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COMMENTARY

Copies of Biological Medicines: Similar But Not the Same?

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1 Introduction

Therapeutic proteins continue to improve the treatment options in several disease areas. In addition, cell and gene therapies are moving into the clinical praxis and open new therapeutic approaches to serious diseases. Unfortunately, the rising costs of these therapies will endanger the sustainability of future pharmacotherapy and restrict patients' access to life-saving medicines even in wealthy countries. The prices of biotherapeutics remain high even after the expiry of data and patent protection. There are several reasons for the high price levels of biologicals, mostly related to a lack of competition, such as the inability of payers to affect price competition, the lack of competitors, aggressive pricing practices, and anti-competitive marketing practices [1]. For the chemically synthesized medicines, this problem was partly solved by price competition triggered by generic medicines. Copies of biotechnology-derived therapeutic proteins aim to achieve the same effect in the market of biologicals [2]. The copy biologicals include biosimilars developed according to the World Health Organization (WHO) guidelines and a heterogenous group of products that have been licensed mainly in low- and middle-income countries [3, 4]. The latter group of products has several different names that may not always cover the same set of products [3]. In this article, "copy biologicals" cover all non-innovator products, "biosimilars" mean products (copy biologicals) that were licensed according to the WHO biosimilar guidelines, and "non-biosimilars" mean other copy biologicals.

2 Evolution of Regulatory Guidelines for Biosimilars

The European Medicines Agency published its first guideline for similar biological medicinal products, later called biosimilars, in 2006 [5]. This guideline, its revisions, and topic-specific guidelines are based on analytical, functional, and clinical comparability studies that are also used in the context of manufacturing changes of biologicals [6]. The same principles were later adopted in guidelines issued by several national regulatory agencies [7]. Biosimilars developed according to these guidelines have been shown to be safe and efficacious [8] and data on the scientific evaluation of these products are available in the public domain. The WHO issued its guidelines in 2009 [9]. It is expected that countries will use this guideline as a template when drafting their national guidance for assessment and development of biosimilars. The WHO insists that only copy biologicals developed according to these guidelines should be called biosimilars. In Europe, biosimilars have increased the access to biotherapeutic products by providing more affordable treatment options [10]. Unfortunately, the competition has remained modest so that biosimilars are still not affordable for low- and middle-income countries.

3 Non-biosimilar Copy Biologicals

Therefore, low- and middle-income countries have licensed more affordable copies of biotherapeutic products that do not or may not fulfill the requirements of WHO guidelines. Data of these products are scarce in the public domain. The WHO has monitored the adoption of its biosimilar guidelines and the presence of products that do not or may not meet the current guidelines by questionnaires to 20 countries [3]. According to the WHO, some regulatory agencies do not or have previously not required adequate comparability studies from the copy biotherapeutics in the local markets. Instead, some national regulatory agencies have chosen a generic pathway designed for chemical medicines [11].

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Nevertheless, there is slow progress towards harmonization of the regulatory requirements, which means that more and more future copy biologicals will be genuine biosimilars. In the latest update, WHO experts reported 264 non-biosimilar copy biologicals in six countries that disclosed the data [3]. Kang et al. also found that some countries still license both biosimilar and non-biosimilar products [3].

4 What is Known About Non-biosimilar Copy Biologicals?

The article of Klein et al. [4] in this issue of *BioDrugs* describe a cross-sectional overview of copy biologicals approved in 15 countries from different regions of the world. The authors retrieved data from different public sources. The authors focused on active substances for which there are licensed copies of originator products, WHO-type biosimilars, or non-biosimilar products. They found 304 copy biologics from different manufacturers for the 18 active substances included in this study. Of these 304 copy biologicals, 67 (22%) are approved as a biosimilar in at least one of the five major biosimilar markets used as a reference (European Union, USA, Canada, Australia, and Japan).

According to Klein et al. [4], some of the remaining 237 (78%) follow-on biologics could not have been developed according to the WHO guideline because they were either licensed before publication of the guideline or before the licensing of the first biosimilar in the European Union in 2006 or even before the licensing of the originator product. In addition, some of these products failed to be licensed in the "highly regulated" ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) countries adhering to the WHO-type biosimilar development. Finally, some products were licensed via the generic pathway designed for chemical drugs. The number of non-biosimilar copy products is an underestimate in studies of both the WHO and Klein et al. because of limited sets of countries that were investigated and limitations of the methodologies [3, 4]. Klein et al. [4] found that of the 304 copy biologicals, the majority are manufactured in India (78 [25.7%]) and China (62 [20.4%]), followed by Russia (25 [8.2%]), South Korea (25 [8.2%]), Iran (23 [7.6%]), and Argentina (20 [6.6%]). Furthermore, only seven follow-on biologics from India and one from China are approved as biosimilars in any of the five major biosimilar markets. The WHO report also mentioned Ukraine as a developer of non-biosimilar copy biologicals [3]. Most non-biosimilar copy biologicals that have not been licensed in the five main markets are manufactured and used in the same country. Only 20% are used in at least two other countries whereas only a few have a wider market distribution [4].

5 What to Do with Non-biosimilar Copy Biologicals?

Klein et al. [4] refer to reports of quality and safety problems of non-biosimilar copy biologicals. They also argue that the insufficient knowledge of the non-biosimilar products and their manufacturers muddles the monitoring of copy biologicals and is a potential public health issue. Retrospective conversion of the non-biosimilar products to the WHO format is neither realistic nor necessary. Instead, the WHO has urged the relevant regulatory agencies to request certain quality and safety data from the manufacturers. This project has progressed relatively slowly, partly owing to the unwillingness of the manufacturers to provide such data [3]. Klein et al. [4] propose further studies that would focus on licensing data of the non-biosimilar copy biologicals. They propose that the WHO could supervise such studies. Transparency in the regulatory decisions is laudable. It is also important that the ongoing transit to WHO biosimilar guidelines is monitored. Obviously, such a study would demonstrate non-compliance with at least some requirements of the WHO guidelines. Such data may be politically and legally sensitive as the grounds of the licenses of copy biologicals may be challenged [12]. Removal of these products that have been used several years without unexpected serious adverse effects from the market of low- and middle-income countries before they have access to reasonably priced biosimilars would certainly be risky from a public health perspective.

6 The Way Forward

Adoption of WHO guidelines is only the first step of national regulatory agencies towards ensuring high quality biosimilars in their market. The WHO is monitoring and facilitating this process and has found promising progress [6]. Klein et al. [4] demonstrated that the proportion of products developed according to the WHO guidelines is increasing. They suggest that the interest of manufacturers in following the WHO guidelines will further increase when the guidelines are more widely adopted. The WHO guidelines have been criticized for unreasonable requirements that go beyond the resources of small manufacturers [12]. This has led to a situation in which the biosimilar market is dominated by large pharmaceutical companies that are unwilling to enter into price competition. The WHO has now revised its guidelines in to simplify the requirements and increase flexibility [8]. The most important changes are the abandoning of routine animal toxicology studies and widening the criteria for waiving the

large clinical efficacy and safety studies. These changes will make development cheaper and faster, which should attract new manufacturers to develop biosimilars.

Thus, national regulatory agencies need to be prepared for increasing licensing applications by manufacturers who may not be familiar with the state-of-the art biosimilar development. Training efforts by the WHO alone will not be sufficient. Reliance/mutual recognition and regional collaboration are encouraged as small agencies may not have enough resources in the foreseeable future. Direct recognition of the regulatory assessments by the major regulatory agencies, notably the European Medicines Agency and the US Food and Drug Administration, may not be possible because of the differences as compared with the WHO guidelines. However, public assessment reports, especially their analytical and in vitro functional comparability parts would provide a valuable source of information. Establishment of proper pharmacovigilance is essential in monitoring the safety of original and copy biologicals [3].

7 Conclusions

The WHO should continue to monitor the adoption of its biosimilar guidelines. Increased transparency of the decisions to license copy biologicals by national regulatory agencies would reduce the suspicions regarding the quality, safety, and efficacy of copy biologicals. Increased regional and international collaboration and reliance/mutual recognition are necessary to ensure sufficient expertise in the evaluation of new biosimilars, especially with regard to analytical and in vitro functional comparability. The WHO should promote the benefits and opportunities provided by its revised guidelines to manufacturers and national regulatory agencies who have previously manufactured and licensed non-biosimilar copy biologicals. There is now a momentum for harmonization of regulatory requirements and for increased access to safe and affordable copy biologicals in low- and middle-income countries.

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