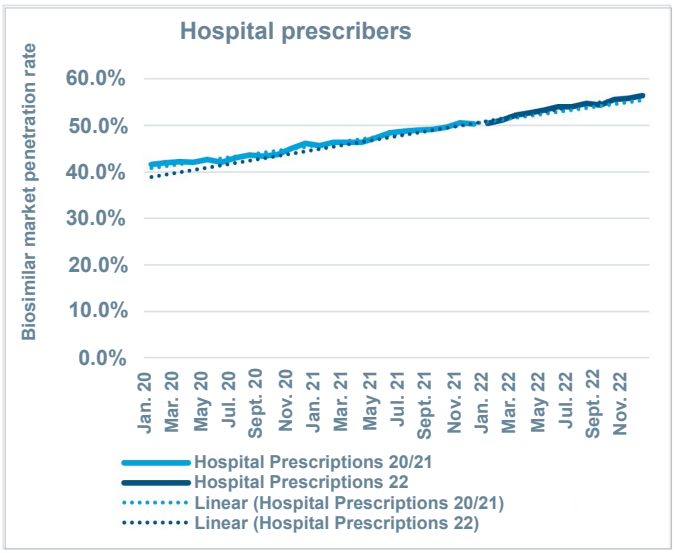
In the report from the February 2023 meeting, the Conseil Strategique de l'Innovation en Santé [strategic council for health innovation] (CSIS) deemed that the test has been successful in the sense that it had enabled the prescription of biosimilars to be increased and the benefit of such a device to be evaluated.[11] However, in the context of the health crisis, it did not reach the objective of a 15 point increase in market penetration of the biosimilars etanercept (+13.2 points), adalimumab (N/A), and insulin glargine (+7.7 points). What was learned from this test should make it possible to improve the incentive mechanism for prescribers.

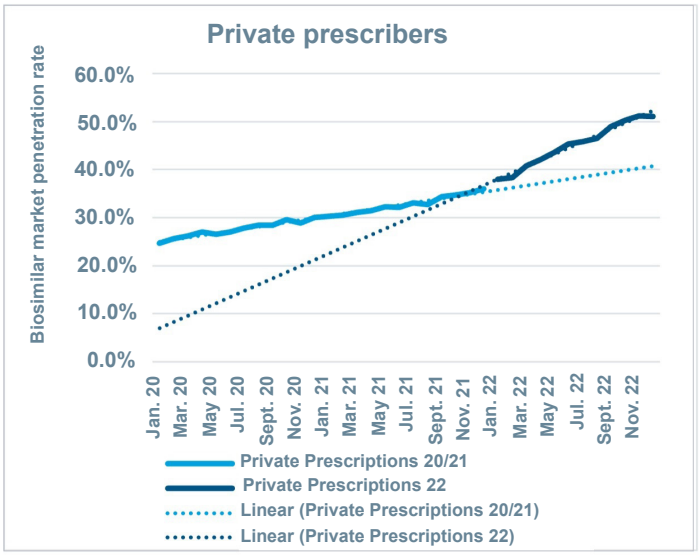
It should be noted that ordinary law, the precursor of the Article 51 test programme, provided for a payment of up to 20% of the savings generated only for the hospitals, taking into account the budget problems of hospitals, unlike Article 51, which concerns prescribers directly, with the aim of improving their hospital departments (additional resources).

Addendum 9 to the national agreement between private physicians and health insurance is a mechanism that values the effort and time spent by the doctor in supporting their patients in this transition from biologic therapy, in accordance with good prescription practice guidelines defined by the HAS [Haute Autorité de Santé (French National Authority for Health)]. It provides for remuneration of prescribing physicians based on the number of patients who switched from a reference biologic to a biosimilar for at least three months. The savings generated are distributed such that 30% and 20% go to prescribers in 2022 and 2023, respectively, and 70% and 80% go to the national Health Insurance. This recent measure, implemented in 2022, has already seen positive and noticeable results with the targeted private physicians (Figure 5) in terms of their contribution volume. A break in the curve was observed, for example, for market penetration with private prescribers of etanercept, which went from 35% in January 2022 to 50% in September 2022 (vs. a projection of 40% without incentives introduced during this period). However, the market penetration of etanercept with private prescribers still does not match market penetration with hospital prescribers.

In the community setting, biosimilars had a 31% market penetration (in volume) in 2021, or 4 million boxes sold.[12] As with hospital prescribers, an incentive was introduced in 2022 for private prescribers.

Figure 5: changes in etanercept prescriptions with private prescribers following the implementation of Amendment 9





In summary, for France, there are multiple and varied incentives to encourage the use of biosimilars, but they are sometimes complex and difficult to read, as highlighted by experts. In addition, associated economic returns for prescribers, departments, and hospitals are often difficult to follow and measure, which may discourage commitment from healthcare professionals.

Despite these challenges, some measures showed noticeable and positive results, such as the Article 51 test programme in the hospital setting, and Addendum 9 to the national agreement between private physicians and health insurance.

OTHER INCENTIVES IN THE EUROPEAN UNION

IRELAND: A SIMPLE AND CLEAR INCENTIVE

In Ireland, the penetration rate of biosimilars was very low prior to any incentives being introduced. To remedy this, a program was developed in the form of a specific incentive. Essentially financial, it translates as a €500 sum paid to the clinical department for each patient who starts or is switched from a reference biologic to a biosimilar.

In less than a year, a significant impact could be observed:[13]

- For etanercept: the 104 patients on it in May 2019, rose to more than 1,800 in May 2020; the penetration rate thus increasing from 2% to more than 45% over the period
- €22.7 million in savings were generated between June 2019 and July 2020, and €3.60 million were paid to specialists within the context of the benefit-sharing agreement, to be re-invested

ENGLAND: LIMITED PRESCRIPTION BUDGETS FAVOR BIOSIMILARS

In England, the market penetration for biosimilars is 72% (as a percentage of the total revenue for the biologics group)[14] and is based on a health model encouraging their use by prescribing physicians. Doctors' budgets are controlled by the Clinical Commissioning Groups (CCG), responsible for allocating resources to local medical practices according to the number of patients registered, the complexity of their health needs and other local factors. CCGs can implement prescription policies to encourage the use of less expensive drugs or alternative treatment options. CCGs may also monitor doctors' prescriptions to ensure that they comply with national and local guidelines. Given their limited prescription budgets, physicians are naturally encouraged to prescribe less expensive medicinal products, such as biosimilars. Incentives can also be implemented, as in France, based on sharing the gain between the NHS, the United Kingdom's health body, and prescribers. For example, the North Bristol NHS Trust implemented a program to share the savings generated with the North Somerset and South Gloucestershire CCG in July 2015 to manage the switch from the reference biologic infliximab to a biosimilar. In this program, 50% of the savings generated were paid to prescribing doctors. Of a total of 65 patients identified as taking a reference drug, 52 switched to a biosimilar in three months, allowing £200,000 to be generated, and reinvested into the gastroenterology departments.[15]

GERMANY: OBJECTIVES ASSOCIATED WITH REGIONAL INCENTIVES

Germany has a high level of market penetration for biosimilars, reaching 78% (as a percentage of the total revenue for the biologic group). The German Health System is based on quotas of prescriptions by drug classes that must not be exceeded and which may vary by region.[16] This regional policy of the German health system makes it impossible to observe any incentive applied across the country. However, in some regions incentives have been put in place in addition to quotas. They encourage doctors to prescribe biosimilars by setting goals for them. When these goals are met, the prescriber is renumerated according to a gain-share model and their quota of biologics increases, allowing them to prescribe more. The pilot program was launched in Westphalia-Lippe in 2015 for infliximab, and this region had faster adoption of biosimilars than the others between 2015 and 2018. The pilot program was considered a success, and has been reproduced with other health organizations. However, the details of these programs vary in terms of prescription and compensation objectives, which makes it difficult to compare between regions.[17]

SPAIN: A HOSPITAL-DRIVEN SYSTEM

In Spain, the biosimilar market penetration rate is 62% (as a percentage of the total revenue for the biologics groups).

This is the country closest to France, which has a market penetration rate in terms of revenue of more than 50%.[18] Spain has introduced incentives focused on hospitals, as only five biosimilar product groups are available from the pharmacy. As a result, all incentive efforts are focused on the use of biosimilars in the hospital setting.

In summary, the incentives studied for these European countries all involve motivating physicians to prescribe biosimilars by sharing the value. However, the experts consulted agree on the high degree of heterogeneity in their functioning and calculation mechanisms based on that of the respective health systems. Thus, the reproducibility of the measures between France, England, Germany and Spain is not evident. Ultimately, it is noted that the adoption and prescription of biosimilars are the main levers chosen by each of the health systems to generate savings.

Critical analysis of the biosimilar incentive tool used in France

The aim of the incentives presented is to accelerate the adoption of biosimilars by prescribers and their patients. Therefore, accelerating their market penetration makes it possible to extend access to biologics to more patients, freeing up resources to invest in new areas, fund therapy innovation and bring some relief to healthcare budgets under pressure. However, not all these measures apply to the same situations: hospital or outpatient use, prescriber category, administration locations and methods, etc., are all points that must be noted when interpreting the effectiveness of incentives.

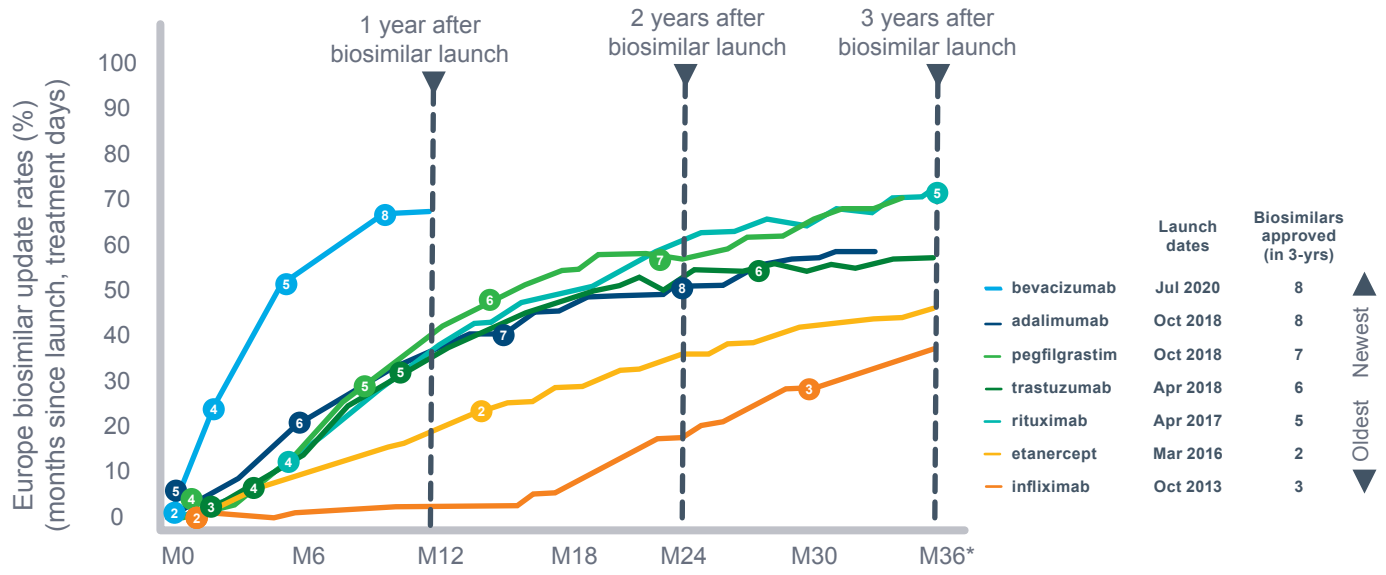
HOSPITALS, THE PRIMARY VECTOR FOR THE DIFFUSION OF BIOSIMILARS

In Europe, bevacizumab is a recent biosimilar (2020) (N=8), for which the administration is only carried out in a hospital setting: 12 months after its launch, its market penetration was approximately 70% (figure 6).[19]

Conversely, etanercept is an older biosimilar (2016), which is initially prescribed in hospital. Renewal and dispensing can then be performed in a community pharmacy, or in hospital. At 12 months after the launch of biosimilars, their market penetration is approximately 20% (figure 6).[20]

A large variability in the market penetration of biosimilars can therefore be seen, varying according to the different molecules involved. The increase in the number of biosimilar medicinal products for the same molecule seems to be one of the factors, among others, that facilitates market penetration of the medicinal product in question.

Figure 6 : Comparison of the progression of market penetration of biosimilars in Europe from the time they arrived on the market



Source: IQVIA MIDAS (Q2 2021); EMA EPAR list of approved medicines ans marketing authorization dates (last accessed November 2021), number of competitors represents the number approved within the market during the first 36 months post-launch
Note: the expiry date of the infliximab patent was different in EU countries.

In France, the gap in market penetration for biosimilars between the hospital and outpatient settings can also be observed in the French national health insurance income and expenses report. Thus, at the end of 2021, market penetration was 31% in the community setting and 80% in hospitals.[21] (see details by molecule in the Appendix)

Biosimilars administered in the hospital setting have two unique features that may explain their higher market penetration rates and the connection to the incentives.

Firstly, the hospital is financially responsible for its own budget, which notably means the purchasing medicinal products, and especially biosimilars.

This seeking to optimize the best quality to price ratio is essential for products funded through the regulations establishing rates for activities (T2A). For products funded outside T2A, the hospital is incentivized to negotiate purchase prices, since the EMI generates additional revenue for the hospital. This logic and the necessity to reduce costs encourages these facilities to turn to biosimilars.

Secondly, hospital-administered biosimilars are reconstituted and dispensed by the internal pharmacy (PUI [pharmacie à usage intérieur]) to be administered directly to patients by the hospital staff. The patient is therefore not part of the dispensing system, and the use of a biosimilar may appear transparent to them. However, in some cases, patients have a strong relationship with their treatment, which makes the prescription and dispensing of biosimilars more complex, and requires the hospital to maintain using the reference treatment. Therefore, biosimilar treatments introduced do not involve the same patients (treated patients or treatment-naive patients).

The influence of hospitals on the community setting, and the specific French situation of hospital prescriptions fulfilled in community pharmacies (PHMEV)

PHMEV are the prescription of medicinal products by a healthcare professional practicing within a hospital but dispensed in a community pharmacy. The pharmaceutical expense is thus attributed to the budget of the outpatient clinic, and not that of the hospital. In this context, the rate of market penetration of biosimilars in the community setting depends on hospital clinicians who have two options:

Prescribing the reference drug, which leads to an increase in outpatient expenses. This works against improving market penetration rates of biosimilars by limiting the knowledge and the ability of hospital prescribers to inspire outpatient prescribers.

Prescribing a biosimilar, which will, on the other hand, make it possible to better control health expenses in the community setting by favoring the market penetration rate from all health professionals in the outpatient setting.

As the results of PHMEV are dependent on hospital prescribers, it seems essential to introduce specific incentives (ordinary law, Article 51, CAQES, etc.) to promote the prescription of biosimilars dispensed in a community pharmacy.

Experience shows that, to be effective, incentives must take into account the specificity of the various pathways and their funding.

GENERAL INCENTIVES NOT TARGETING SPECIFIC ISSUES

PATIENTS PREVIOUSLY TREATED WITH A REFERENCE BIOLOGIC

In the hospital setting, treatment-naïve patients primarily start treatment with a biosimilar (80% according to the French national health insurance income and expenses report of July 2022). The true

leverage for short-term acceleration of market penetration of biosimilars in the hospital setting, therefore resides in patients who are already being treated with a reference biologic.

These numbers are confirmed in a study of biosimilars in the anti-TNF-alpha class. After the introduction of the biosimilars infliximab, etanercept, and adalimumab, the percentage of treatment-naïve patients who started treatment with one of these biosimilars in 2021 was 78%, 46%, and 53%, respectively. Over the same period, the percentage of patients electing to switch from a reference medication to a biosimilar was 46%, 19%, and 17% for these molecules.[22]

These figures demonstrate the complexity and time needed to transition a treatment to a biosimilar. This change must take place at the appropriate time: the patient's disease must be stable and the patient must be convinced. This measure also depends on the frequency of consultations between the patient and their specialist physician who is able to modify the treatment.

The risk of a nocebo effect[23] is often detected by doctors. This is a phenomenon through which the negative expectations regarding an adverse event may itself cause the event. It is therefore important to prepare the patient by providing clear information about the benefits and risks of the biosimilar. The availability and mobilization of the entire medical team (doctors, nurses, pharmacist, etc.) to reinforce information provided by the prescriber are identified as factors for the success of this transition.

Private practitioners, whether general practitioners or specialists, can play a key role in monitoring patients for whom the question of a transition arises. However, this leverage has not yet been used, which was corrected with Amendment 9 to the Contract with private physicians recently implemented (2022).

Finally, in this particular case of treatment transition, the measures taken do not really target the main protagonists in this change: the patients. They may not perceive the general and individual benefits of the use of biosimilars well or even at all. To support them, the HAS, ANSM and the CNAM have developed educational tools on biosimilars. Patients are not, however, likely to have uniform and equal support to promote a positive and successful experience with biosimilars.

BIOSIMILAR MEDICINAL PRODUCTS THAT ARE DIFFERENTIATED BASED ON THEIR THERAPEUTIC OBJECTIVE

In the case of a biologic used as a support therapy, i.e. temporary and in most cases a single prescription, the switch from a reference drug to a biosimilar product has very little impact on the patient. The adoption of these biosimilars thus becomes easier and faster.

Conversely, when the biologic is the long-term treatment for a chronic disease, experts note that changing the proprietary medicinal product is more difficult to execute in patients who feel attached to a treatment that they know and feel comfortable with. Switching to a biosimilar then requires more time and education from physicians.

Thus, treatments used in the context of long-term conditions are more difficult to switch, which tends to explain the slower market penetration of these biosimilars

AN OVERVIEW OF BIOSIMILARS THAT DIFFER DEPENDING ON THE SPECIALTY

A difference in market penetration of biosimilars (both in terms of starting treatment and in switching treatments) may be observed depending on the prescribers' specialty.

Specialist familiarity with biosimilars and their use facilitates the adoption of new biosimilars. This has been observed for short half-life G-CSF growth factors (filgrastim) and long half-life factors (peg-filgrastim) by hematologists, but also by rheumatologists who have become familiar with biosimilars through infliximab, followed by etanercept and adalimumab.

Thus, rheumatology has more frequently resorted to biosimilar medicinal products than other medical specialties who are less used to them.[24]

This partly explains why the more recently marketed biosimilars have had faster market penetration than the ones that came on to the market first (Figure 6).

THE STRENGTH OF EVIDENCE IN THE ACCEPTANCE OF BIOSIMILARS

Another factor determining the adoption of biosimilars is phase 3 studies. As part of the development of biosimilars, the concept of extrapolation of indications allows laboratories, after demonstrating physicochemical comparability to the reference drug, to conduct a study in a so-called "sensitive" indication. This allows them to obtain all indications of the reference drug. With regard to adalimumab, rheumatologists and dermatologists, unlike gastroenterologists, received scientific publications reinforcing evidence of equivalence between reference and biosimilar medicinal products in their therapeutic area very early on (see Appendix 4). This contributed to supporting them in the adoption of biosimilars.

Over time and with use, familiarity and experience with biosimilars is reinforced. Publication of scientific studies with real-world data is an important factor in increasing the confidence of physicians in these innovative treatments.

CLEAR, BUT OFTEN FORGOTTEN, INCENTIVE RULES ENCOURAGING EFFECTIVE MEASURES THAT ARE SIMPLE TO UNDERSTAND

The payer, in its role as instigator of these incentives, is important in the explanation, encouragement, monitoring and payment of these incentives, but especially in the preparation of their implementation, which must take place with the cooperation and compliance from the parties, such as:

* Art. 51, in the creation by the departments and hospital of a project, validated by the authorities.

* Amendment 9, which is the result of a cooperation between medical federations and the CNAM.

Thus, healthcare professionals often deal with a significant workload, as well as a lack of means and tools.[25] Thus, complex measures that require a deeper understanding and/or work-intensive and specific implementation are often less effective in the market penetration rate of biosimilars.

Furthermore, it is also important that the financial benefits associated with an incentive are easily calculated and seen, to maintain true confidence and motivation in the measure.

SUPPORT OF HOSPITAL MANAGERS, KEY TO INCENTIVES

Management of incentives within hospitals is key to their success. In marketing the biosimilar rituximab, some hospital directors did a tour of user centers giving a presentation promoting biosimilars directly in the departments. Similarly, in managing the implementation of Article 51, some departments acted as motivators and facilitators for the success of this test.

MEASURES TO BE INCLUDED COLLEGIATELY...

Teamwork and the adoption of an interprofessional vision are other key factors to consider. In hospitals, biosimilar product training needs to be conducted with a collegiate approach, to build a common language that will be key in supporting the patient in this prescription change, and promoting their continued use biosimilars. Similarly, information sharing with regard to incentives and professional training can be approached in a collegiate manner, especially as part of COMEDIMS [Commission du Médicament et des Dispositifs Médicaux Stériles (Drug and Sterile Medical Device Commission)] that are shared medical and pharmaceutical decision-making bodies.

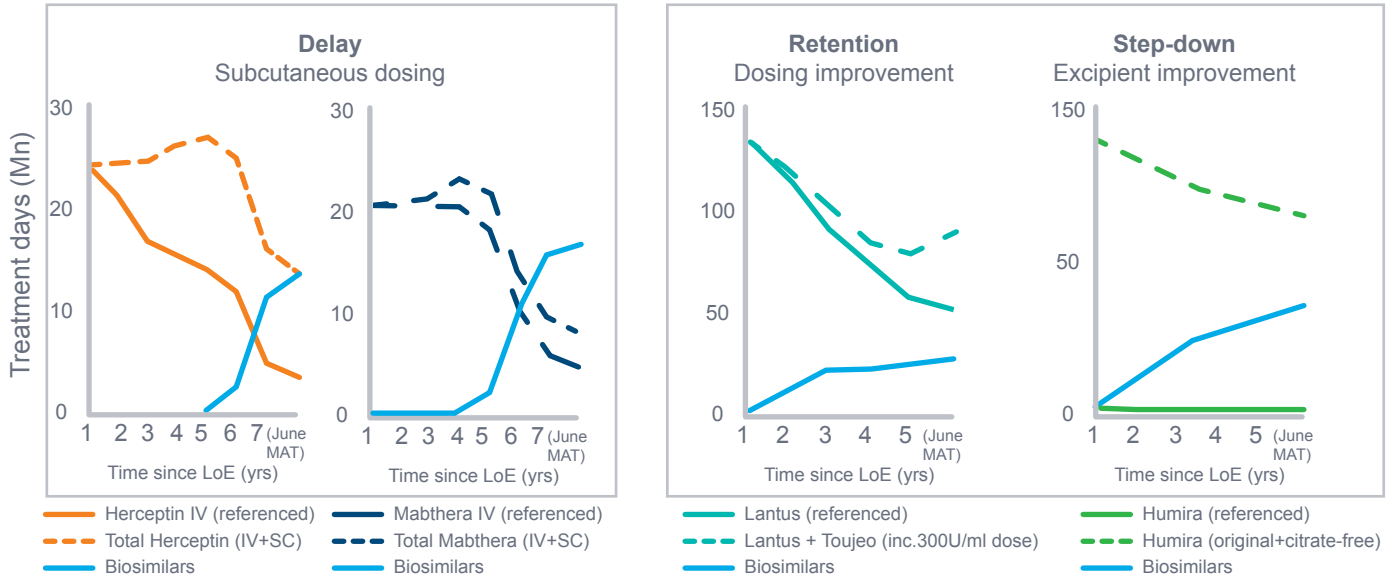
However, in the community setting, the decision to prescribe a biosimilar is made on an individual basis, and depends on the professional's ability to undertake CPD on the latest provisions for the prescription of biosimilars and supporting their patients.

...AND TO BE ADAPTED TO NEW FORMS OF REFERENCE DRUGS

The provision of new forms (pharmaceutical, dosage, formulation) of reference biologic drugs may negatively affect the speed of market penetration of biosimilars. In particular, this was observed with:[26]

- The delayed decline of the market by the introduction of subcutaneous formulations, e.g., trastuzumab, rituximab
- Retention by the historical market after expiration of protection with dosing changes, such as: Lantus and Toujeo (insulin glargine)
- The gradual decrease of the market with product improvement, such as: Humira (adalimumab) without citrate
- The transfer of volumes to combined forms of molecules, e.g.: trastuzumab => trastuzumab + pertuzumab

Figure 7: Authorization of new pharmaceutical forms observed in Europe by manufacturers of reference biologics and the consequences for biosimilars (in days of treatment)



Source: IQVIA MIDAS© MAT June 2020
Notes: Curves are normalized to allow comparaison. After protection expiry, only a portion of the product is catogorised as 'referenced' as innovation and additionnal protection is afforded to the product through alternative administration, excipients, or dosing.

Whether to meet a therapeutic need and/or to extend the protection provided by patents, new forms of reference biologics have the effect of impacting market penetration or the expected effects of biosimilars, and limiting any potential savings that may result from them.

Conclusions and perspectives

IN THE SHORT TERM

The financial incentives implemented in recent years have proven their effectiveness in increasing market penetration of biosimilars in Europe. Although the mechanism differs depending on the country, taking into account specific local situations, these measures share the same approach, i.e. a change in practice by sharing value between the payer and healthcare provider.

To be effective, incentives must:

- Be appropriate for the health system,
- Be co-constructed between the payer and prescriber
- Take into account the specificities of prescribing and dispensing the medicinal product, and patient treatment pathway
- Be known, explicit, followed, encouraged by all parties, prescribers, healthcare professionals and patients

Nevertheless, the target of 80% market penetration has not yet been reached – although relatively close, for all the countries studied.

With a 31% rate of market penetration of biosimilars in the community setting,[27] France is the country with the highest margin of progression, especially for patients already treated with a reference biologic therapy. This leverage originates in the need to support patients in facing their fears and the amount of time being invested by the healthcare team – which is what the incentives put in place allow for. However, it is important to note that French doctors, unlike what has been observed in other countries, prescribe biosimilar medicinal products outside any constraints specific to the use of these treatments.

On this point, on 2 February 2023, DREES (Direction de la recherche, des études, de l'évaluation et des statistiques [directorate for research, study, evaluation and statistics]) presented the positive results of the evaluation of the test on the efficiency of biologics to the Conseil National Strategique de l'Innovation en Santé (CSIS). In particular, it explains that the financial incentives sometimes helped fund a therapeutic education program for patients, facilitating their acceptance of biosimilars through discussions they could have with the hospital pharmacist or nurse in addition to the prescribing doctor. A particularly effective approach for patients previously treated with reference biologic.

To be effective the incentives should be adapted:

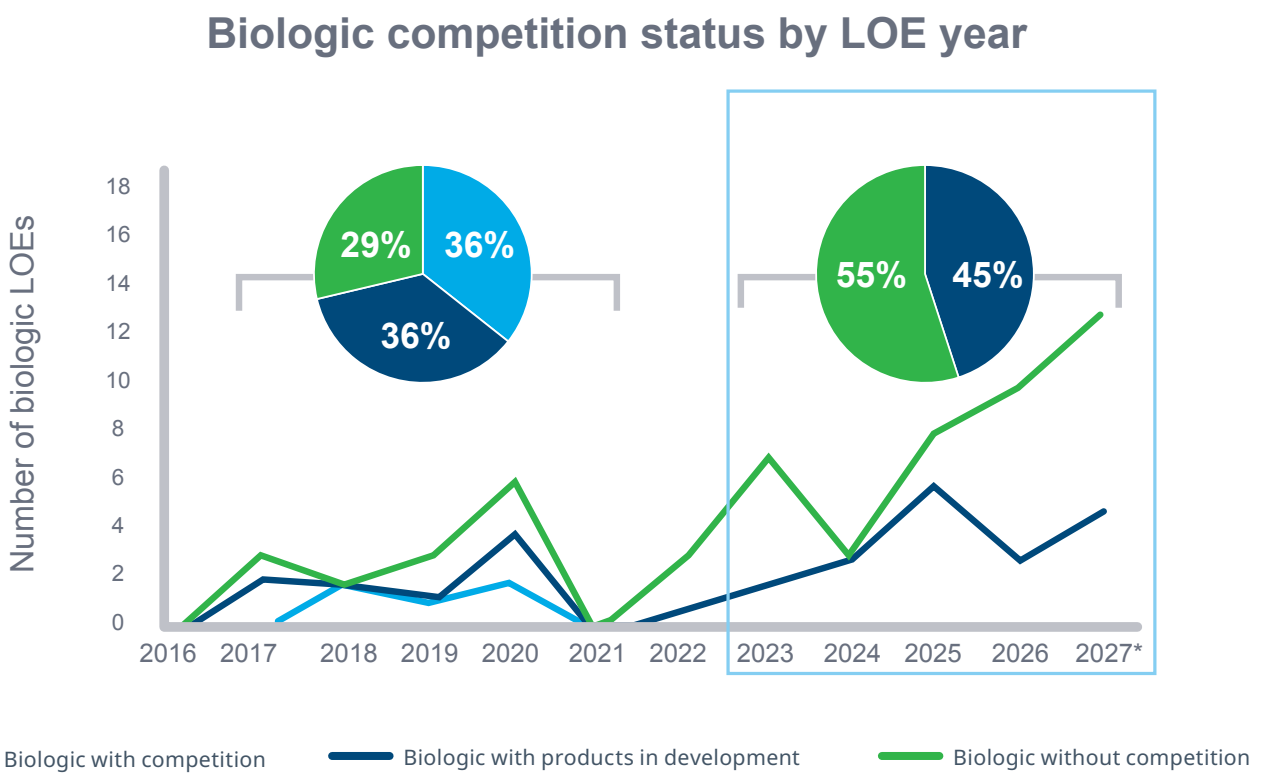
- on the one hand, to the targeted market, be it, the community or hospital setting. Transition drivers are specific as shown by existing incentive mechanisms
- and on the other hand, the type of patient concerned. With regard to the biosimilars that have already been on the market for some time, the goal is to more specifically target patients who are already being treated, and who are still on reference biologic that are more difficult to change given that the patient has an attachment to their treatment. In addition, for biosimilars arriving on the market, incentives should be systematically addressed, as provided for by Addendum 9
- Finally, it is important to reiterate the point every time a biosimilar arrives on the market, to optimize its market penetration by reassuring prescribers and patients

IN THE MEDIUM TERM

Among the biologics that will lose their exclusivity by 2027, there is a growing proportion of orphan drugs for which no competition is expected, due to the lack of biosimilar development.[28] Figure 8 shows that in the end, only one biologic in two will have competition from a biosimilar. Thus, the current incentives must be sufficiently strong to encourage manufacturers to develop biosimilars with the assurance that transitions will be supported by a prescription efficiency policy. The complexity of these incentives must remain at an acceptable level, and their number low, to make them effective and easily understood by healthcare professionals. However, the proposal of new types of incentives must be considered in order to maintain a dynamic rate of market penetration for biosimilars in the event of the arrival of new forms of reference drugs on the market (subcutaneous or IV or in combination with reference treatments).

The anticipation of the arrival of future biosimilars (see Appendix) and the implementation of specific incentives will be the key factors to success in guaranteeing the increased use of biosimilars, and therefore the sustainability of health costs.

Figure 8: Competition of biologics per year of loss of exclusivity



Source: IQVIA Patent Intelligence, Pipeline Intelligence, and IQVIA Forecast Link analysis (November 2022); Historic analysis sourced from IQVIA Institute report, Protection expiry and Journey into the Market (2022)

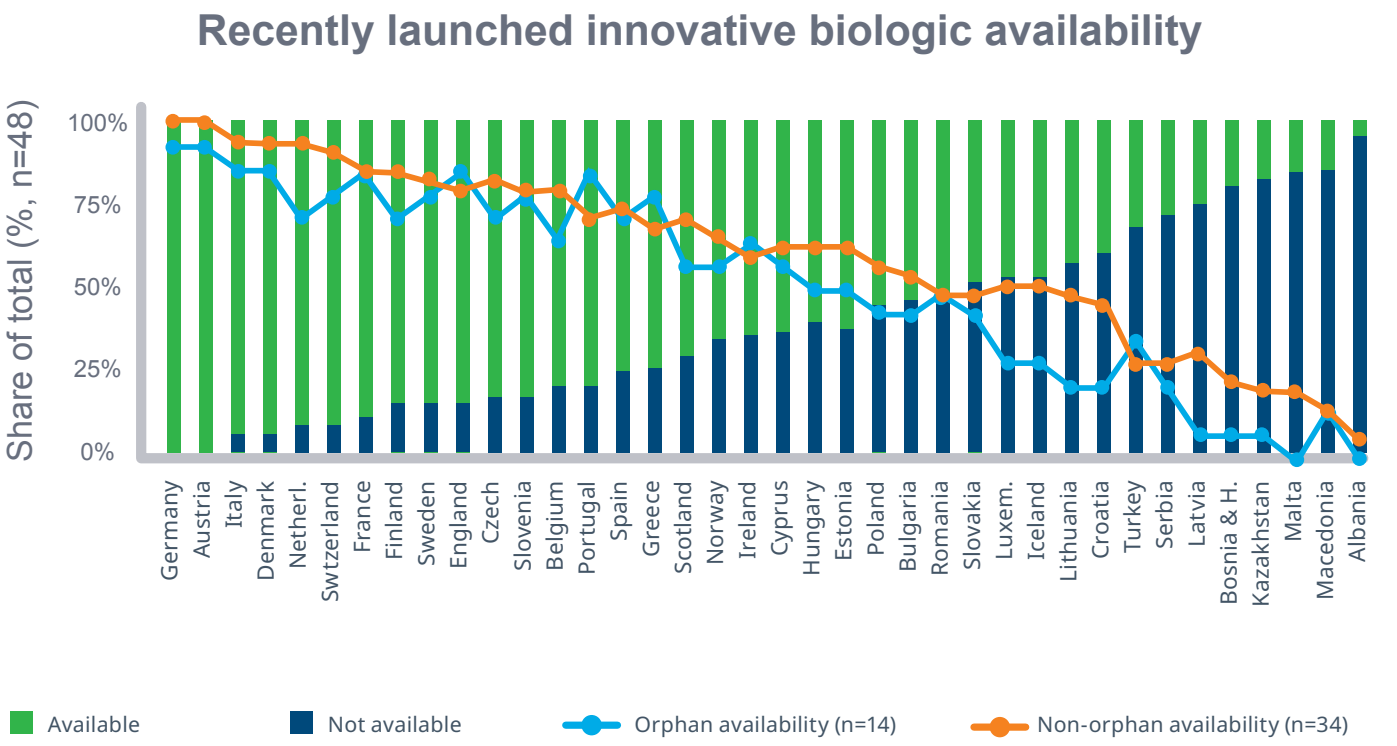
Note: The intellectual property for biologicals can involve multiple patent, timelines, data exclusivity, and litigation for each individual product and therefore it is difficult to give an exact date for protection expiry for biologicals. It should be noted that these results are estimates as determined from IQVIA MIDAS® and ARK Patent Intelligence where available, and historical products are cross-referenced to public sources

IN THE LONG TERM

Biologics recently authorized in Europe (between 2014 and 2020) and whose protection can thus be expected to remain in place until 2027 are not all available for patients, given that they are not all included on the reimbursement lists of the various European countries.[29]

That is to say, in order for a biosimilar to effectively penetrate the market, the reference biologic must be present on the market, that is, reimbursed, and accumulated experience in the clinical setting and additional data. Therefore, countries that do not have the means to fund reference treatments risk not being able to benefit from their corresponding biosimilars. Market sustainability is a delicate balance between stimulation and competition, long-term savings and the anticipation of the next wave.

Figure 9: Availability of biologics authorized by the EMA between 2014 and 2020



Source: Based on IQVIA W.A.I.T dataset and IQVIA HTA Accelerator datasets covering active substances (NAS) molecules launched within 2014 - 2020 (November 2022 analysis), including all current EU members, EEA members, and countries considering ascension. Reimbursement defined by availability on a public reimbursement list in a country. Orphan medecines defined by EMA EPAR list (last accessed 2022)

Appendix 1

IQVIA Methodology for calculating the savings related to biosimilars in France:

Purpose of the model: to compare the revenue generated by biologics over the period 2010-2022 and modelled revenue (market simulation without biosimilars), to obtain the savings generated by the arrival of biosimilars on the market.

SCOPE AND DATA SOURCES

- 15 biosimilars marketed in France
- Rate reference: CNAM [Caisse Nationale de l'Assurance maladie (French National Health Insurance Fund)] Price
- Reference sales of biosimilar medicinal products: IQVIA proprietary database (MIDAS)

HYPOTHETICAL SAVINGS CALCULATION:

1. The prices are considered on a quarterly basis regardless of the month when the price reduction is applied
2. Some products have been removed from the scope (e.g., dosages without a corresponding biosimilar) but others have been kept in order to align with the calculation parameters for the market penetration of biosimilars
3. The savings estimate was only calculated in the community setting for products whose hospital sales ratio is less than 25%
4. Mixed products (hospitals sales greater than 25%) with no CNAM reference price (e.g., enoxaparin) will be valued based on the mean MIDAS price
5. For some molecules, the price was reported at the equivalent unit (IU, MG, etc.)

CALCULATION METHOD:

- Modeling the new price of the reference products without the arrival of biosimilars and calculation of a market carried out using this hypothesis:

Total Standard Unit per dosage of reference product (IQVIA data) + Total Standard Unit for biosimilars (IQVIA data) x reference PFHT [prix fabricant hors taxes (manufacturing price net of tax)] according to hypothesis (CNAM) = modelled revenue

- Estimated saving by market:

Model revenue - actual revenue = Estimated saving

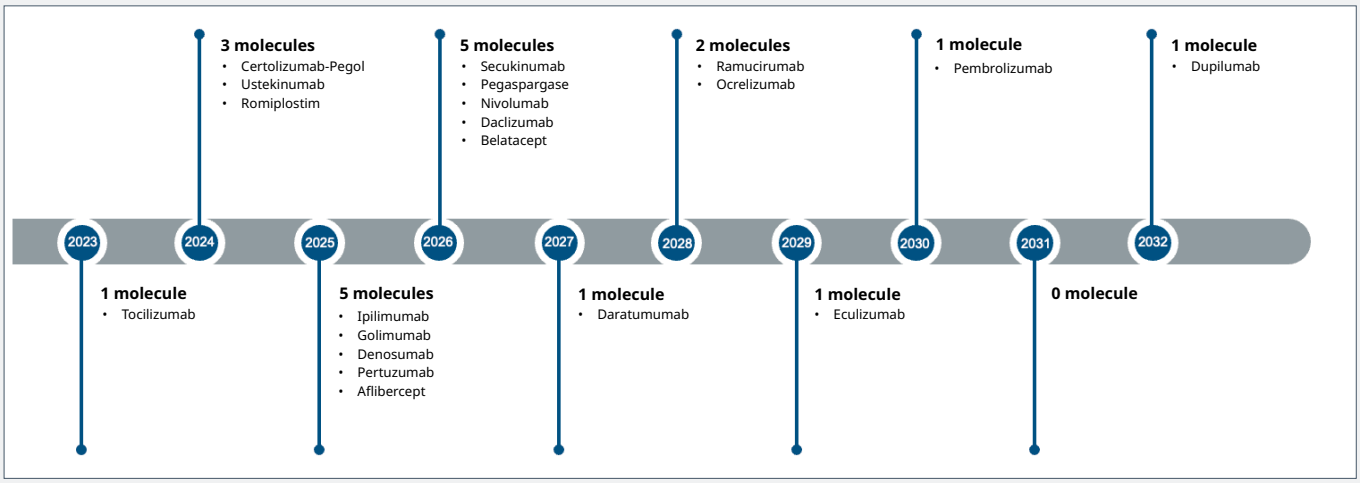
Appendix 2

Overview of market penetration of biosimilars (by volume) in 2021 by International Nonproprietary Name (INN) and dispensing location[30]

Active substance	Dispensing in community pharmacies		Intra-hospital dispensing *(list of drugs and services reimbursed on top of inpatient care)*	
	Proportion of biosimilars in the corresponding biologic group *(in volume)*	**Amount reimbursed** *(in million euros)*	**Proportion of biosimilars in the corresponding biologic group** *(in volume)*	**Amount reimbursed** *(in million euros)*
Adalimumab	32%	€503 million		
Bevacizumab			87%	€154 million
Enoxaparin	11%	€115 million		
Epoetin	83%	€104 million		
Etanercept	39%	€166 million		
Filgrastim	92%	€95 million		
Follitropin alfa	61%	€63 million		
Infliximab			81%	€157 million
Insulin aspart	0%	€89 million		
Insulin glargine	34%	€131 million		
Pegfilgrastim	73%	€164 million		
Rituximab			84%	€130 million
Somatotropin	48%	€52 million		
Teriparatide	23%	€27 million		
Trastuzumab			60%	€172 million
Total	**31%**	**€1,510 million**	**80%**	**€613 million**

Appendix 3

Horizon scanning of patent losses for biologics by 2032



Appendix 4

Summary table of studies developing biosimilars for Adalimumab (Clinical Trials)

Product	Rheumatoid arthritis	Psoriasis
Amgevita	NCT01970475	NCT01970488
Imraldi	NCT02167139	-
Hulio	NCT02260791 NCT02405780	-
Hyrimoz	NCT02744755	NCT02016105
Idacio	NCT03052322	NCT02660580
Amsparity	NCT02480153	-
Yuflyma	NCT03789292	-
Hukyndra	-	NCT04453137

Appendix 5

Summary table of the incentives for using biosimilars in France

Name of incentive	Drugs concerned	Date of implementation	End date	Mechanism	Details	Indicators	Targets concerned	Payment	Source of budget	Beneficiary
CAQES 1	National indicators: GCSF, EPO, Insulin glargine, ANTI-TNF Alpha.	End date	31/12/2022	bonus for objectives met	CAQES 1 proposed to orient the assessment of actions at hospitals using two aspects (per 19 national indicators): quality and safety on the one hand, and efficiency (controlling expenses by using the correct health product) on the other hand.	*Quality indicators *Intra-hospital consumption objectives *Market penetration objectives of biosimilars in PHMEV	Hospital prescribers	annual	Regional Intervention Fund	Hospital budget
CAQES 2	No national indicators, regional indicators.	01/01/2018	5 years	bonus for objectives met	CAQES 2 is just a non-mandatory incentive tool, that makes it possible to promote national and/or regional interest following an annual evaluation. It is divided into 3 parts, and consists of 14 indicators: 7 national indicators and 7 regional indicators.	* Regional indicators on the use of IV form biosimilars and SC form references* PHMEV indicators	Hospital prescribers	annual	Regional Intervention Fund	Hospital budget
EMI	Rituximab, Infliximab, Bevacizumab, Trastuzumab	31/12/2022		value sharing	Specific to medicinal products on the list of drugs and services reimbursed on top of inpatient care, not specific to biosimilars: payout of 50% of the difference between the standard rate and the net purchase price	hospital Compensation = 50% x (Standard rate - Purchase price)	Hospital purchasers (Pharmacists) and hospital prescribers.	annual	CNAM	Hospital budget
Ordinary law	Adalimumab, Etanercept, Insulin glargine, for all care institutions participating in CAQES and who are not participating in the Article 51 test programme	01/01/2023	31/12/2022	value sharing	Payout of 20% of the difference between the reference drug price and the biosimilar price = marginal compensation	Annual Compensation Calculation = Prescription Volume x Marginal Compensation (20%) x Use Rate	Hospital prescribers	annual	Regional Intervention Fund	Hospital budget
Article 51 test programme	Adalimumab, Etanercept, Insulin glargine	5 years	31/12/2022	value sharing	Payout of 30% of the difference between the reference drug price and the biosimilar price	Annual Compensation Calculation = Prescription Volume x Marginal Compensation (30%) x Use Rate	Hospital prescribers	Biannually	Regional Intervention Fund	Payout to hospital departments within the context of the project submitted via the hospital budget
Amendment 9	only participating institutions with a chosen project	2015		value sharing	* Year 1 payout of 30% of the difference between the reference drug price and the biosimilar price * Year 2 payout of 20% * Year 3 payout of 10%, subject to an agreement between the federations and the CNAM	If the patient consumed 3 months of biosimilars, the prescriber receives an amount corresponding to twelve months of consumption. This amount is only accounted for over one year. Annual interest calculations = Patients started or swapped X annual savings X distribution key	Private prescribers	annual	CNAM	Payout to the prescriber

References

Biosimilars – ANSM [Agence Nationale de Sécurité du Medicament et des Produits de Santé (French National Agency for Medicines and Health Products Safety)] (ansm.sante.fr)

[1] Biosimilars: what are the challenges for health professionals?
Morgane Beck, Bruno Michel, Marie-Christine Rybarczyk-Vigouret, Dominique Levêque, Christelle Sordet, Jean Sibilia, Michel Velten

[2] The Impact of Biosimilar Competition in Europe in 2022 - IQVIA

[3] Biosimilars in the EU - EMA

[4] IQVIA analysis of EMA EPAR list – IQVIA (November 2022)

[5] Social Security report: Setting the price of medicinal products – Public Finance Court (2017)

[6] Income and expenses report - French national health insurance proposals for 2023 (July 2022)

[7] The Impact of Biosimilar Competition in Europe in 2022 - IQVIA

[8] Income and expenses report – French national health insurance proposals for 2023 (July 2022)

[9]Pricing for healthcare institutions – Ministère de la Santé et de la Jeunesse et des Sports [Ministry of Health, Youth, and Spor

[10]Contrat d'Amélioration de la Quality et de l'Efficience des Soins [improvement in the quality and efficiency of care contract] (CAQES) – ARS Occitanie, 2023

[11] Plenary meeting - Conseil Strategique de l'Innovation en Santé [strategic council for health innovation] (2 February 2023)

[12] Income and expenses report - French national health insurance proposals for 2023 (July 2022)

[13] Shared Savings Programs in Europe - IQVIA Institute

[14] IQVIA Model – Bx_Cost_Savings_Model_Q2_2022

[15] "Shared Savings Programs in Europe, Lessons for the United States" Report – IQVIA Institute (December 2022)

[16] How to develop the market of generic and biosimilar medicinal products in France – Observations and proposals – Le GEMME (drugsgenerics.info)

[17]"Shared Savings Programs in Europe, Lessons for the United States" Report – IQVIA Institute (December 2022)

[18] IQVIA Model – Bx_Cost_Savings_Model_Q2_2022

[19] IQVIA MIDAS; IQVIA, The Impact of Biosimilar Competition in Europe, December 2021

[20] IQVIA MIDAS; IQVIA, The Impact of Biosimilar Competition in Europe, December 2021

References

[21] Income and expenses report for 2023

[22] TNF-alpha inhibitors biosimilar use in France: a nationwide population-based study using the French National HealthData System - Hugo Jourdain, Léa Hoisnard, Emilie Sbidian & Mahmoud Zureik, Scientific reports

[23]Presentation by the French Rheumatology Society on the substitution of an original biologic treatment by a biosimilar – SFR, 2019

[24] TNF-alpha inhibitors biosimilar use in France: a nationwide population-based study using the French National Health
Data System - Hugo Jourdain, Léa Hoisnard, Emilie Sbidian & Mahmoud Zureik, Scientific reports

[25] The observation panel of practices and practice conditions in general medicine – DREES (2020)

[26] The Impact of Biosimilar Competition in Europe, December 2020 - IQVIA

[27] Income and expenses report - French national health insurance proposals for 2023 (July 2022)

[28] The impact of Biosimilar Competition in Europe – IQVIA

[29] The Impact of Biosimilar Competition in Europe - IQVIA