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Review Article

The biosimilar pathway in the USA: An analysis of the innovator company and biosimilar company perspectives and beyond

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ABSTRACT

In order to improve access to costly biological treatments, a biosimilar pathway in the United States of America (USA) was enacted under the Biologics Price Competition and Innovation Act (BPCI Act) of 2009. The aim of the present study was to investigate how the health policy, the establishment of the biosimilar pathway, influenced related companies by studying their respective perspectives and strategies revealed in literatures and publicly available resources. Perspectives of companies reveal the points of concern for the biosimilar pathway, such as data requirements, patents, interchangeability, naming, and exclusivity. Innovator companies may utilize expedited programs for serious conditions, enhance patent protection, launch programs for life-cycle extension, and develop biosimilars as well. The biosimilar companies overcoming technical barriers might need to gather convincing evidence to facilitate market penetration as well as to distinguish their products from those of other biosimilar competitors. More challenges are expected for innovator companies if international harmonization takes place, which might be worth further investigation.

1. Introduction

A biological product ('biologic') is defined in the United States of America (USA) Code of Federal Regulations as "… any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man [1]." While biologicals often offer advances in the treatment of diseases, such as cancers and rheumatic diseases, the medical expenditure is a potential limitation for patients' access [2–5]. The biosimilar pathway in the USA, enacted under the Biologics Price Competition and Innovation Act (BPCI Act) of 2009, and the recently announced Biosimilars Action Plan, are expected to improve the access to biological treatments through the approval of biological products that are demonstrated to be biosimilar to, or interchangeable, with a reference product, i.e., the original or innovator biological

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product initially approved by the US Food and Drug Administration (USFDA) [5–8]. Although cost savings have not been as dramatic as expected after the approval of the first biosimilar in the USA [9], the estimated future reduction in the direct spending on biological products due to the use of biosimilars is substantial [10,11]. Therefore, the biosimilar pathway undoubtedly has great impact on innovator companies and paved a way for biosimilar companies to thrive.

Biological products are generally large molecules that are more complex than small molecule drugs with defined chemical structures [5,6,12–14]. Consistency in quality remains an essential yet challenging issue for the manufacturing of biological products [14,15]. Differences could result from manufacturing process, formulation, and environmental conditions, which may include changes in glycosylation patterns, as well as higher order structures for protein products [14,15]. While some of the differences may not be clinically meaningful, others could have an impact on safety and/or effectiveness [14,15].

In response to the challenges in the demonstration of biosimilarity and interchangeability due to the inherent complexities of biological products [5,6,12–14], the USFDA has published several clarifying guidance documents [5,6,14,16–24]. The aim of the present study was to investigate how implementation of the current regulatory framework for biosimilar products has impacted both innovator companies and those producing biosimilars through studying their viewpoints and strategies. Experience from the European Union (EU) and its influence on the USA are discussed to further inform the possible global trends.

2. Methods

The investigation was performed by the analysis of regulatory policies, guidance documents and related information for the biosimilar pathway as well as the review of related literature and opinions in the publicly available websites described as follows. The websites of the USFDA [25], European Medicines Agency (EMA) [26], and PubMed database [27] through November 9, 2018 were utilized to search for current updates of regulatory framework for the biosimilar products. In order to investigate the strategies and perspectives of related companies, the PubMed database [27] was searched and the Google search engine [28] was used to look for associated opinions. The search terms were 'biosimilars' and/or 'perspectives' or 'strategies' (last accessed on November 9, 2018). Further updates were made pursuant to reviewers' comments during manuscript revision.

3. Results

3.1. *Brief overview of the biosimilar pathway in the USA*

Pursuant to section 351(i) of the Public Health Service Act (PHS Act) [29], biosimilarity means "that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product [14]." The determination of biosimilarity involves a rigorous, comprehensive evaluation process based on 'totality of the evidence' provided by the applicants [6,14]. The USFDA has recommended a stepwise approach to collect evidence necessary for demonstration of biosimilarity to better address residual uncertainty about biosimilarity after each assessment [6,14].

The extensive investigation of biosimilarity starts with a comprehensive structural and functional characterization of the proposed product and the reference product using state-of-the-art technology [6,14]. Animal studies may be performed, which could include animal toxicity studies, pharmacokinetic and pharmacodynamic studies, and immunogenicity assessments [6,14]. Finally, clinical studies might consist of comparative human pharmacokinetic and pharmacodynamic studies, a clinical immunogenicity assessment, and head-to-head clinical studies, if necessary [14]. The scope and extent of the studies would rely on the residual uncertainty remaining at each level, which could vary on a case-by-case basis [6,14].

However, being biosimilar to a reference product does not necessarily mean that the product is therapeutically interchangeable with the reference product unless additional requirements are met [6,16]. Section 351(i) of the PHS Act [29] stipulates that "… the term 'interchangeable' or 'interchangeability', in reference to a biological product that is shown to meet the standards described in subsection (k)(4) [30], means that the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product [6,16]." Evidence to support that the proposed alternative product "can be expected to produce the same clinical result as the reference product in any given patient" [30] must be provided in addition to demonstration of biosimilarity [6,16,30]. Such data might include an evaluation of the pharmacokinetics, biodistribution, and the immunogenicity risk of the product in different patient populations [16]. The type and extent of the data depend on the product-specific characteristics and the postmarketing data for the biosimilar product [16]. Moreover, product design and user interface such as the differences in the container closure systems have to be taken into considerations as well [16].

Unlike a generic drug product, where the labeling is typically identical to that of the reference listed drug, except in certain cases where claims are still under patent coverage [31,32], the labeling of a biosimilar product may differ from the reference product in many aspects, such as having fewer indications, differences in administration, preparation, storage, or safety information [18]. The USFDA recommends the findings of safety and effectiveness for the reference product be incorporated since the approval of biosimilar products is based on the demonstration of biosimilarity with the reference product [18]. On the other hand, the information of the clinical studies used to support biosimilarity should not be included due to the possibility of misinterpretation [18].

3.2. *An analysis of the perspectives of innovator companies and biosimilar companies*

3.2.1. *The biosimilar pathway and the data requirements*

The development of biological products involves huge investment of resources [12]. The biosimilars approved through biosimilar pathway could be a threat to the innovator company [12]. The main arguments, which the innovator company generally made for differentiation from biosimilar products, were based on the inherent complexity of the biological products [33–35]. It was held that due to the complicated characteristics, the unknowns behind the biosimilar products remained to be discovered [33–35]. Comprehensive study and analyses are critical to ensure the quality, safety, and efficacy of the biosimilar products [33–35]. Therefore, innovator companies emphasized on the transparency as well as the science-based assessment regarding the regulatory approval process [33–35].

Among various considerations, the concept of 'extrapolation' has been vigorously discussed [33–37]. According to the USFDA, "extrapolation of clinical data across indications" could only be accepted with sufficient scientific justification which may include the detailed elaboration on the mechanisms of action, pharmacokinetic and pharmacodynamic profiles, the immunogenicity, expected toxicities, any other relevant and influential factors for each condition of use [14,16,17]. While innovator companies generally support the approach, they have pointed out that the special attention should be paid to the representativeness of biomarkers across different indications, the shift of safety profiles due to concurrent conditions or concomitant medications, as well as the treatment with nonlinear pharmacokinetic characteristics [35].

Meanwhile, from the perspective of biosimilar companies, the patent expirations of major biological products in the years to come could be a great opportunity for them to thrive through the utilization of the biosimilar pathway [38]. Moreover, the USFDA has made efforts to decrease regulatory uncertainties through publishing guidance documents which provide clarification on the data requirements, labeling considerations as well as the procedures for formal meetings to facilitate intensive and early communications [5,6,14,16–24]. Nonetheless, the technical barriers for the manufacturing of the biosimilars are much higher than that for generic products [12,38,39]. The cost reduction could not be as dramatic as that for generic products [12,38,39]. Moreover, market penetration of the biosimilar products is closely associated with the acceptability of health care professionals and patients, which could be challenging and dependent on the characteristics of individual products [12,38–41]. However, the reduction of health care expense is a global trend, which makes room for biosimilar products to grow [5,6,12,38–41]. In addition, some innovator companies have started manufacturing biosimilar products, which could reshape the competitive landscape as well as potentially facilitate the overall development and recognition of biosimilar products [40–42].

3.2.2. *Patents*

Unlike the reference product of small molecule drugs for which the associated patents are listed in the so-called Orange Book, the exchange of patent-related information has to be proceeded between the innovator and biosimilar companies [43,44], a process often termed the 'patent dance' [43–50]. Pursuant to section 351(l) of the PHS Act [51], once the biosimilar application is accepted for USFDA review, the biosimilar applicants should provide the application information to the reference product sponsor within 20 days. The reference product sponsor should reply to the biosimilar applicants with a list of patents regarding patent infringement, as well as the patents to be licensed to the biosimilar applicants not later than 60 days after receiving the information. If mutual agreement can't be reached, there could be patent infringement actions. In addition, the biosimilar applicants should provide notice of commercial marketing to the reference product sponsor "not later than 180 days before the date of the first commercial marketing" while the reference product sponsor may respond by seeking a preliminary injunction.

However, the process is often not as smooth as one might hope, which is demonstrated by the approval of the first biosimilar product, Zarxio, under the BPCI Act of 2009 [43–50]. The applicant of the biosimilar product, Sandoz, refused to provide related regulatory or manufacturing information to the reference product sponsor, Amgen, and Sandoz was supported by the Federal Circuit determining that the 'patent dance' was voluntary [43–50]. However, the Federal Circuit Court ruled against Sandoz by holding that the notice of commercial marketing should be sent after approval [43–50]. Finally, the Supreme Court ruled in 2017 that the notice could be sent either before or after the approval [50]. Meanwhile, the development of an enhanced Purple Book, including information on exclusivity, has begun according to the recently announced Biosimilars Action Plan [8]. The impact deserves further observations.

3.2.3. *Interchangeability*

As mentioned above, innovator companies stressed the complexity of the biological products and pointed out the difficulties in establishing the comparability between reference products and the corresponding biosimilar products [33–35]. As for the demonstration of interchangeability, the level of concerns expressed by the innovators was undoubtedly higher [33–35]. Generally, innovator companies hope that the reference product can be clearly differentiated from the biosimilar so that health care professionals and patients can be fully informed about the therapeutics they are using [33–35]. From the innovator company's perspective, the biosimilar products could never be the same as the reference products so that they could only be referred to as biosimilar products instead of biogeneric products [33–35]. Switching between reference and biosimilar products could potentially pose additional risks on patients [33–35]. Therefore, rigorous standards for granting interchangeability to biosimilar products are anticipated, which are recently addressed in a USFDA draft guidance document [16,33–35].

Despite increased clarification of regulatory standards, many challenges remain for biosimilar companies to overcome. Technical barriers for demonstration of interchangeability are high and the acceptance of health care providers and patients may not be easy to attain [52]. Thimmaraju et al. have suggested that biosimilar companies may need to make

efforts on gathering compelling evidence to prove comparability, such as results from pharmacovigilance studies, to facilitate market penetration [52].

3.2.4. *Naming*

The USFDA has recently detailed in a guidance document about their current thinking on the nonproprietary naming convention [24]. For both newly licensed and previously licensed originator biological products, related biological products, and biosimilar products, a distinguishing suffix composed of four lowercase letters should be attached with a hyphen to the core name to form a proper name [24]. For example, the proper names for biosimilar products approved before November 9, 2018 with the core name filgrastim include filgrastim-sndz and filgrastim-aafi [53]. The measure is expected to aid in accurate identification of the concerned biological products and to minimize the potential for inadvertent substitution of these products which have not been designated as interchangeable [24].

Nonetheless, the differentiation was considered insufficient by some of the innovator companies [35,54]. They, as well as physician groups and some patients, were inclined to have biosimilar products to be assigned unique nonproprietary names [54]. On the other hand, the biosimilar companies worried about the consequences of the differentiation which would impede the marketing penetration of their biosimilar versions [54].

3.2.5. *Exclusivity for the reference product*

At the time when the BPCI Act of 2009 was about to be enacted, there was vigorous discussion for the period of data exclusivity and market exclusivity [55–57]. Optimal exclusivity time is critical to ensure a balance between innovation and price competition [55–57]. It has been estimated that the break-even lifetime for the reference product would be between 12.9 years and 16.2 years [55], based upon which the president of the Biotechnology Industry Organization (BIO, now Biotechnology Innovation Organization) recommended a 14-year exclusivity for reference products [57] and after which, the legislation granted an exclusivity period of 12 years [23]. The relevant text of the statute states that the licensure of an application for a biosimilar or interchangeable product may not be made effective by the USFDA until the date that is 12 years after the date on which the reference product was first licensed under the PHS Act [23] and that the application may not be submitted to the USFDA for review until 4 years after the date of first licensure of the reference product [23]. The period of 12 years is considerably longer than that for a new chemical entity reference product (reference listed drug or RLD) which offers 5 years as described in 21 CFR 314.108 [58]. The more complicated nature, as well as much higher level of technical complexity and investment, support this longer period of exclusivity [12]. Nonetheless, whether there would be a reassessment for the length in the near future is worth paying attention to.

3.2.6. *Possible strategies for innovator companies and biosimilar companies*

Being faced with the inevitable competition from biosimilar products, the innovator companies are likely to apply multiple strategies to overcome the challenges, such as exploiting expedited programs for serious conditions (if applicable) [59], enhancing patent protection [40,41], and launching programs for life-cycle extension which may include repositioning of the original product and product improvement [40,41]. Meanwhile, as revealed in the comments made on various issues discussed in the previous sections, the innovator companies make efforts to stress product differentiation, such as the arguments regarding the uncertainty remained even after comprehensive comparison, the representativeness of biomarkers used to support extrapolation, the concerns on the interchangeability, and the insufficiency of the distinguishing suffix in the name of biosimilar products [33–35,54]. For biosimilar companies, as mentioned earlier, they may need to gather convincing evidence from pharmacovigilance studies to facilitate market penetration [52]. Moreover, differentiation from other biosimilar products may be achieved by the superiority in characteristics such as better stability profile and less painful injections [39].

Some innovator companies have started to take on dual roles, which may diminish the impact from the competition of biosimilar companies [40–42]. Since the innovator companies have established production capacity with in-depth technical knowledge and abundant experience, the technical barrier is relatively easy to overcome [40–42]. Meanwhile, careful pipeline strategy would need to be in place so as to not interfere with the capacity for developing innovative products [40].

3.3. *A comparison of the biosimilar regulatory pathways in the USA and the EU*

Long before the BPCI Act was enacted, the regulatory pathway for the approval of biosimilar products (similar biological medicinal products) has been established in the EU in 2003 [60,61]. Prior to November 9, 2018, 50 biosimilar products were authorized in the EU and 14 biosimilar products were approved under the BPCI Act in the USA [53,62]. Like the regulatory considerations stated by the USFDA, comparability studies are also required to demonstrate the similarity between the biosimilar product and the reference product in terms of quality, safety, and efficacy [60,61]. Similarly, a stepwise approach starting from a comprehensive physicochemical and biological characterization is recommended by the EMA and the level of evidence obtained from previous step(s) could serve as a guide for the determination of the extent and nature of the following studies, such as nonclinical and clinical ones [60,61]. Applicants are encouraged to discuss with regulatory authorities if simplified approaches are to be used [61]. While the considerations in demonstrating interchangeability have been proposed by the USFDA [16], the substitution policies depend on each EU member state [61]. In addition to the publication of general considerations, the EMA has published product-specific biosimilar guidelines detailing the product class-specific considerations such as the recommended nonclinical and clinical studies [61,63–72].

As for the naming for biosimilar products in EU, the criteria are the same as those for any other medicinal products [63,64]. Therefore, a single name using an invented name or a common name or scientific name, together with a trademark or

the name of the Marketing Authorization Holder may be utilized [63,64]. Herein, a common name refers to "the international non-proprietary name (INN) recommended by the World Health Organization, or, if one does not exist, the usual common name" [63,64]. In the EU, the same nonproprietary name for the biosimilar product is used without the addition of distinguishing suffix as mentioned in the guidance document published by the USFDA [24,63,64]. Besides, the exclusivity period is at least 10 years depending on the protection period applicable for the reference medicinal product [73]. Although the process like 'patent dance' is not used in the EU, patent litigation process is also a barrier for the entry of biosimilar products, which could be different in each member states [43]. Therefore, the reference product and/or the biosimilar product manufacturers may need to consider various factors, such as the primary target market, the place for manufacture, before initiation of the litigation process [43].

Despite that the USA established the biosimilar pathway six years later than the EU, the USA pathway is unique in many ways as mentioned above [60]. After the approval of the first biosimilar product in 2015, there are more to come and the market acceptance is worth observing [45]. The development of biosimilar products seems to be global trend [60]. Although scientific approaches and overall concept may be analogous, the regulatory framework and the market characteristics could vary, which could be an obstacle for biosimilar product development [60]. Since the regulatory pathway is still new for many countries, international harmonization might be difficult nowadays [60]. Nonetheless, while more experience is obtained in most countries, especially in stringent regulatory authorities, harmonization might still be possible, which may bring another impact on the innovator companies.

4. Discussion

While reducing health care expenditure and improving patient access for biological products are imperative, the encouragement of the development of biosimilar products is unavoidable despite the complex nature of biological products. Extensive comparative studies based on stepwise approaches are fundamental and widely recognized by regulatory authorities for demonstration of biosimilarity [6,14,60,61]. Although many studies evaluating the comparability of clinical outcomes are still ongoing, studies have demonstrated promising results with comparable safety and efficacy profiles at lower cost [74–78]. For example, a systematic literature review of 90 switching studies for 17 disease indications did not show significant difference in treatment-related safety events and loss of efficacy due to switching from the original or innovator biological products to their biosimilar counterparts [74]. These findings may support the principal concept for developing biosimilar products and the current rationale for the assessment, although more evidence is still required.

Despite that the biosimilar pathway poses a threat to the innovator companies, the innovator companies are still able to defend through product differentiation from biosimilars. Meanwhile, they may make the most of the expedited program to accelerate market entry as well as their production knowledge and capacity to develop biosimilar products so as to mitigate the impact of the competition from biosimilar companies. Among 81 development programs for biological products approved by the Center for Drug Evaluation and Research (CDER), USFDA between 2003 and 2016, more than half of them have utilized the expedited program [79]. Regarding life-cycle management, many innovator companies have successfully improved their products, such as a facilitated mode of administration for Rituxan Hycela in comparison with Rituxan, a longer-acting type like Aranesp in comparison with Epogen [80].

Although the biosimilar pathway creates opportunities for biosimilar companies [5–8], the US biosimilar market seems not yet as flourished as expected [81,82]. The suboptimal development has been attributed to the more challenging and costly nature of manufacturing, which also led to a limited amount of companies specifically targeted at developing biosimilar products [81]. Other reasons included complicated 'patent dance' process, the case-by-case regulatory considerations regarding the data requirements to address the uncertainty in biosimilarity, patent litigation issues, skepticism from health care professionals and patients, as well as other marketing barriers [81]. On the contrary, the market penetration and acceptance in the EU were greater than that in the USA, although they could vary across different EU countries [81,82]. Despite that the US biosimilar market may not thrive at the beginning, the potential is still anticipated [81,82]. After more research findings for comparability studies and the postmarketing surveillance studies are available, the public perceptions of biosimilar products may improve. Data requirements for demonstration of biosimilarity could be more clarified and mutually accepted by regulatory authorities and applicants after more products are reviewed. The enhanced Purple Book with more information on exclusivity is expected to promote transparency, which may simplify the process of 'patent dance' and may as well reduce litigation burden. Moreover, although international harmonization may be challenging for the time being, the trend is expectable. The USFDA has actively taken steps to foster international harmonization for generic drugs [83], which may have revealed the future trend for biosimilar products.

5. Conclusion

The ultimate goal of the health policy is to improve the welfare of citizens by establishing a sound system. The biosimilar pathway in the USA aims at striking a balance between the innovation and the reduced expenditure for biological products without compromising quality, safety, and efficacy. The analysis of the perspectives and/or strategies of the innovator companies and the biosimilar companies show the opportunities and challenges brought by the biosimilar pathway. Although long-term effects of the biosimilar pathway need further observations, the experience of the EU may have given a clue while the potential international harmonization may bring further changes warranting more investigation.

Conflicts of interest

The author declares that there are no conflicts of interest.

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