Seminars in Arthritis and Rheumatism 45 (2016) S1–S10

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

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

Biosimilars: Rationale and current regulatory landscape

Ewa Olech, MD

Department of Internal Medicine, University of Nevada School of Medicine, 1707 W Charleston Boulevard, Suite 220, Las Vegas, NV 89102

ARTICLE INFO

Keywords:
Biosimilar
Biologic
Innovator
Reference product
Chronic inflammatory diseases
Nomenclature
Biosimilarity
Regulatory guidance
Regulatory pathways
Generics
Small-molecule drugs
Development

ABSTRACT

Objectives: To discuss current terminology and the regulatory standards and processes involved in the development of biosimilars.
Methods: An Internet-based literature search through April 2015 was performed for information related to biosimilars in chronic inflammatory disorders. Keywords were as follows: biosimilar, development, manufacturing, characterization, structural, functional, preclinical, clinical, immunogenicity, rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and ankylosing spondylitis. The European Medicines Agency (EMA) and US Food and Drug Administration (FDA) websites were searched for guidelines and information related to biosimilars.
Results: Biosimilars are products that are highly similar to the reference product regarding quality, biological activity, safety, and efficacy. Biosimilars are biological products and not generic drugs and, thus, do not follow the same regulatory pathways as generic molecules. Rigorous early-stage structural, functional, and analytical testing, followed by nonclinical and clinical analyses comparing a biosimilar with its reference product, are required to demonstrate biosimilarity in regulatory markets worldwide.
Conclusions: The addition of biosimilars to the market has the potential to improve access to biologic therapies. Many regulatory agencies have enacted stringent pathways, which must be followed for a biosimilar to be labeled and approved as such; following the pathways will help protect and maintain the integrity, quality, and safety of the biosimilar product.

Introduction

Biopharmaceuticals, also known as biologicals or biologics, are large complex molecules produced in living organisms [1]. Most biopharmaceuticals are proteins, but they can also include other biological products such as vaccines, toxins, antitoxins, allergenic products, nucleic acids, or other tissue and cellular products [1,2]. In turn, protein biologics include those purified from their natural sources, although they are most often manufactured using recombinant technology [1]. Biologics cover a range of complexity, including peptides such as human insulin, small proteins such as erythropoietin, and large proteins such as monoclonal antibodies (mAbs) or receptor fusion proteins [3].

Since the introduction of the first biopharmaceutical, recombinant human insulin approved in 1982 for therapeutic use [4], the number of biologics, including mAbs, approved for human use has greatly increased [5]. Biologics have revolutionized the management of many diseases, including chronic inflammatory diseases such as rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), psoriasis (PsO), inflammatory bowel disease (IBD), and more recently, juvenile idiopathic arthritis (JIA) [1,6–8]; however, because of their complexity, the development process for biologics is very time-consuming and costly [9,10].

The expiration of data protection or patents for first-generation biopharmaceuticals, followed by patent expiration on the first approved mAbs [5], have opened the possibility of developing biosimilars, that is, biological products similar, but not identical, to the originator or reference products. Biosimilars may be approved through a rigorous, though abbreviated, pathway that relies upon the extensive knowledge and experience gained with the reference product [3]. The advent of biosimilars could be beneficial by broadening access to biologic therapy for patients with chronic inflammatory disorders and other conditions as recommended in practice guidelines [10].

Due to the various regulations and nomenclature used through time and across geographical areas, some confusion exists about

This supplement was funded by Pfizer Inc. Ewa Olech, MD, was a paid consultant to Pfizer Inc for the research and/or authorship of this supplement. Medical writing and editorial support to prepare this supplement was provided by Guidemark Health and funded by Pfizer Inc. Ewa Olech has the following additional conflicts of interest to disclose: *consultant:* AbbVie Inc., Amgen Inc., Celgene Corporation, Genentech Inc., Janssen Pharmaceuticals Inc., Regeneron Pharmaceuticals Inc., Sanofi-Aventis U.S. LLC, and UCB Inc.; *research grants:* AbbVie Inc., Amgen Inc., Genentech Inc., UCB Inc., and Vertex Pharmaceuticals Incorporated.

E-mail addresses: eolech@unr.edu, ewaolech@yahoo.com

http://dx.doi.org/10.1016/j.semarthrit.2016.01.001
0049-0172/

what constitutes biosimilarity. This article aims to clarify the concept of biosimilarity and the surrounding terminology, as well as provide an overview of the regulations governing the licensing and approval of biosimilars. The second article in this supplement, "Development of Biosimilars," describes in more detail the scientific principles underlying the development and manufacture of biosimilars.

The biosimilar opportunity

More than a decade ago, biologic therapies were introduced for the management of patients with a variety of chronic inflammatory diseases. Biologic disease-modifying antirheumatic drugs (bDMARDs) such as tumor necrosis factor (TNF) antagonists have proven to be effective in controlling RA symptoms, delaying joint damage, and improving outcomes in patients who do not respond to first-line therapy with conventional (or small-molecule) disease-modifying antirheumatic drugs (DMARDs) [11]. Furthermore, a number of clinical trials have supported the commonly accepted view that early intervention can help slow progression, leading to improved patient outcomes [12]. The same is true for other inflammatory diseases (PsO, PsA, AS, and IBD) [6,11]. In fact, early intervention and use of biologic therapy are recommended in many guidelines for the treatment of these conditions [11,13–15].

Biosimilars may help address unmet medical needs by increasing the accessibility of biopharmaceutical therapies. If access to biologics can be increased, it is reasonable to expect that it may result in more treatment and earlier initiations, as recommended in the guidelines, as well as greater continuity of treatment. With the intent of reducing healthcare expenditures while preserving the quality of patient care, many governments have (or are in the process of) enacting legislation to allow for the regulation and licensing of biosimilars [16]. Since the approval of the first biosimilar in Europe in April 2006, somatropin (Omnitrope) [17], other countries also have adopted rigorous regulatory standards for biosimilar development, and additional biosimilars have been approved globally [10].

Biosimilar nomenclature and terminology

Biosimilars

Through time, various terms have emerged or been used in the literature to refer to biosimilars, including, but not limited to, biocomparables, biogenerics (now obsolete), follow-on biologics, noninnovator proteins, similar biopharmaceuticals, similar biotherapeutic products (SBPs), and subsequent entry biologics (SEBs) (Table 1). Inconsistent nomenclature has created confusion and has even fostered apprehension regarding biosimilars, especially since similar terms have received different definitions, and some of these terms have been sometimes applied to products that may not have followed stringent regulatory guidelines to be considered biosimilars, such as intended copies or noncomparable biotherapeutic products [18,19].

The EMA's Committee for Medicinal Products for Human Use (CHMP), which is responsible for the scientific assessment of human medicines and pioneered the development of a regulatory framework, defines a biosimilar as a version of an already authorized biological medicinal product (the reference product) with demonstrated similarity in physicochemical characteristics, efficacy, and safety, based upon a comprehensive biosimilarity exercise between the reference product and the biosimilar [19,20]. The FDA initially used the term "follow-on protein products" to refer to "proteins and peptides that are intended to be sufficiently similar to a product already approved under the Federal Food, Drug, and Cosmetic Act or licensed under the Public Health Service Act" [21]. Following the enactment of an approval pathway for such products [through the Biologics Price Competition and Innovation (BPCI) Act, part of the Patient Protection and Affordable Care (PPAC) Act, signed into law on March 23, 2010], the term was changed to biosimilars in the United States, as recommended by Weise et al. [19] in order to avoid confusion with the terminology [22].

Currently, the FDA defines a biosimilar as "a biological 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 for safety, purity, and potency of the product" [22]. Other regulatory agencies with rigorous regulatory processes in place have adopted their own terms for "biosimilars," such as Health Canada's "subsequent entry biologics" [23] or Mexico's "biocomparables" [24], while the World Health Organization (WHO) refers to "similar biotherapeutic products" [5,25]. Although slightly different, these regulatory definitions and underlying regulations are based on consistent scientific principles [5]. It is important to note that the term "biogeneric" has now become obsolete and use of the term may lead to the erroneous interpretation that biosimilars are generics (see section Biosimilars are not generics) [1,19].

Second-generation biologics, biobetters, and intended copies

It is important to understand the difference between the concept of biosimilar and second-generation biologics, biobetters, and intended copies.

Table 1
Biosimilars nomenclature and definitions of biosimilars/biosimilarity according to different guidance documents

Country/region	Agency	Nomenclature	Definition
Canada	Health Canada	Subsequent Entry Biologics (SEBs)	A biologic drug that enters the market subsequent to a version previously authorized in Canada with demonstrated similarity to the reference biologic drug [23].
European Union	EMA	Biosimilar	Version of an already authorized biological medicinal product (the reference product) with demonstrated similarity in quality characteristics, biological activity, safety, and efficacy based on a comprehensive comparability exercise [20].
Mexico	COFEPRIS [24]	Biocomparables	Subsequent entry (after patent expiration) biopharmaceuticals that demonstrate comparable quality, safety, and efficacy profiles to those of the innovator reference product [24].
United States of America	FDA	Biosimilar (formerly, follow-on protein products) [21]	A biological product that is highly similar to the reference product notwithstanding minor differences in clinically inactive components and demonstrates no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency of the product [47].
Worldwide	WHO	Similar biotherapeutic products (SBPs)	Biotherapeutic product that is similar in quality, safety, and efficacy to an already licensed reference biotherapeutic product [26].

COFEPRIS, Comisión Federal para la Protección contra Riesgos Sanitarios; EMA, European Medicines Agency; FDA, US Food and Drug Administration; WHO, World Health Organization.

This supplement was funded by Pfizer Inc.