
Preface

The biological medicinal products' market has considerably expanded since 1998. The worldwide sales for these types of medicines have increased much faster than other types of medicines—12 % on average between 1998 and 2007 versus only 4 % for the sector beside biological medicinal products. The share of these in the global market will have risen from 10 to 15 % between 2007 and 2012, according to IMS (*Intercontinental Marketing*¹ lists 633 biological medicinal products are being developed worldwide to treat more than 100 diseases; including: 254 drugs developed for cancer; 162 for infectious diseases; 59 for auto-immune diseases and 34 related to HIV/Aids pathologies).

Numerous recombinant proteins are currently in the public domain after expiration of the patents that protected them, thus they are an interesting target for classic generics companies. If the pressure put on by institutions that provide payment services and a simpler licencing process have contributed to their very large development, then the difficulty to develop copies of biotechnological products could be a factor of weaker progression.

The term “generic medicinal product” is used to describe a medicine that has an active substance made of a small, chemically synthesised molecule with a well-known structure and a therapeutic action equivalent to the original product's. Generally, the demonstration of bioequivalence with a comparator through bio-availability studies is enough to deduct the therapeutic equivalence between the generic and reference medicine. This approach is not considered sufficient for the development, evaluation and approval of a biological medicine claiming its similarity to a reference medicine because of the molecular complexity and the difficulty to characterise active structures. On top of that, efficacy and therapeutic safety may be influenced by the biological source and the manufacturing process. Clinical studies are therefore necessary to demonstrate the efficacy and safety of these copies. As these copies are not identical to their originator but only “similar”, they are called “biosimilars”, as a contraction of the official European designation of “biological medicinal product similar to a reference biological medicinal product.” Other designations can be found in the literature as “biogenerics” but this term can not be retained because of the “only similar” feature that

¹ IMS Health analyse Développement and Conseil, juillet 1998.

a copy may have. In the U.S.A., the term *follow-on biological product* (FOBP) is used to designate the copies of bio medicinal products. The World Health Organisation (WHO) uses the term *similar biotherapeutic product* (SBP) to designate biosimilars.²

The purpose of this book is to show how biosimilars are developed, what the criteria and aspects that are taken into account for their licencing are, how patients safety is preserved, what it is about the particular angle of immunogenicity, what response must be considered concerning substitution and interchangeability of these products, what particular follow-up must be implemented (in terms of pharmacovigilance and traceability) and what the perceptions of the players, prescribers and dispensers of these products are. Biosimilars are medicines destined to be present in doctors' therapeutic tool box. Then, this book tackles the certain aspects of strategies underlying the use of biosimilars and the resulting medical responsibility, if this latter may ever be particular for this new type of medicine.

This book limits itself to the analysis of European licencing of biosimilars as it is currently on a worldwide basis, the most advanced regulation since the first 2001 guidelines that allow with time to build constructive supports designed to help industrialists or companies to develop biosimilars.

The marketing of biosimilars is characterised by many more barriers than for generics; that is to say, developments necessary in order to master their manufacturing and their quality, safety and efficacy evaluation. The biosimilars market has induced high development costs, and higher risks; it needs a longer development time and an expertise related to the clinical development of these products. Biosimilars development strategies are not the same as those of generics. Their development complexity as well as their production costs will favour companies with significant financial resources, experience in the field of biological medicinal products production and even an expertise in marketing innovating products.

In relation to biological medicinal products development costs, the average cost of treatment per patient for this category of products is much higher. Worldwide, 7 medicines of the "top 10" sales will be in 2014 products of biological origin and their individual cost will comprise between 10,000 and 100,000 Euros per person. The appeal of the marketing of copies similar to the original product ensuring the same level of quality, safety and efficacy is obvious for the organisations that provide payment services, as well the as the patients with incomplete or no coverage. However, because of the complexity of the development and production of biosimilars, a reflection on the necessary reduction of these products' costs is needed. Will this reduction be as significant as for generics?

To the effect of the cost less attractive for biosimilar prescriptions may be added a stronger reluctance to use biological products (in their vast majority) that only

² Medicines in development. Biotechnology. Billy Tauzin. 2008 Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs). WHO/BS/09.2110. Source: EP Vantage June 2009; Evaluate Pharma: World preview 2014, report.

specialists could master. The statute of prescription and dispensation of biological medicinal products is subject to international regulations based upon international studies that often underline the complexity of their use and of patient follow-up. Biosimilars do not escape from these rules and obligations. Consequently, it is important for the doctors who are in charge of treating patients with biological medicinal products to know the respective contributions of each available medicine, whether it is a reference product or biosimilar. This book is aiming at simplifying the approach of products as complex as biosimilars. To do so, it reminds the reader:

- the complexity of biotechnology products and their mode of production;
- factors of safety for their approval application and their marketing authorisations;
- the risk analysis and possibilities of interchangeability;
- the French authorities' interdiction of substitution of a prescription by the pharmacist;
- the analysis of the rules laid down by some learned societies or professional associations, for a better follow-up and a better prescription of biosimilars.

Today, thanks to a centralised and specialised European licencing process, the number of biosimilars that got their marketing authorisation is limited but advanced when compared to some countries, like the United States or Japan. In some other countries, some companies offer copies of biotechnological products without having to apply for approval based on an approach equivalent to that of Europe. Currently, Europe is essentially concerned by the growth hormone haematopoietic growth factor G-CSF (*Granulocyte Colony Stimulating Factor*) and erythropoietin. The next approval applications should be affected by the arrival of copies of other therapeutic proteins like insulin, interferon α and monoclonal antibodies. Similarly, copies of medicines other than therapeutic proteins should reach the biosimilars market, such as fragmented heparins; for which a recommendation by the licencing authority has been published. This sector of medicine is thriving. It requires a professional's deep knowledge in order to maintain the quality and the safety of patient treatments.

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Biosimilars

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