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Selecting the best-value biosimilar in emerging countries

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Abstract

The aim of biosimilars is to alleviate the financial burden of biological medicinal products. A most relevant challenge for emerging countries is how to select the best option available. In most cases, price is the major determinant, as budgets are chronically scarce. However, initial savings due to price reductions can be overridden if there is a lack of supply due to product shortages or withdrawals. These events can be prevented by a best-value strategy. According to the concept of best-value medicinal products, price is only one of the various criteria to be considered. The purpose of the present paper is to provide suggestions of criteria that can be useful for selecting the best-value biological in emerging countries. Six criteria, that are not limitative, have been selected as follows: standards of regulatory approval, quality of the product, good distribution practices, security of supply, pharmacovigilance, and price.

Keywords

Biosimilars, best-value, emerging countries, follow-on biologics

Introduction

According to the European Medicines Agency (EMA), a biosimilar medicine (biosimilar) is a medicine highly similar to another biological medicine already marketed in the European Union [1]. The US Food & Drug Administration (FDA) defines a biosimilar as a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product [2]. Finally, the World Health Organization (WHO) defines a biosimilar as a biotherapeutic product that is similar in terms of quality, safety, and efficacy to an already licensed reference biotherapeutic product [3].

Biosimilars are versions of brand-name medicinal products that may offer more affordable treatment options to patients but require a different regulatory approach with regard to generic products. The term "generic" refers to chemical, small-molecule medicinal products that are structurally identical to an originator. On the other hand, biosimilars, like their reference biological products, are produced from living systems and therefore exhibit inherent variations as a natural part of the manufacturing process. The first regulatory pathway for biosimilars was established by EMA in 2005, the first biosimilar being approved in

2006. However, in the USA, the biosimilar regulatory pathway was not ready until 2010, with the first biosimilar being approved in 2015 [4]. Official biosimilar regulations and guidelines have also been put in place worldwide, including in a considerable number of emerging countries [5].

Biosimilars are expected to reduce the costs of expensive biopharmaceutical products due to the enhancement of competition in biological medicine markets [5, 6]. At present, a considerable number of biosimilars are commercialized globally. Moreover, for some active substances, various biosimilar options are available [7]. The WHO has issued guidelines for the evaluation of biosimilars [3]. However, these guidelines are not mandatory. At present, biosimilar medicines are manufactured by a number of companies with facilities in different countries. As standardization of regulatory requirements is still wanting, there are significant variations in biosimilar approval criteria among countries. According to Klein et al. [7], two main groups can be distinguished. The first group is constituted by countries with highly regulated markets, that is, a suitable regulation consistent with WHO Guidelines has been put in place and is fully enforced. The second group includes countries that have a biosimilar regulation, but it is not enforced in all cases.

A most relevant challenge, especially in the case of emerging countries without highly regulated biosimilar markets, is how to select the best option available. In most cases, price is the major determinant for selection, as budgets are chronically scarce. Notwithstanding, it should be noted that price reductions for biosimilars are not as important as in the case of generics [8]. On the other hand, excessive price reductions result in unsustainable markets and product shortages [4]. Therefore, price must not be the sole driver in biosimilar selection. Other criteria should also be considered in order to obtain the best-value biologicals [6, 9].

Best-value biological

The concept of best-value medicinal products has been proposed for biosimilar selection [6, 9–11] and models allowing the selection of the best-value biological have been provided [9]. According to these models, price is only one of the various criteria to be considered. Moreover, the best-value option in a given moment needs not to be a biosimilar, as originators have responded to biosimilars by reducing prices [12]. Best-value initiatives have been implemented in some European countries [10], but have not yet been adopted in emerging countries. Alnaqbi et al. [4] have published a roadmap to sustainable biosimilar markets and demonstrated that the strategies working well in high-income countries may differ substantially from those that can be applied in emerging countries. Hence, the criteria for a best-value biologic need not be the same between all countries and regions. The purpose of the present paper is to provide suggestions of criteria that can be useful for selecting best-value biologicals in emerging countries. Six criteria, which are not limitative, have been selected as follows:

1. Standards of regulatory approval
2. Quality of the product
3. Good distribution practices
4. Security of supply
5. Pharmacovigilance
6. Price

Standards of regulatory approval

Best-value criteria can be applied to both, generics and biosimilars. However, a generic is structurally identical with regard to the originator. Demonstration of analytical sameness and pharmacokinetic bioequivalence are sufficient to guarantee therapeutic equivalence and interchangeability in most cases. Therefore, standards of regulatory approval are practically the same among countries. On the other hand, biosimilars show structural differences with the originator [1–3]. It is necessary then to demonstrate that

such differences do not have any significant effect in clinical efficacy and safety. Therefore, variations in standards of regulatory approval play a role of paramount importance in biosimilar selection.

Several companies located in various countries presently manufacture non-innovator biologics, coined follow-on products [7], and pretend to commercialize them as biosimilars [13]. However, many of these products do not qualify as biosimilars in highly regulated markets. Klein et al. [7] comparatively examined the situation in 15 countries from Asia, Africa, Latin America, and the rest of the world with that of five major highly regulated biosimilar markets: the European Union (including UK), USA, Canada, Australia, and Japan. Three hundred and four follow-on biologics for 18 active substances from different manufacturers were identified. Sixty-seven products (22%) were approved in at least one of the five major markets. The remaining 237 (78%) were authorized in one or more of the 15 countries that were not considered as highly regulated markets.

Of these 304 follow-on biologics, 78 were manufactured in India, 62 in China, 25 in Russia, 25 in South Korea, 23 in Iran, and 20 in Argentina [7]. Only seven follow-on biologics manufactured in India and one in China were approved in at least one of the major biosimilar markets. It then appears that the term "biosimilar" does not have the same meaning in different countries and regions. However, there is a growing consensus that only products manufactured according to WHO Guidelines should be considered as true biosimilars [13]. Therefore, transparency in regulatory decisions is absolutely necessary. In general terms, it can be considered that those products that have been approved as biosimilars in one of the major markets, particularly by the FDA or EMA, can be selected [13]. For products authorized by other regulatory agencies, an in-depth analysis must be performed. If the product fulfills with local regulations and complies with WHO Guidelines, it can be selected. On the other hand, if evidence on biosimilarity is incomplete or not available, it is advised not to select the product.

One of the main hurdles for biosimilar market penetration is the lack of trust from both, physicians and patients [4]. Transparency builds up trust. FDA and EMA decisions are fully transparent, as data about biosimilar evaluation are available for consultation in their respective websites. On the other hand, full transparency concerning the approval process is seldom practiced in emerging countries. A good example is RTXM83, a rituximab biosimilar developed by the Argentinian company mAbxience. RTXM83 was authorized in Argentina in 2013 without any published evidence of its biosimilarity, and it is presently marketed in several Latin American countries (Table 1). Evidence on RTXM83 biosimilarity was published several years later [14]. However, this product has not been authorized in any of the five major biosimilar markets [7].

Table 1. Examples of follow-on biologics used in rheumatology that are commercialized in Latin America by licensee companies that are not the actual manufacturer

INN	Manufacturer of follow-on biologic (Country)	Local licence (Country)
Rituximab	mAbxience (Argentina)	PiSA-Farmacéutica (Mexico)
		Laboratorios Bioéticos (Paraguay)
		Urufarma (Uruguay)
	Celltrion (South Korea)	Saval (Chile)
	AryoGen Pharmed (Iran)	PeruLab (Peru)
Adalimumab	Amgen (USA)	Asofarma (Central America)
Infliximab	Celltrion (South Korea)	Gobbi Novag SA (Argentina)
		SAVAL Pharmaceuticals (Chile)
		OXIALFARM CIA LTDA (Ecuador)
		AC Pharma (Peru)
Etanercept	Shanghai CP Guojian Pharmaceutical Co. Ltd. (China)	Lafrancol (Colombia)

INN: international non-proprietary name

Quality of the product

Quality of the product is also a criterion of paramount importance for biosimilar selection, being strongly linked to the standards of regulatory approval. It is well documented that biologics, unlike originator and generic small molecule drug products, exhibit batch-to-batch modifications due to the nature of the manufacturing process involving living organisms [3, 15]. For the reference product, critical quality attributes associated with clinical efficacy and safety should be identified. For example, peptide and glycan maps, indicators of secondary and tertiary structures, and binding properties to target antigens and receptors. Experience with originator products has allowed determining the ranges of these quality attributes that are associated with clinical efficacy and safety. Hence, all critical quality attributes of a biosimilar should meet these acceptance ranges [15].

An international group examined the quality attributes of seven etanercept follow-on products from China, Colombia, India, Mexico, and Iran [16]. All the studied products failed to comply in at least one of the quality assays. These are, values that did not fall within the acceptance range established for the reference etanercept. None of the etanercept follow-on products has clinical studies documenting efficacy and safety according to WHO Guidelines, nor has been approved in any of the major biosimilar markets [7].

Good distribution practices

According to EMA [17], a good distribution practice describes the minimum standards that a wholesale distributor must meet to ensure that the quality and integrity of medicines are maintained throughout the supply chain. Compliance with good distribution practices implies that:

- Medicines are stored in the right conditions at all times, including during transportation
- Contamination by or of other products is avoided
- An adequate turnover of stored medicines takes place
- The right products reach the right addressee within a satisfactory period
- The distributor should put in place a tracing system to enable finding faulty products, as well as an effective recall procedure

Good distribution practices apply for both, small molecules and biologics. However, biologics are more fragile and require a suitable cold chain, posing a greater challenge to equitable delivery [18]. In emerging countries, it is frequent that distribution and commercialization of follow-on biologics are not carried out by the manufacturing company, but by a local licensee that may have limited experience in handling biologics. Table 1 shows some examples of follow-on biologics presently used in rheumatology that are commercialized in Latin America by companies that are not the actual manufacturers. Due to the potential risks of inadequate storage and distribution, decision-makers must ensure that biosimilars comply with good distribution practices in all components of the distribution chain, foreign or local [4].

Security of supply

Security of supply is crucial for both, generic and biosimilar medicinal products, but there are several particularities to point for the latter. A biosimilar policy should warrant high-quality medicines with robust and transparent evaluations and monitoring systems to provide confidence to patients and health professionals. Policies should facilitate cost savings to ensure long-term budget sustainability. However, policies should minimize risks of supply shortages and ensure there is sufficient demand for biosimilars to avoid wastage or incentives to sell at unsustainable prices [4, 19]. At present, the insulin supply is insufficient to meet global needs, with emerging countries being the most affected [20]. As suppliers of both, originators and biosimilars located in high-income countries are not being able to meet the demand, it has been suggested that local manufacture of insulin biosimilars may be a suitable solution for emerging countries. Local manufacture has been successful in Egypt, but this has not been the case in other countries [21].

An important problem with biosimilars in emerging countries is the lack of traceability. Biologics and biosimilars are dispensed according to the international non-proprietary name (INN), identifiers for manufacturers being seldom used [4, 22]. Moreover, certain follow-on products are used in public institutions for a certain period, but then, vanish from official records. For example, Huerta-Sánchez et al. [22] published a pharmacovigilance study on filgrastim at the National Cancer Institute of Mexico in 2015. The authors reported that three biosimilars, Inmunef®, Dextrifyl®, and Biocilyn®, as well as the originator Neupogen®, were being used at the time of the study. However, in the list of authorized filgrastim biosimilars published by the regulatory authority (COFEPRIS, Comisión Federal para Protección contra Riesgos Sanitarios) in May 2024, Biocilin® and Dextrifyl® are not included [23]. There is no explanation available on the motives of these discontinuations.

Therefore, security of supply is an important criterion for the selection of a biosimilar. Decision makers should investigate the offering companies and determine their capacity of importation, storage, distribution, and financial competence in order to ensure a sustainable supply [4, 19].

Pharmacovigilance

Companies commercializing biosimilars should provide well-designed pharmacovigilance programs [3]. Pharmacovigilance for biosimilars is more important than it is for generics because of the need of strict temperature regulation, a specialized delivery system in the form of a device, and the risk of post-translational changes [24]. Pharmacovigilance activities vary greatly among emerging countries, with poor resources restricting the use of such systems and adverse events often being underreported [25]. Furthermore, biologics are frequently identified exclusively by INN, complicating traceability and representing an important hurdle for pharmacovigilance activities [4, 22, 26]. In general terms, pharmacovigilance systems exhibit limited efficiency in emerging countries. For example, Kikizubam®, a rituximab follow-on product that had been authorized in Mexico. Severe adverse reactions were reported in 2012. However, it took two years of legal action to finally withdraw the product in 2014 [27], as there was no timely intervention by health authorities [14].

Emerging countries still lag behind those with highly regulated markets in establishing effective pharmacovigilance systems [26]. A sound national pharmacovigilance system is especially necessary for follow-on biologics that have not been approved in highly regulated markets and, therefore, do not generate warnings by the main regulatory agencies, such as EMA and FDA. Hence, it is recommended to select biosimilars commercialized by companies with the capacity of carrying out pharmacovigilance activities.

Price

The purpose of biosimilars, as it is for generics, is to reduce the acquisition costs of biological agents [9, 12]. The biosimilar market has had an important growth in recent years, in a manner that a wide variety of follow-on products are available [7]. Therefore, decision-makers should select among the various available options. In the case of emerging countries, price reductions frequently constitute the sole criterion for acquisition, whereas major markets are switching to best-value products according to a multicriteria strategy [6, 9–11].

Although price reductions are certainly attractive for biosimilar acquisition, savings may be overridden if a suitable selection strategy is not followed, as can be appreciated from the cases discussed above. Moreover, if a biosimilar is withdrawn or a company cannot honor its commitments, the healthcare system will be forced to make emergency acquisitions at higher prices to cover patient needs. In such cases, initial savings will be overridden resulting in a higher economic impact [4, 20].

Additional factors

The points discussed above show the advantages of implementing best-value initiatives for biosimilars in emerging countries. However, they are not limitative, as there are several other factors that may intervene

in actual decision-making. Moreover, each country has particularities that may lead to the choice of certain criteria and to apply different decision weights for each one of them. Barbier and coworkers have provided a detailed model on how to select a best-value biological medicine, that can be adapted to the situation of each individual country [9].

Conclusions

Price reduction is not the only criterion that should be considered for biosimilar selection. Best-value strategies, based on multicriteria decision-making, have been demonstrated to be more adequate. Moreover, a best-value strategy is not difficult to implement by health care systems, as it does not require additional budgets or high-tech facilities. The adoption of best-value strategies is therefore recommended for biosimilar selection in emerging countries.

Abbreviations

EMA: European Medicines Agency

FDA: US Food & Drug Administration

INN: International non-proprietary name

WHO: World Health Organization

Declarations

Author contributions

GCH: Conceptualization, Visualization, Writing—review & editing. The author read and approved the submitted version.

Conflicts of interest

G.C-H has received consultancy fees from companies commercializing both, originator and biosimilar products, namely AbbVie, Amgen, Asofarma, BeiGene, Merck, Sharp & Dohme, Novartis, Pfizer, Roche, Sandoz, Sanofi, and UCB.

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Not applicable.

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