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Biological agents and biosimilars: Essential information for the internist

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ABSTRACT

Biologics embrace a wide range of substances synthesized by cells or living organisms by means of different biological processes, including recombinant DNA technology, controlled gene expression, or antibody technologies. A biosimilar establishes similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety, and efficacy based on a comprehensive comparability exercise. Minimizing development costs and accelerating their market access create a convergence of interests between health services, worried about sustainability, and generic manufacturers. While the demonstration of bioequivalence is sufficient for small synthetic molecules, this approach is not scientifically applicable to a copy of biological drug constituted by large and complex molecules, which are similar but not identical to the originator and are also subject to different post-translational processes. Internists should be confident that the development process of biosimilars ensures a comparable risk-to-benefit balance with the originators. On the basis of available evidence and pharmacovigilance network, there are no grounds to believe that the use of a biosimilar carries more risks for the patient than the use of an originator. Since the first biosimilar was authorized in Europe in 2006, no clinical alerts have raised red flags about the established EMA biosimilar pathway. In this article, we discuss some of the most frequent concerns raised by clinicians about biosimilars and try to explains the scientific principles underlying the biosimilar concept established in the EU in order to license biosimilar drugs.

1. Introduction

Biological medicines have revolutionized the treatment of many acute and chronic conditions including neutropenia, enzyme or hormone deficiency, a wide range of inflammatory and autoimmune diseases, and cancer [1]. They have improved the management of diseases, including a more effective control of symptoms, quality of life, productivity and other relevant clinical and social outcomes [2]. By the end of 2009 biological drugs in phase III of clinical development made up to 38% of all pipeline products for the pharmaceutical industry [3]. These shifts in drug development and approval have subsequently been reflected in commercial adoption rates. Most new drugs that receive regulatory approval are under patent protection. Patent life is typically 20 years from the time of filing a submission, which is usually done before clinical testing on humans begins. The forthcoming patent expiries of several, widespread biological drugs open the opportunity to the market for biosimilars, which should be able to improve the sustainability of health services especially in therapeutic areas such as oncology, where demand and costs of new therapies are consistently high [4].

In the last decade, the health authorities have established specific guidelines to demonstrate clinical comparability between biosimilars and their originators [5]. Recently, the European Medicines Agency (EMA) received the first marketing authorization application (MAA) for the biosimilar monoclonal antibody (mAb) infliximab. The intrinsic complexity of antibody structure, the heterogeneity introduced by subtle changes in product manufacturing, and the potential complications associated with the introduction of biosimilars to the marketplace must be brought to the forefront of critical discussion [1].

In this article, we discuss some of the most frequent concerns raised by clinicians about biosimilars and try to explain the scientific principles underlying the biosimilar concept as established in the EU community in order to allow the licensing of biosimilars.

2. What is a biological agent? How are they manufactured?

Biologics embrace a wide range of substances synthesized by cells or living organisms by means of different biological processes, including recombinant DNA technology, controlled gene expression, or antibody technologies. The *biopharmaceutical era* began in the early 1980s and currently represents one of the fastest growing sectors of the drug industry worldwide. Monoclonal antibodies (e.g. infliximab, etanercept,

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adalimumab, golimumab, trastuzumab, rituximab), recombinant hormones (e.g. somatropine, human erythropoietins, glargine insulin), and blood growth factors (e.g. filgrastim) are commonly used in Western countries to treat rare diseases as well as high prevalence illnesses, such as cancer and diabetes. Several advanced medicinal products based on gene and cell therapy are expected to become available in the next decade.

Compared with chemically synthesized drugs, biologics have 100- to 1000-fold larger molecular weight and are relatively heterogeneous. Hence, their physiochemical structure is much more complex and difficult to characterize. Table 1 summarizes the different characteristics of chemically synthesized drugs and biosimilars. The biopharmaceutical manufacturing process is more complex, requiring several steps (Fig. 1) [6], each of which is subject to variations affecting the biological characteristics and the clinical properties of the drug.

Changes in qualitative and quantitative biological parameters can result from unknown deviations (*drift*) and known changes (*evolution*) in the manufacturing process. Although some variability is normal, some product attributes may fall outside intended target values [7]. Discussions on the issues related to manufacturing biologics are often summarized stating that "*the process is the product*." Because the manufacturing process is the basis for the characterization of biologics, there will never be two identical biopharmaceuticals.

3. What is a biosimilar?

A biosimilar is defined by the European Medicines Agency (EMA) as "a biological medicinal product that contains a (copy) version of the active substance of an already authorized original biological medicinal product (reference medicinal product). A biosimilar establishes similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise." This requires a full qualitative documentation, appropriate preclinical pharmacokinetic and pharmacodynamic studies, and ultimately comparative studies with the originator to determine the relative efficacy and safety [8]. Similarly, the Food and Drug Administration (FDA) defines biosimilar as "a product that is highly similar to a US-licensed reference biological product, notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity and potency of the product." Both EMA and FDA require that a biosimilar product deliver the same dosage and strength as the reference product and that it can be used for the same indications as the reference product [8,9].

4. Manufacturing process of biological agents and biosimilars

Biological agents and biosimilars are essentially similar, thus the statement "*the process is the product*" is sometimes used to emphasize the differences between an originator and biosimilar(s). However, it applies to several manufacturing changes of any biologics, including an originator. Any originator is actually characterized by *micro-heterogeneity* between different batches of the same product, due to the inherent variability of the expression of biological systems and production process. It reasonable to affirm that most of the marketed originators are no longer equal to the molecule initially tested in pre-marketing development (see "Is the comparability exercise also applied to the reference product?").

Is it possible to manage this variability in order to comply with the quality standards and the parameters of safety and efficacy? Quality by Design (QbD), introduced in 2004, is a systematic approach to define a range of variations that do not modify quality, safety, and therapeutic properties of a biotechnology drug [10]. Identifications of the Quality Target Product Profile (QTTP) and Critical Quality Attributes (CQAs) are the cornerstones of the roadmap for QbD (Fig. 2). The purpose is to identify all key characteristics and properties determining quality, safety, and efficacy of a specific biological product and to establish their acceptable variability. These assessments should be revised over time as soon as new stability, non-clinical and clinical data become available. Subsequently, all variables and their multidimensional combination and interaction are evaluated in order to design product and process spaces, complying with quality requirements of a specific product. In addition, a planned set of controls is established. Both product and process designs are reviewed and approved by regulatory bodies. At any time, any movement outside the approved space is considered as a post-approval change requiring further regulatory assessment. Then, production process validation is performed to demonstrate its effectiveness and capability of delivering a product complying with quality parameters. Once the product is marketed, compliance with CQAs must be monitored constantly and continuous improvements are implemented through risk assessment, raw material management, enhancement of analytic techniques, and development of stochastic models to predict potential risks. Starting from the wide initial variability related to the different cell lines developed to produce a biosimilar, QbD allows to progressively control key variables of subsequent manufacturing steps,—cell culture, purification, and product formulation—in order

Table 1
Main differences between chemically synthesized drugs and biosimilars.

Characteristics	*Chemical drugs*	Biosimilars
Type of molecule (molecular weight)	*Mostly small chemical molecules* (*molecular weight usually less than 1 kDa*)	Large polypeptide chains (usually more than 10 kDa)
Structure	*Usually fully known*	Complex, frequently partially unknown
Synthesis	*Standard chemical synthesis*	By living systems (using recombinant DNA technology)
Physico-chemicals	*Well-defined*, *stable structures*	Complex, heterogeneous, and labile structures
Impurities	*Very rare*	Measures required to prevent viral, bacterial, or fungal impurities
Stability	*Typically stable molecules*	Measures required to monitor and maintain stability
Characterization	*Easy to fully characterize*	Complex molecular composition and heterogeneity make it almost impossible to characterize
Immunogenicity	*Very rare*; *non-antigenic* (*generally*)	Potentially immunogenic: immunologic tests and pharmacovigilance needed to monitor immunogenicity and antigenicity
ADME (absorption, distribution, metabolism, and excretion)		
- Absorption	*More rapid*	Slower (subcutaneous or intramuscular)
- Distribution	*High*	Low or limited
- Metabolism	*Metabolized to active and non-active metabolites*	Catabolism to amino-acids similar to endogenous ones
- Disposition	*Often target-mediated*	Rarely target-mediated
Pharmacokinetic profile	*Non-linear* (*often*)	Frequently linear
Half-life	*Short or shorter*; *variable*	Long
Safety		Exaggerated pharmacology; immunogenicity