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Editorial

A long war begins: biosimilars versus patented biologics

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The world of medicines is currently facing up to radical disruptions. After generics—copies of medicines of a chemical origin—the market of biologics is now opening up to competing 'copies' with biosimilars[1]. As was the case with generics 20 years ago, the goal with biosimilars is to guarantee patients optimal access to treatments as efficient and secure as their originators, but at substantially reduced prices[2]. As several biologic 'blockbusters'—monoclonal antibodies (Mabs) used in oncology, for inflammatory or rheumatic chronic diseases, products used in diabetes, multiple sclerosis—have expiring European and American patents, healthcare payers are looking forward to biosimilars, as the situation has become highly strained regarding health systems funding.

However, unlike generics, there is still much uncertainty as to the development of this incipient market, as to the ability of biosimilars to be competitive in the highly innovating biologic sector and as to the key factors determining their access to the market[3]. This uncertainty stems from various factors. First, from a scientific viewpoint, the structures of copied biological molecules are highly more complex and variable than their chemical counterparts, as their molecular weight often stands for almost '1000-times less than a traditional chemical' medicine[4]. Then, whereas manufacturing processes of chemical medicines produce repeatable molecules, the production of biologics leads to a range of structurally comparable molecules, which are not, however, absolutely identical to each other. This variability is due to the fact that microorganisms used in the production of biological molecules are *per se* unable to repeatedly synthesize exactly the same molecule. Consequently, whereas generics can be regarded as identical copies of their references, biosimilars are 'similar' copies of their originators[4]. From an economic viewpoint, biologics are generally characterized by high prices compared to chemical medicines. This can be explained by substantial costs resulting from long and complex development processes implemented for biologics and from the fact that they are intended for limited patient groups[5].

Today, few medicines are copied under the form of biosimilars around the world (biosimilars in the strict meaning of the term—copies of biologics developed and registered according to a regulatory and dedicated approach equivalent to that developed by the European Union since 2004). The biosimilar market indeed essentially corresponds to the European market (80% of the global biosimilar market in 2011)[6] and to the Japanese market. Only three therapeutic classes now include commercialized biosimilars: human growth hormones (somatropin), short-acting G-CSF (filgrastim) (Granulocyte-Colony Stimulating Factors), and short-acting EPO (epoetin alfa). Another essential aspect is that, in the US—which represents half of the global biologics market in volume and value—no biosimilar has been commercialized up-to-date. A single G-CSF biosimilar obtained a FDA approval in March 2015 in the US without being commercialized (Zarxio)[7].

Table 1. Main characteristics of national EPO markets studied in 2012.

	Japan	France	Italy	Spain	Germany	UK
EPO-BIOSIM uptakes (volume)	6.8%	5.8%	8.6%	11.5%	30.4%	2.0%
EPO market sizes (million €)	818.8	405.6	500.2	215.9	164.0	112.5
EPO distribution channels						
Retail	50.0%	81.3%	3.1%	0%	81.9%	50.5%
Hospital	50.0%	18.7%	96.9%	100.0%	18.1%	49.5%
Market share of the 1G-EPOs	21.7%	25.6%	65.1%	53.0%	58.7%	60.8%
Market share of the 2G-EPOs	78.3%	74.4%	34.9%	47.0%	41.3%	39.2%
BIOSIM-EPO prices discounts (€/DDD) vs REF	−26.9%	−14.0%	−22.2%	−3.6%	−10.8%	−11.6%

EPO-BIOSIM, EPO biosimilars; 1G-EPOs, first-generation EPOs; 2G-EPOs, second-generation EPOs; DDD, defined daily dose. The DDD is a statistical measure of drug consumption defined by the WHO as the assumed average maintenance dose per day for a drug used for its main indication in adults. REF, reference 'biosimilarized' first-generation EPO.

In order to describe the dynamics at work on the biosimilar market and to determine the biosimilar capacity to compete with other biologics—and after having previously analyzed the G-CSF market[8]—the EPO market was a natural analysis to make in retrospect[9,10]. The EPO class is that which generates more expenses around the world (7.6 billion dollars in 2012), where the highest number of biosimilars can be found, for which the number of laboratories is the most important and for which we have the highest number of biosimilar-using experiences. From 2007–2012 we studied the main EPO global markets where biosimilars (EPO-BIOSIM) were commercialized (Japan, France, Italy, Spain, Germany, and the UK) and categorized each national market by dominant distribution model: dominant retail market distribution (R), dominant hospital market distribution (H), or mixed distribution channels (retail + hospital, R + H)[10]. We excluded the following countries from our study: those which did not implement either any legislation for biosimilars or any specific regulatory framework for their development; those where biologics' copies are regularly developed and manufactured without any strict regulatory, technical, and scientific requirements, without respect for international standards in terms of intellectual property and infringing the right of international patents; those for which the biologics market value on a national scale was below 2.5 billion dollars in 2010. The main characteristics of the national EPO markets studied are presented in Table 1. We analyzed the factors that were likely to affect the EPO-BIOSIM uptake in these markets[10].

As shown in Table 1, in 2012, the Japanese market of EPO was the largest of the analyzed markets (818.8 million Euros per year). It is a R + H market, of which three quarters are made up of second-generation long-acting EPO (2G-EPO). No incentive for prescription or substitution of EPO-BIOSIM had been implemented, and the EPO-BIOSIM uptake in Japan amounted to 6.8% in volume. The French market of EPO was assessed this same year to 405.6 billion Euros. In France, it is a R-type channel and no incentive to use EPO-BIOSIM had at this time been implemented. Like in Japan, the 2G-EPO represented three quarters of the market, and the EPO-BIOSIM uptake in France amounted to 5.8% in 2012. The Italian and Spanish markets' values were, respectively, of 500.2 and 215.9 million Euros. They were in many respects quite similar. Both were H-type markets, no incentive for prescription or substitution had been implemented for biosimilars in 2012. On these markets, the 2G-EPO, respectively, accounted for 34.9% and 47.0% of consumed EPO in volume in 2012 and the EPO-BIOSIM uptake this same year amounted to 8.6% in Italy and to 11.5% in Spain. The situation was totally different on the German market—valued to 164.0 million Euros—where, like in France, it is a R-type market, but where incentive for biosimilar prescription towards physicians (quotas) and for biosimilar substitution towards pharmacists (approved substitution for products regarded as 'bioidenticals') had been implemented by some local health insurance funds. On the German market, the 2G-EPO stood for 41.3% of the market and the EPO-BIOSIM uptake rate amounted to 30.4% in 2012. Only valued to 113 million Euros per year, the UK is a R + H-type market and, like in Japan, no incentive incites the use for biosimilars in this country. The 2G-EPO stand for 39.2% of the market and the EPO-BIOSIM only correspond to a marginal share of it (2.0%).

Thanks to these results[10], we were able to stress that analyzed EPO national markets are very heterogeneous whether in terms of volume, of composition, of distribution channels and of EPO-BIOSIM uptake. Moreover, we showed that there is no correlation between EPO dominant distribution channels and the EPO-BIOSIM uptake on a national scale. Discounted prices between EPO-BIOSIM and their reference (REF) did not affect the biosimilar EPO global uptake rate on national markets (e.g., −10.8% in Germany vs −26.9% in Japan, for biosimilar uptake rates of 30.4% vs 6.8%, respectively) (Table 1). It is, however, worth highlighting the limit of our study, for which we only considered the products'

ex-manufacturer prices in order to carry out international comparisons, whereas these latter do not consider either the discounts granted by laboratories in the scope of tenders conducted at the hospital, or the claw-back systems implemented in some countries. The fact that 2G-EPO stand for a great share of EPO national markets is actually a major pitfall for EPO-BIOSIM to access the market. In Germany, the heterogeneously implemented incentives promoting the use of biosimilars seem to significantly increase the EPO-BIOSIM uptake. Their impact nonetheless has to be put into perspective, as biosimilar G-CSF uptakes in Germany remain weak in relation to other European countries, which have not implemented equivalent incentives[8]. Moreover, the non-coercive aspect of implemented quotas cannot guarantee their real efficiency, and other studies show that biosimilar uptake rates can easily vary from one German region to another[11].

As for G-CSF, the results show that the factors influencing the market's biosimilar uptake are numerous and specific to the countries where they are commercialized. This country analysis will have to be updated and completed with other studies related to other biosimilar therapeutic classes—and particularly that of Mabs—but it already highlights that, today, there is no unique economic model for biosimilars, unlike for generics. Whereas biosimilars stand on a 'specialty market' with high-priced products, generics—that can resemble homogeneous economic items—develop on a so-called 'low-cost facilities market'. This class and country-specific approach is essential to understand the biosimilar market. Regional, sub-regional, or even local market analyses are now needed to further determine the factors influencing the market entry of biosimilars for countries like Spain, Italy, or Germany. This territorial approach by therapeutic class will definitely have to direct the future policies developed by public authorities and by public or private insurance health funds, in order to support the development of the biosimilars market.

Transparency

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