Biogenerics: how far have we come?

Introduction

Biopharmaceutical products began to expire since 2004. This has resulted in the development of biogenerics as second generation products. The term biogenerics is used to define a product that is equivalent to a currently marketed biopharmaceutical product that is a recombinant DNA-derived product (Enrico and Little, 2001 and Chamberlain, 2004). Biogenerics are follow-on products of a brand (reference) drug. They may have different physicochemical and/or biological properties to the reference drug, however, they are expected to have similar clinical effects and safety profile when compared to the reference drug. This may be because they may contain the same active ingredient used in the original brand product (Chamberlain, 2004 and Kirmani and Bonacossa, 2003). However, they may have different excipients of non-active ingredients to the original brand drug (Kermani and Bonacossa, 2003).

Biogenerics are found to be beneficial in aiding large companies in saving the large amount ofmoneybeing spent onhealthcare when prescribing a brand product. For example, in 2005, around 5. 3 billion dollars has been spent on health care in which almost of 2 billion dollars of this was spent on prescription drugs (Fredrick, 2007). The similar quality, safety, efficacy and the reduced cost of biogenerics compared to the reference brand product have arisen the interest of developing biogeneric products in oncology. However, there are a number of regulatory, developmental, and manufacturing barriers associated with the generation of biogenerics. Such issues are the lack of specific regulatory guidelines for biogenerics. Having regulatory standards may avoid the large sum of money from being spent to

develop a biogeneric file (Enrico and Little, 2001). However, having eligible abbreviated procedures for biogenerics is not solving the issue as the Committee on Similar Biological Medicinal Products (CHMP), 2005, has recommended the need of carrying out comparability studies in order to generate evidence of the similarity in quality, safety and efficacy of biogeneric products to the original branded products (Rathore, 2009). Unfortunately, studies have failed in proving biogenerics essential similarity to the original brand products already being marketed (Kermani and Bonacossa, 2003).

Furthermore, biogenerics are protein products in which their complexity is the central to challenges associated with safety and efficacy (Enrico and Little, 2001). Biogenerics are heterogeneous products and may exhibit sensitivity towards a specific manufacturing process and may degrade during freezing, melting, formulation, sterile filtration, filling, freeze-drying, and assessment. Moreover, the presence of impurities during manufacturing processes may reduce the efficacy and increase immunogenicity of the product. Immunogenicity may also be affected when handling the product. This may occurs during purification, exposure to light, distribution, or adding excipients, or may be due to the route and frequency of administration (Rathore, 2009).

Since such changes may result in alteration in the product quality, safety, and efficacy profile, the need of carrying out extensive clinical trials are important in order to achieve regulatory approval (Enrico and Little, 2001). Also, other factors such as the therapeutic target, and patient’s immune

status and clinical condition may be used in determining the immunogenicity of the product (Rathore, 2009).

The quality of a biogeneric product is not only affected by the variability between the different steps of manufacturing, but may also be affected by the inconsistency of the starting materials (Kirdar et al, 2008). For example, minor changes in manufacturing biogenerics, such as the use of different DNA vectors, cellcultureand purification processes compared to what is being used in the original brand product may result in undesirable effects in the quality of the product (Sharma, 2007).

Also, leachable of vulcanising agents from syringes may affect safety and efficacy of the product. The use of phthalate plastic and latex rubber surfaces may result in leaches which may contaminate the product resulting in allergic reactions and enhanced immunogenicity. Therefore, it may be safer if glass surfaces, air-liquid interfaces, and lubricants are used instead (Sharma, 2007).

The high complexity of the products, processes and untreated materials are the key challenges in manufacturing. However, having a designed experiment process to carry out experiments and perform data may result in better quality products (Rathore, 2009).

Moreover, the interest of customers including patients and healthcare professionals to biogeneric products may also act as a potential barrier. The majority of biopharmaceuticals available in the marker are indicated for chronic diseases, for example cancer, in which switching the patient into a biogeneric product may be unacceptable by healthcare professionals. This

may be due to the insufficient evidence of biogenerics quality and the lack of policies relating to such products (Enrico and Little, 2001).

The majority of generic medicines depend on the clinical trial data obtained from the original brand drug studies. Only simple tests are required though for these generic medicines to prove bioequivalence of the product quality, safety, and efficacy to the reference drug. However, biogenerics failed in proving bioequivalence to the original brand drug using simple tests, hence, more studies may be required for biogenerics approval (Miller, 2009).

Miller, 2009, has stated that the nature and the percentage contamination of biogeneric product is mainly relates to the host systems used to generate the drug and the purification methods used. A 100% purity is unachievable, however, avoiding any source of purity limitation may result in a high quality product. But this does not solve the problem, as protein folding and enzymatic modifications may lead to unacceptable results.

Also, biogeneric mechanism, toxicity and contamination human cells are unknown. Therefore, the need to carry out standard sophisticated screening tests or the use of animal studies to ensure drug purity and quality may be necessary (Miller, 2009). Moreover, the FDA stated for a biogeneric to be approved, once bioequivalence tests are successful, safety and efficacy tests are required. This may involve sophisticated analytical chemistry, preclinical (animal) studies, as well as clinical studies (Miller, 2009). However, it is unacceptable to expose patient to unnecessary clinical trials in order to get the approval, and that bioequivalence tests must be decided on a case-by-case basis (Fredrick, 2007). The Coordinated Framework for Regulation of

Biochemistry, FDA, 1986, stated that new marketing applications are required for biogeneric products. This may be due to that biogenerics are characterised by having different structures, heterogeneity, and the possibility of contamination availability, which may affect the safety and efficacy profile of the drug.

Biogeneric products may be better if developed in big pharmacy companies rather than a start-up company. This is may be because big companies may already have the experience and resources to carry out the necessary testing. Hence, less money will be spent to develop biogenerics in big pharmacy companies compared to a start-up company (Miller, 2009).

Since cancer treatments are very expensive, focus has been shifted on producing biogenerics that would control the large sums of money being spent in biologic cancer treatments. However, it is important to ensure that patients get high quality of care and evidence-based medications. Therefore, principles of approval of biogeneric use in oncology have been published. The principles state the need of clinical trials being carried out to order to test similar efficacy, safety and immunogenicity of biogeneric to the reference biologic drug. This would clear the essential processes to patients and healthcare professionals. Guidance documents may be necessary in order to ensure standards consistency. However, FDA would never accept a system that would limit clinicians' choices amongst biogeneric products. Biogenerics must be of high quality and fully tested for efficacy. Interchangeability of biogenerics that allows substitutions without affecting the product safety and efficacy must be determined through clinical trials (American Society of Clinical Oncology, 2007).

The key issue of scientific and regulatory approval of biogeneric products is the lack of understanding of how different quality aspects of a product may result in changing the product safety and efficacy. Also, the lack of being successful in collecting data, analyze and report, and the insufficient non-clinical tools which may help in predicting clinical safety and efficacy of the product. Moreover, the complexity of biogeneric products and the biotechnology processes are extra challenges added to the development of biogenerics (Rathore, 2009).

Finally, biogeneric guidelines are still unclear. However, the European Medicines Agency (EMEA) has decided the future of biogenerics will still require a comparability studies between the biogeneric and the reference brand drug. It may be possible that clinical studies will be carried out instead of bioequivalence studies for the purpose of proving the safety and efficacy of the biogeneric drug, and in particular immunogenicity of the product. Moreover, less non-clinical studies might be carried out and post-market pharmacovigilance plans may possibly be needed as a measurement of authorization promises (Zuniga and Calvo, 2009).

In conclusion, the decision on approving biogenerics will remain to be dealt on a case-by-case basis, and will rely on a number of different factors including manufacturing processes, structural similarity to the original product, mechanism of action, pharmacodynamic assays, pharmacokinetics and immunogenicity, and quantity and quality of clinical data. Even though, the major improvements in our knowledge on biogenerics production processes and analyticaltechnologyhave been achieved, key barriers remain

to hinder the development of biogenerics. However, the overall ofscienceand biotechnology fields is rapidly developing (Enrico and Little, 2001).

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