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Biosimilars: from Technical to Pharmacoeconomic Considerations

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Abstract – A biosimilar is a biological medicinal product claimed to be similar to a reference biological medicinal product. Its development plan includes studies comparing it with the reference product in order to confirm its similarity in terms of quality, preclinical safety, clinical efficacy, and clinical safety, including immunogenicity. Biosimilars differ from generics both in their molecular complexity and in the specific requirements that apply to them. Since patents on many biological medicinal products will expire within the next 5 years in major therapeutic areas such as oncology, rheumatology and gastroenterology and as those products are so costly to the French national health insurance system, the availability of biosimilars would have a considerable economic impact. The round table has issued a number of recommendations intended to ensure that the upcoming arrival of biosimilars on the market is a success, in which prescribing physicians would have a central role in informing and reassuring patients, an efficient monitoring of the patients treated with biologicals would be set up and time to market for biosimilars would be speeded up.

Abbreviations: see end of article.

† Articles, analyzes and proposal from Giens workshops are those of the authors and do not prejudice the position of their parent organization.

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1. Introduction

Biosimilars became a topical issue and a matter of public interest in France in September 2013 when an article in the 2014 French Social Security Finance bill introduced the principle of substitution by pharmacists for biosimilars. Having previously received relatively little attention, biosimilars suddenly became a hot topic, with public authorities, industry representatives, academics and the media, all rushing to discuss the scientific issues and the potential value of biosimilars in containing escalating health costs. In this controversial climate, the 2014 Giens meeting dedicated one of the round tables to address both the scientific and economic aspects of biosimilars, listening to the points of view of all interested parties, in order to propose a series of balanced recommendations to help ensure that the upcoming arrival of biosimilars on the French market would occur under optimal conditions. In the first part of this article, we describe the regulatory definition of a biosimilar, an important prerequisite for understanding the subject: this definition was proposed to make a clear distinction between copies of chemical medicinal products (so-called generics) and copies of biological medicinal products (so-called biosimilars). This distinction has consequences for the development of biosimilars, which we set out in the second part. We then address the economic aspects: general financial issues, the problems surrounding market access in France, and the conditions required for successful biosimilar market uptake, drawing on the lessons learnt from previous experience with introduction of the generics for chemical medicinal products. The article concludes with our five recommendations.

2. Definitions, origin of the concept of biosimilar medicinal products

A biosimilar is a biological medicinal product claimed to be similar to a "reference" biological medicinal product,[1] the quality, safety, and efficacy profile of which has been proved, through an appropriate development plan, to be "similar" to the profile of the reference product. Because a copy of a biological molecule can only be similar, rather than strictly identical to the reference product, due to differences in the biological source and the manufacturing process, it is called a "biosimilar", a contraction of the official term given in Article 10 of European Directive 2001/83/EC:[2] "biological medicinal product which is similar to a reference biological product".

The European Commission and its groups of experts proposed, along with the "biosimilar" status, the concept of comparability and a development approach that is more demanding than the one that applies to developing a generic medicinal products: "*where a biological product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided*".[2] This wording makes a clear distinction between generics and biosimilars, and stipulates that the development plan for a biological medicinal product requires more supporting studies than required for a generic (the latter being essentially based on the identity of the chemical molecule and proof of bioequivalence), mainly to take account of the intrinsic variability of these complex molecules (see below).

This definition of biosimilars therefore makes a clear distinction between copies of chemical medicinal products and copies of biological medicinal products and has implications for patient and prescriber information, substitution or interchangeability and finally on traceability and medical records, as discussed at the Giens round table.

As the European Medicines Agency (EMA) states, "*A biosimilar medicine is a biological medicine that is developed to be similar to an existing biological medicine (the 'reference medicine'). Biosimilars are not the same as generics, which have simpler chemical structures and are considered to be identical to their reference medicines*".[3]

To understand the term "biosimilar", proposed for copies of active substances of biological origin, it is important to know the definition of a biological medicine and a number of physicochemical, biological and structural characteristics of these molecules that make them more difficult to copy.

2.1. Definition of a biological medicinal product

Biological medicinal products are defined in Annex 1, Part I of European Directive 2001/83/EN:[1] "*A biological medicinal product is a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality* (quality profile, including impurities, variants, degradation products, etc.) *a combination of physico-chemical-biological testing, together with the production process and its control*". This definition confirms the well-known dogma that holds that a biological substance is described in part by the process through which it is obtained, or in other words "the process makes the product".

From a regulatory perspective, the classification of a product as a biological medicinal product requires specific variables to be measured to determine its quality, given the molecular complexity of these substances and the processes through which they are derived. The final quality and inter-lot reproducibility of biological products are more difficult to control and demonstrate than for chemically synthesized products.

2.2. The particularities of biological molecules

Active substances of biological origin feature a series of characteristics both at the molecular level and as regards their manufacturing