



Review Article

Biosimilars: Review of regulatory, manufacturing, analytical aspects and beyond

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ABSTRACT

Biologics have more complex production processes compared to small-molecule drugs. They may even prove labile when drifting from batch-to-batch or in different production locations. The development of new similar biological product was regulated early to face the relevant challenges of this industry. As a result, since 2006 biosimilars were introduced to biotechnology arena with a massive competition in pharmaceutical industry. In this review, the aspects related to similarity testing of biosimilars to the original biological products are discussed involving manufacturing challenges to ensure the quality, safety, and efficacy of these products to the patient health. Immunogenicity studies are highlighted as an important part of the safety assessments. Additionally, several analytical methods that are usually used to evaluate biosimilars in comparison to their reference biologic are summarized and categorized in terms of the intended physicochemical and biological characterization. On the other hand, the international efforts of several regulatory agencies including the European Medicines Agency, World Health Organization and United States Food and Drug Administration for biosimilar development are discussed according to updated revised guidelines.

1. Introduction

Biopharmaceuticals patent expiration opened the door to tremendous competition between pharmaceutical companies worldwide. Economically, the global market value for biosimilar is continuously growing and is expected to rise by about 25% by 2026 compared to the value in 2020 [1]. Among others, monoclonal antibodies are considered the highest selling class of biopharmaceuticals [2]. Since their introduction more than a decade ago, biologics have shown high contribution in therapies of several serious diseases such as cancer, crohn's disease, turner syndrome, diabetes, and rheumatoid arthritis. As such, some of the innovator biologics are scheduled to come off patent license. Actually, pharmaceuticals that contain small drug molecules have relatively simple structures in terms of their active substances. Thus, identical copies of patents, which are known as generic, can be easily achieved. The approval of these generic drugs depends on the equivalent proof

compared to the reference drug product [3]. This abbreviated approval eliminates the costly clinical trial of drug development and allows manufacturers to provide small molecule generics at a lower price [4]. Biopharmaceuticals have a totally different pathway. They are developed using living cells, such as blood and plasma products, vaccines, recombinant proteins, and monoclonal antibodies [3]. Therefore, the active substance in biological medicine is not only one molecule but an entity population of different molecules reach to several hundreds of small molecules (Fig. 1). Manufacturing of these large molecules is subjected to unintended changes or drift during manufacturing processes such as batch-to-batch variability, a change in characteristics, strength, and purity. Producing a new identical copy of these kinds of medicines cannot be achieved [5].

Herein, biosimilar was born to be an alternative term for "bio-generic" medicinal product whereas it is defined as a similar copy of officially registered reference biological product [6].

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