Critical Reviews in Oncology/Hematology 104 (2016) 98–107

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Understanding the biosimilar approval and extrapolation process—A case study of an epoetin biosimilar

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ARTICLE INFO

Article history:
Received 19 December 2014
Received in revised form 1 April 2016
Accepted 27 April 2016

Keywords:
Biosimilar
Erythropoietin-stimulating agent
Comparability
Extrapolation
Retacrit™

ABSTRACT

The World Health Organization defines a biosimilar as "a biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product." Biosimilars are biologic medical products that are very distinct from small-molecule generics, as their active substance is a biological agent derived from a living organism. Approval processes are highly regulated, with guidance issued by the European Medicines Agency and US Food and Drug Administration. Approval requires a comparability exercise consisting of extensive analytical and preclinical in vitro and in vivo studies, and confirmatory clinical studies. Extrapolation of biosimilars from their original indication to another is a feasible but highly stringent process reliant on rigorous scientific justification. This review focuses on the processes involved in gaining biosimilar approval and extrapolation and details the comparability exercise undertaken in the European Union between originator erythropoietin-stimulating agent, Eprex®, and biosimilar, Retacrit™.

1. Introduction

While the vast majority of therapeutics are small-molecule drugs (SMDs), the last two decades have seen the rise of biologics in the treatments of various disease states. SMDs are generally simple molecules that are highly reproducible. Biologics, in contrast, are intricate and complex molecules that are produced in living cells through processes such as recombinant DNA technologies. Their production process is exclusive; hence, it is impossible for manufacture to replicate exactly. Consequently, the end product cannot be considered a "biogeneric," but is termed a "biosimilar."

The World Health Organization defines a biosimilar as "a biotherapeutic product which is similar in terms of quality, safety and

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http://dx.doi.org/10.1016/j.critrevonc.2016.04.016
1040-8428/

Table 1
A comparison of the key differences between biosimilars and generics (Roger, 2006; Calvo and Gómez, 2013; Schellekens, 2005; Sekhon and Saluja, 2011; Ventola, 2013; Davit et al., 2009).

	Biosimilars	Generics
Properties		
Size	• Large macromolecules (eg, ~100 kDa)	• Small molecules (eg, ~100 Da)
Structure	• Complex, involving primary, secondary, tertiary, (possibly quaternary) levels, and posttranslational modifications	• Usually simple and easily characterizable molecules
Degradation mechanism	• Typically multiple processes	• Complex and not always completely known.
Variability	• Heterogeneous product	• Usually a single, defined structure
Synthesis	• Produced in living cells; unlikely to manufacture identical copies	• Produced through standard chemical synthesis; identical copies can be manufactured
Stability	• Less stable, sensitive to external conditions	• Typically stable molecules
Similarity with reference product	• Designed and engineered to be similar, but not 100% identical	• Identical to reference product
Characterization	• Difficult to fully characterize	• Usually easy to fully characterize
Interchangeability (per FDA)	• May or may not be interchangeable with the reference product	• Interchangeable with the reference product
Immunogenicity	• Higher potential	• Lower potential
Analytical comparability exercise	• Physiochemical characterization • Functional assessment	• Not required
Nonclinical development	• In vitro comparative assays • In vivo assays may also be required • Pharmacokinetic analysis *(not required in EU if data from in vitro studies is considered satisfactory)* • Pharmacodynamic analysis *(not required in EU if data from in vitro studies is considered satisfactory)* • Immunogenicity *(not required in EU)* • Toxicity *(only required in EU for risk-based approach)*	• Not required
Clinical development	• Bioequivalence testing • Efficacy and safety studies • Pharmacovigilance • Risk management	• Bioequivalence testing • Large clinical trials not required

efficacy to an already licensed reference biotherapeutic product" (World Health Organization, 2009). Biosimilars, and their manufacture/approval processes, are very different from their chemical counterparts, generics, as Table 1 summarizes (Roger, 2006; Calvo and Gómez, 2013; Schellekens, 2005; Sekhon and Saluja, 2011; Ventola, 2013; Davit et al., 2009).

Biosimilars are intrinsically more complex, less reproducible, and susceptible to even small changes in manufacturing and product characterization. The production platform and chosen cell line/expression system defines the product's attributes. Variability in bioreactor conditions can lead to ranges in product attribute (Roger, 2006; Schellekens, 2005; Mellstedt et al., 2008), which can lead to alterations to the three-dimensional structure, pattern of posttranslational modifications and/or impact levels of other product quality attribute levels (Schellekens and Ryff, 2002; Schellekens, 2002; Hesse and Wagner, 2000), potentially impacting safety and efficacy. Consequently, unlike generics, biosimilars must undergo a highly regulated, stringent approval process that is based on a multistep comparability exercise.

2. Regulation of biosimilar development

The European Union (EU) was the first to establish legislative procedures for the approval of follow-on biologics, with the original overarching biosimilar guidelines published in 2005 by the European Medicines Agency (EMA) (European Medicines Agency, 2005). A series of complementary guidelines has since been published to reflect the evolving knowledge base (European Medicines Agency, 2012a; European Medicines Agency, 2013a), and the overarching biosimilar guidelines (European Medicines Agency, 2014a) and accompanying "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues" (European Medicines Agency, 2014b) were both updated in 2014. These guidelines state that "Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise needs to be established" (European Medicines Agency, 2014b). The comparability exercise applies similar scientific fundamentals to those used when evaluating the impact of a manufacturing process of a biological medicine product (detailed in ICH Q5E (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2004)). Biosimilarity should be demonstrated using a stepwise approach that involves comparison to the reference product in analytical, nonclinical, and confirmatory clinical studies. Analytical data include information on the manufacturing process and quality of the biosimilar; protein binding, signal transduction, and functional activity/viability assessment, as well as concentration-activity/binding relationship of the biosimilar. In addition, sufficient nonclinical data including in vitro pharmacokinetics (PK), pharmacodynamics (PD), if a suitable measurement exists, and toxicology studies may be required.