



Biosimilars: An European Overview

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Abstract

Biosimilar drugs represent the possibility to improve patient access to medicines but also alleviate financial burden faced by stakeholders in the currently constrained European budgetary environment. We reviewed key drivers and policies of biosimilar uptake in Europe, underlying national authorization pathways, timing and strategies. National healthcare systems features as well as physicians prescribing culture, have been featured resulting in a deep heterogeneity and in various policies referable to three main areas: pricing, reimbursement and demand. Unlike Italy and UK, where incentives for prescribers are planned at regional level, France and Germany extended them nationally. There are now substantial evidences of a common reduced familiarity with biosimilar drugs in countries where substitution is not allowed. To date, Germany, Spain, Portugal, Sweden, Norway, Finland, Austria, Holland, Czech Republic, Hungary and Romania introduced rules to avoid or limit automatic substitution by the pharmacy without physician consent. We evaluated where and why awareness-rising initiatives could be more adequate if tailored on physicians rather than on poorly informed patients. Furthermore, being an extensively mentioned issue within scientific community, we focused on biosimilar pre and post marketing risk/benefit profile assessment. No Regulatory Agencies requires clinical studies to confirm the originator maintained pharmacological characteristics over time or after major variations in productive process. Based on November 2019 European Commission 'Health and Food Safety Directorate working Group' discussion, a final commentary on the predictable increment of biosimilar duplicate marketing authorizations is given.

Keywords: *Biosimilar; Access; Sustainability; Pricing; Market Penetration; Policy*

Abbreviations

AMNOG: German Pharmaceuticals Market Reorganisation Act; AIFA: Italian Medicine Agency; CESP: Economic Committee for Medicinal Product; CIPM: International Committee for Weights and Measures; CPR: Italian Pricing and Reimbursement Committee; CTS: Italian Technical Scientific Commission; EMA: European Medicine Agency; EOF: Greek National Organization for Medicines; EU: European Union; FIMEA: Finnish Medicines Agency; G-BA: German Federal Joint Committee; HPRA: Health Products Regulatory Authority; MAA: Duplicate Marketing Authorizations; MoH: Minister of Health; NICE: National Institute for Health and Care Excellence;

NHS: National Health Service; PEI: Netherlands Paul Ehrlich Institute; RPS: Reference Price System; SHI: Statutory Health Insurance; UK: United Kingdom

Introduction

Pricing and reimbursement situation in different countries

Unlike originator drugs, for biosimilar drugs there are different ways of submission for pricing and reimbursement dossier. In United Kingdom, there is no need to submit any price and reimbursement dossier to NICE but they have to submit it to the NHS Department of Health. It is a small dossier that mainly contains in-

formations from the 'Summary of Product Characteristics' and the necessary proxies for the marketing of the drug. The definition of prices for biosimilar medicines has an accelerated procedure, the submission takes place between 8 and 12 weeks before the launch of the product. The dossier states the list price of the medicine, generally starting with a price 10% lower than that of the originator drug. The opening price is set by the manufacturer. There are no defined pricing rules for originator drugs after the launch of biosimilar medicines [1].

There is no specified price discount for biosimilars in the UK/England [2]. NICE does not routinely review biosimilars. NICE can apply the guidance for the originator to the biosimilar, unless it decides that an evidence summary for a new medicine is required. Benefits and risks are inferred by the similarity to the reference medicine in terms of quality, efficacy and safety [3]. In Italy, prices of pharmaceuticals reimbursed by the NHS are regulated at the central level and remain the same across the whole country. The pricing and reimbursement procedure is regulated by the Italian CIPE Deliberation, 1 February 2001.

Legislative Decree No. 219/2006 introduced a definition for 'biosimilar or bioequivalent' and indicated the documentation necessary to obtain approval for a biosimilar [the applicant will need to submit to AIFA a complete and exhaustive dossier containing pre-clinical tests and clinical trial results in order to obtain the marketing authorisation of a biosimilar product] [4]. Pricing and reimbursement procedures for biosimilars are the same as for other medicines. The price-setting system is based on a negotiation procedure applicable to all reimbursable pharmaceuticals. AIFA Technical Scientific Committee (Commissione Tecnico-Scientifica, CTS) expresses an opinion on reimbursement classification and the process of negotiation takes place only after this reimbursement evaluation. The negotiation procedure is managed by the Committee for Pricing and Reimbursement (Comitato Prezzi e Rimborso, CPR) [5].

The negotiation procedure is conducted following criteria based on product therapeutic value; pharmacovigilance data; price in other EU Member States; price of similar products within the same pharmacotherapeutic group; internal market forecasts number of potential patients; and therapeutic innovation. The prices are negotiated at ex-factory level and are also defined the

pharmacy retail prices. Prices negotiated represent, in the case of hospitals, the maximum sale price for the NHS, but pharmaceutical companies must grant a rebate/discount to hospitals. For generic and biosimilar medicines, the pricing negotiation procedure should guarantee at least a 20% price reduction with respect to the price of the originator reference medicine. Nevertheless, in order to stimulate the uptake of biosimilars through physicians, a progressive price reduction is applied, starting from an initial price reduction ranging from 22% to 15%, a further price reduction is set once a predefined volume threshold is achieved. In Spain, the P&R procedure is decided by the MoH. There is a 10-year protection period for new medicines. After this period, they are included in specific price systems: Reference Price System [RPS] and/or Homogeneous Groups System. An RPS is composed by different groups of drugs with the same active ingredient and the same route of administration. Each group must include at least two different presentations with the same active ingredient, one of them should be the original drug and the other one must be a generic or biosimilar medicine or another drug with the same active ingredient but different to the original one. The price of each group is established taking into consideration the lowest cost/treatment/day and the number of daily doses that has each package. RPS establishes the maximum price for each group. As defined by the CIPM, conventional generics must have a price 40% lower than the reference price of the originator, while for the biosimilar, the reduction is 30% compared to the reference organic [6].

In Germany, referring to traditional drugs, biosimilar excluded, until 2011, pharmaceutical firms were free to set their own wholesale prices for prescription medicines. The 11 November 2010 law - Act on the Reform of the Market for Medicinal Products (AMNOG) there is a policy that for the first year biosimilars have a Free pricing; after this there is a Price group system; and after all biosimilars goes to Rebate system to SHI. Rebates have been introduced to reduce the net price to SHIs particularly for infliximab and partially for epoetins, filgrastim and somatropins.

In France for biosimilars, price and reimbursement evaluation process is the same as for innovative medicines. It goes through two phases which see the TC and the CESP as key actors. For the pricing, for the biosimilars there is the Originator price set as limit; after all mandatory price cut of the originator medicine (at least -10%) and the pharmaceutical agencies participates at Hospital tenders.

Biosimilar price must be equal to or lower than originator price. There is the same dispensation status for biosimilar and originator medicines. Biosimilar medicine ends to price at -25 to -35% relative to innovator's initial price [7].

Discussion

Access to the market

Several articles describe the process of authorization for biological drugs in the main European countries: Italy, Britain, France, Spain and Germany. Marketing authorization is finalized at national level by the competent local agency, although the authorization procedure used for a biological/biosimilar drug is centralized and it is decided by the European Commission. According to early com-

parisons in the main European countries, it is immediately evident that the average access time for originator drugs is between 11 and 14 months and between 7 and 9 months for biosimilars. Likewise, similar analyses suggest that the placement on the market requires approximately one year for originator drugs, whereas biosimilars require fewer months. The reasons behind that are manifold, mainly: the complexity and novelty of the originator dossier, the issues raised during the calculation of the price, and the reimbursement evaluation process. Entrance in a structured market for the originator requires an economic evaluation that goes more in-depth and is more comprehensive compared to that undertaken for a biosimilar. The figures in the box below represent the average time that a drug, originator or biosimilar, takes to be placed on the Italian, French and Spanish markets.

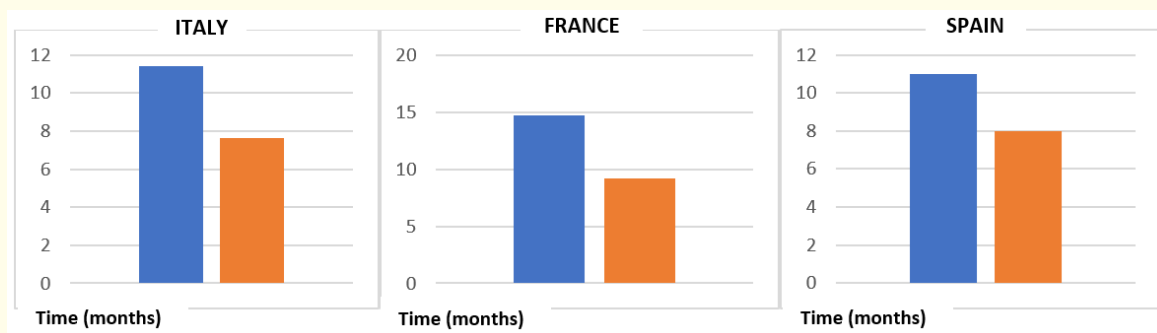


Figure 1: Originator vs biosimilar time to market in Italy, France and Spain.

More difficult, instead, is the gathering of information regarding access to market for biological drugs in Britain. However, looking at the general framework of the other countries, it is likely that in Britain access times depend on a careful assessment carried out by the National Healthcare System. This assessment aims to evaluate the cost-effectiveness ratio, and to reach an agreement for the reimbursement of the drug. Thus, it could be inferred that access times for the British market hover around 12 months.

The situation in Germany, on the other hand, is different. In Germany, where the access procedure for all drugs is standardized, manufacturers can freely set the price point, which is maintained for a maximum of 12 months until the G-BA evaluates a fair price in accordance with the Statutory Health Insurance (SHI) Head Association. After six months, the G-BA's conclusions are then used as a basis to negotiate reimbursement prices with the industry.

However, the AMNOG process does not apply to biosimilars. Biosimilars do not have to undergo the additional benefit assessment like newly authorized pharmaceuticals as defined in the AMNOG. Biosimilar manufacturers set their own pricing, but this cannot be higher than that of the brand drug. These reference price groups are used as a cost containment tool. Taking Germany into consideration, the average time of a drug to access the national market and therefore the patient remains unchanged. In sum, once authorization from the European Commission is obtained, it takes around 12 months for a biological drug to reach the patient, whereas times are slightly reduced for biosimilars, which require a lower threshold of control. However, it should be emphasized that, in every country, regardless of the time required to obtain the reimbursement, a biosimilar drug can be marketed only after the expiration of the patent coverage of the reference organic product.

Market penetration

Uptake of biosimilar will be shaped by multiple factors including physician and patient perception of safety, costs saving for most stakeholders, regulatory burden and the effectiveness of educational programs. Pricing is considered a significant driver in Europe, in fact, biosimilar and follow on biologics are largely competing on price. A study conducted by Remutaz, *et al.* 2017 showed that the number of incentive policies dedicated to enhance biosimilar uptake is an important driver of biosimilar penetration. In addition, increasing the number of biosimilar in a therapeutic class, the difficulties coming from the penetration will increase. Another aspect that has been demonstrated is that a longer time on the market offers a higher opportunity to be established and to gain market share over the originator [8].

As the substitution of biosimilar is not always allowed or recommended, prescribers are less price sensitive and not familiar with biosimilar and as a consequence this clinicians' receptiveness and willingness to use biosimilar is considered as an important lever for their uptake in EU countries. For what concern incentives policies for biosimilar they have been applied and are heterogeneous across European countries. These policies have been implemented to promote access to biosimilar and are classifiable in three main area with regard to pricing, reimbursement and demand side.

Analyzing UK, Italy, Germany and France some differences raised. In UK, there is a regulated market with a free pricing by the company, after a definition of a volume-based pricing scheme, if the total amount of medicines sold is above the threshold then the government gets a rebate. In addition, there is the absence of internal reference pricing and the presence of incentives to prescribe. In Italy, biosimilar are priced approximately 20% below the price of the reference product and external reference pricing are used as supporting information for the pricing reimbursed medicines, and in some regions there are incentives to prescribe these drugs. In Germany the price is freely set by the company and discount may be negotiated through tenders by individual healthcare funds, there are internal reference pricing, incentive to prescribe and substitution is allowed.

In France prices are fixed upon negotiation between pharmaceutical companies and the Economic Committee for Medicinal Product (CEPS). The price is typically 10 - 20% below the price of the reference product, taking into account a range of factors including drug's improvement in medical benefit rating versus therapeutic equivalents, the price of the drug in Europe and sales

volume forecast. In addition, there are internal reference pricing, incentives to prescribe and substitution is allowed. In all countries reimbursement depend on national authorities and in Italy also regional budgets can be involved. When internal reference pricing is used, it refers to the fact that the originator medicinal product and biosimilar may be subject to internal reference pricing so a common reimbursement level is set for a group of medicinal products.

Understanding the key drivers of biosimilar uptake is a critical issue for policy decision makers, it has been demonstrated that incentives policies constitute an important driver of biosimilar penetration. Because of the heterogeneity coming from different countries, the reason for uptake biosimilar in one country could be different in another. For instance, in Germany where there are large numbers of incentive policies to support biosimilar uptake it could be a key driver. In other countries where the originator is not reimbursed and the biosimilar is reimbursed, it captures most of the market.

In conclusion, the heterogeneity of healthcare systems as well as the physicians prescribing culture and practice should be considered in order to develop an efficient penetration policy.

European interchangeability policy and sustainability

Patient access to the growing number of biologic therapies developed and approved over the past decade, has been limited, partly due to their relatively high cost. Biosimilars are increasingly available across Europe, bringing with them the opportunity to generate competition for biologic therapies and thereby lower medicine costs and improve the lives of patients worldwide. The establishment of policies and centralized regulatory frameworks for biosimilars at the European and country levels reflect the effort to facilitate biosimilar use and emphasize their role in expanding patient access to biologic medicines while lowering treatment costs [9].

Biosimilar medicines can be awarded the same indications as the respective reference originator biologic, once biosimilar comparability has been demonstrated. However, even if the regulatory authorization pathway has demonstrated that their risk-benefit ratio is the same of the reference originator, due to the complex nature of biologic medicines, biosimilars can't be simply considered as generic or equivalent product.

One of the most important issue with biological drugs, including biosimilar, is their risk of immunogenicity which requires a special

consideration and ongoing pharmacovigilance programs in order to ensure the safe use of these therapies [10].

Even though biosimilars developed in line with EU requirements are considered by EMA to be therapeutic alternatives to their reference biologicals, the decision on interchangeability is not regulated by the European Agency but is left to individual countries as part of national policy.

Interchangeability is a fundamental element of biosimilar policies.

In the information guideline published by EMA, has been clearly highlighted the difference between switch, based on physician and patient joint decision-making process, and substitution, automatically done at the pharmacy-level without consulting the prescribing physician [11].

in France, with the introduction of a new law concerning the social security budget for biosimilar substitution under certain conditions. The substitution is admitted at treatment initiation for “molecule naïve” patients and if not prohibited by the prescriber; furthermore, in order to ensure continuity in the treatment, once a substitution to a biosimilar is carried out, a second substitution to another biosimilar cannot take place. Greece’s medicines agency, National Organization for Medicines (EOF), released a document in 2013 recommending against automatic substitution/interchangeability of reference biologicals and their biosimilars [13]. In 2015, the Finnish Medicines Agency, FIMEA, announced that biosimilars can be considered interchangeable with their reference biologicals. Automatic substitution at the pharmacy level, however, is not included in the current recommendation [14,15]. Other EU national authorities, including the Medicines Evaluation Board (MEB) in The Netherlands, the Paul-Ehrlich-Institut (PEI) in Germany and the Health Products Regulatory Authority (HPRA) in Ireland [16], have adopted similar positions. In the same year, Portugal published interchangeability regulations that contain an exemption that switching must be justified based on scientific opinion. In 2018, with a second position paper, the Italian Medicines Agency moved towards the other EU policies, establishing the interchangeability between the biosimilar and its originator also during the treatment. The decision is in charge to the physician who can choose the best treatment on the patient’s interest ensuring treatment continuity [17]. In Spain, while there is a legal regulation against automatic substitution, no specific guidelines on the switch to the treatment with biosimilar have been developed, hence biosimilars are more used in naïve patients [18].

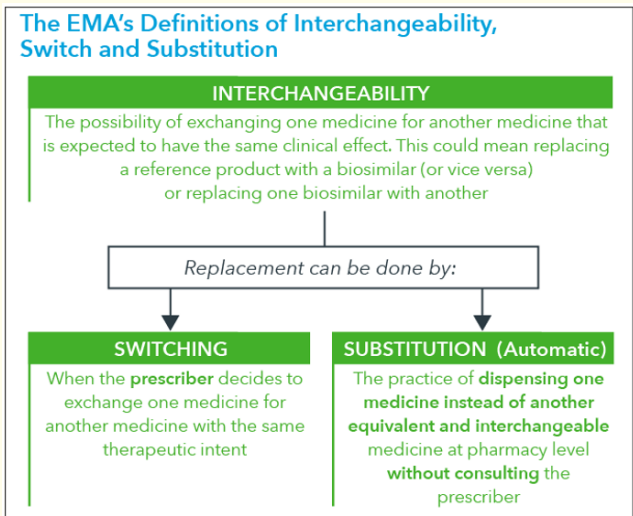


Figure 2: EMA's definitions of interchangeability, switch and substitution.

Among EU countries, national Guidelines and rules provisions on the interchangeability of biosimilars have been developed ‘slowly and steadily’ and evolved in last years. In 2013, the Italian Medicines Agency [Agenzia Italiana del Farmaco - AIFA] stated that physicians should consider biosimilars as the preferred option only for naïve patients where it positively impacts the health-care budget [12]. A similar position was adopted in the same years

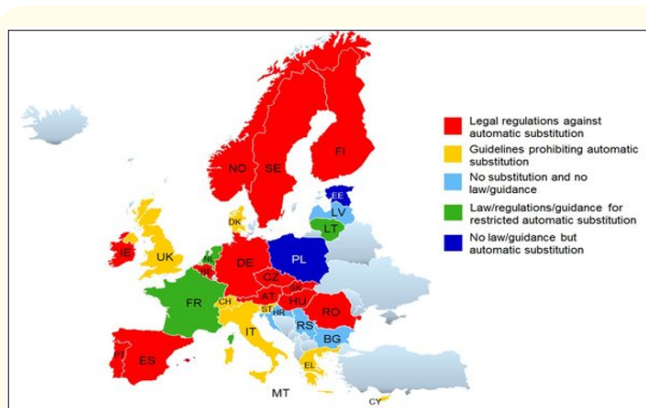


Figure 3: Biosimilar substitution roadmap in Europe.

To date, although most Member States do not allow automatic substitution by the pharmacy without physician consent, and many have introduced rules to avoid or limit this practice. This is due to concerns regarding traceability and that repeated switching between the biosimilar and reference biological may increase immunogenicity. Finally, the choice of treatment should remain a clinical decision and be entrusted to the prescribing physician and automatic substitution cannot be carried out only for economic reasons.

Biosimilars represent the possibility to improve patient access to innovative medicines but are also a key means to alleviate financial challenges faced by many stakeholders in the currently constrained European budgetary environment, providing the opportunity for cost savings and contributing to the sustainability of Healthcare Systems [19].

In order to deliver these benefits, the main challenge is to guarantee a long-term sustainability of biosimilar markets in Europe, considering the ongoing needs of all stakeholders [patients, healthcare professionals, payers, manufacturers]. Maintaining healthy competition among both makers of biosimilars and originator and developing specific policies and guidelines (relating to Switching, Substitution, Indication Extrapolation) based on the development of clinical evidence are the building blocks for an ethic and sustainable market.

Future Perspectives

For pharmaceutical companies with patent expired products, the progressive loss of patients treated with reference drug will drive the strategic introduction of new products in the field of both incremental and disruptive pharmacological innovations. As well, this trend will generate important opportunities for companies willing to enter the new sector [20]. In Italy, where savings are foreseen and tangible, patients and healthcare professionals suggest to use them for alleviating the great regional and local access variability. A recent study published on GITHAD, Italian Journal of Health Technology Assessment, estimated a cumulative cost saving resulting from the introduction of infliximab, etanercept and adalimumab biosimilar of about € 551.1 million in 2020 [23].

Further efforts should be directed at implementing strategies to improve traceability and to evaluate benefits and risks of multiple

switches between originators and biosimilars to better explore the issue of interchangeability. In the next few years, a growing number of biologics and biosimilars will be available on the market, thus highlighting the need for specific post-marketing short and long-term monitoring programs for these drugs. It is essential to understand how the concept of interchangeability will be managed and regulated in the future [24].

As highlighted in various AIFA reports and scientific guidelines, the cooperation between healthcare professionals and patients both in prescriptive decisions and during therapy monitoring, will be crucial for integrating pivotal data with real world evidences. Moreover, these two habits will be fundamental in order to ensure a continuous re-assessment of the benefit/risk ratio of each biosimilar. Safety and efficacy data collected by general practitioners will need to be translated in patient accessible disclosure materials. In quite a different way, French and UK governments adopted an economic incentive based strategy to drive medical doctors and hospitals in prescribing biosimilar drugs or switching to them.

For example, switching from Remicade to the infliximab biosimilars Inflectra and Remisma has become a common practice in UK. As well, with the launch of adalimumab biosimilars in October 2018, the guidance now recommend that nine out of ten treatment-naive patients and eight out of ten established patients on the reference product should receive the best value adalimumab within three and twelve months of a biosimilar entry respectively [25].

Because of European growing number of duplicate marketing authorizations (MAA), the European Commission 'Health and Food Safety Directorate working Group' discussed in November 2019 about risks and impacts of potential future biosimilar duplicate authorization requests. European Commission also refers to these drugs as 'Autobiologicals', biosimilars produced and marketed by the same company who own the reference biologic. Despite asking for a generic 'clone product authorization' may not turn out as a convenient and strategic choice for drug companies, an increment in number of biosimilar MAA is expected. The majority of Member State Competent Authorities considered that duplicate authorizations could have potential negative effects on availability of biosimilar alternatives and could also result in a privileged position in terms of pharmacy-level substitution in some EU states. Moreover, autobiologicals outbreak could allow reference biologics producers to significantly reduce the potential biosimilar competitors prices

without lowering their own originator. Such a similar scenario could also result in the common winning of both co-owned biological and autobiological drugs in the same tender, particularly in Italy. However, all member states in the consultation agreed that the commission should revise its guidance on this probable future crux [26].

Conclusion

The advent of biosimilars generated important opportunities for all stakeholders both in oncologic and non-oncologic disease area. From the payer perspective, biosimilars will represent an important driver in increasing pharma companies market competition besides being an indirect tool for better cover patient needs. For clinicians, the primary advantage comes from savings generated by the use of biosimilar drugs where the reallocation of resources will provide them the opportunity to prescribe new therapeutics otherwise unaffordable. A significant increase in payers purchasing power will reduce financial pressure generated by population ageing and new advanced drugs costs.

In Europe, the awareness-rising initiatives on biosimilar medicines mainly focus on physician rather than on patient perspective. The implementation of policies aiming to increase biosimilar market penetration through training and informative materials for Medical Doctors, will be a crucial strategy to generate trust among patients [20]. This choice will better fit in Nations such as Italy and Spain, where the main barriers against biosimilar success are loath health practitioners and poorly informed patients. In clinical practice, spontaneous reporting and healthcare databases will represent valid instruments for post-marketing surveillance of biosimilars.

Nowadays, more than ten years after the introduction of the first biosimilar drug, despite the publication of two position paper to clarify Italian National Regulatory Agency's formal opinions [17,21], there are still unclear ethical and legal aspects on how to regulate risk benefit profile definition and how to set standardized evidence generation studies to support European and National approvals path. Several publications focusing on biosimilar access and related policies highlight an intriguing aspect. While there are rigid guidelines regulating the similarity exercise between biosimilar and originator biologic product, no Regulatory Agencies requires clinical studies to confirm the originator maintained

pharmacological characteristics over time or after major variations in productive process at international level [22,23].

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