Biosimilars: The Need, The Challenge, The Future: The FDA Perspective

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OBJECTIVES: **This article summarizes the brief history of the biosimilars industry, the FDA's regulations and guidance for biosimilars development, and the issues and challenges facing developers and regulators in bringing biosimilars to market.**

METHODS: **Current literature, regulations, and FDA guidance documents were summarized and interpreted to define biosimilars and to present their financial and clinical implications.**

RESULTS: **Some biologic agents that will lose patent protection during the next few years may be replaced with lower cost follow-on biologics. However, unlike generic drugs, biosimilars may be structurally and functionally different from the reference product they are designed to resemble. The FDA has yet to approve any agent via the abbreviated licensure pathway for biosimilars that was passed as part of the Affordable Care Act. The FDA has issued new guidance describing processes by which manufacturers may demonstrate either biosimilarity or interchangeability with an FDA-approved biologic agent, which is required for abbreviated licensure. Biosimilars approved in Europe consist of relatively small molecules; complex large-molecule biosimilars could be subjected to a rigorous and prolonged FDA approval process, which would defeat attempts to develop lower-cost versions of biologic drugs.**

CONCLUSIONS: **Biosimilar development is a consequence of the financial success of biologic therapies and their eventual patent expiration. The pharmaceutical industry must now develop complex biosimilars that resemble FDA-approved biologic agents and invent analytical tools and end points to demonstrate similarity to regulatory authorities. Already in development is a new wave of "biobetter" or "biosuperior" drugs that mimic but also improve upon a biologic drug's chemistry, formulation, or delivery.**

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Over the past 30 years, there has been tremendous growth and development of biologic agents in the pharmaceutical industry. The National Cancer Institute has defined a biologic drug as "a substance that is made from a living organism or its products and is used in the prevention, diagnosis or treatment of cancer and other diseases" (1).

Biologics are proteins that are created by the process of recombinant DNA in living cells; some have been major therapeutic breakthroughs. Examples of biologics include hormones, cytokines, monoclonal antibodies (mAb), and fusion proteins (**Table 1**) (2). The production of biologics involves a complex series of steps that are individually developed for each agent by the manufacturer. Because of the unique nature of biologically derived therapeutics, the safety regulation of most biologics by the Food and Drug Administration (FDA) falls under the jurisdiction of the Public Health Service Act (PHSA) (3), whereas chemically synthesized small-molecule drugs are regulated under the Federal Food, Drug and Cosmetic Act (FFDCA) (4).

Although the overall number of prescriptions for biologics is relatively modest compared with that for small-molecule medications, their development and production are associated with significant costs. Administration of a biologic agent to an individual patient ranges between $15,000 and $150,000 per year. Biologics account for about 16% of worldwide pharmaceutical sales (http://www.imshealth.com/ims/Global/Content/Home%20Page%20Content/IMS%20News/Biosimilars_Whitepaper.pdf). The US and European markets for biologic agents presently account for approximately $60 billion in annual

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Table 1. Examples of Food and Drug Administration-approved biologic agents[a]

Drug classes
Hormones
Erythropoietin, follicle-stimulating hormone, glucagon, human chorionic gonadotropin, human growth hormone, insulin, thyrotropin
Cytokines
Granulocyte colony-stimulating factor, interferon alfa, interleukins
Clotting factors
Factor VII, factor VIII, factor IX
Monoclonal antibodies
Antibodies to vascular endothelial growth factor, CD20 (rituximab), and tumor necrosis factor (TNF-α)
Vaccine products
Hepatitis B surface antigen, human papillomavirus major capsid proteins
Enzymes
DNase, Glucocerebrosidase, thrombolytics, pancreatic enzymes
Newly synthesized proteins
Soluble TNF receptor linked to IgG Fc (etanercept)
Newly developed conjugates
Pegylated proteins: interferon (peginterferon alfa-2a), human growth hormone
Metal chelators covalently bound to proteins
Ibritumomab tiuxetan
Radioactive iodine covalently bound to proteins
Iodine-131 tositumomab
Chemotherapeutics covalently bound to proteins:
Gemtuzumab ozogamicin

[a]Modified from Saenger (22).

sales (5), and rapid expansion of the number of marketed biologics is anticipated.

Development

Agents that have biologically similar properties to FDA-approved biologics are termed "biosimilars". Unlike the fabrication of generic drugs, the manufacturing of proteins derived by DNA recombinant technology to mimic the effects of currently marketed biologics does not result in the production of an identical product (6). Because of the complexity of molecular structures and manufacturing processes, biosimilars may have unique structures compared with the products that their activities resemble.

Biosimilar development represents a large profit potential for pharmaceutical manufacturers. Consumers and policy makers view appropriate market introduction of biosimilars as high priority because of the prospect of reduced medical costs. A number of biologics with very high annual sales will lose patent protection in the next few years. These include Rituxan (rituximab, an anti-inflammatory and chemotherapeutic agent), Enbrel (etanercept, used for rheumatoid arthritis), and Remicade (infliximab). Production and sales of biosimilars is estimated to reach $20 billion in annual business by 2020 (7).

FDA regulation of biosimilars

The Biologics Price Competition and Innovation Act (8) (BPCI Act) was passed as part of the Affordable Care Act that President Obama signed into law on 23 March 2010. The BPCI Act creates an abbreviated licensure pathway (known as the 351k path) for biological products shown to be "highly similar" to or interchangeable with an FDA-licensed reference product.

A biosimilar product is one with "no clinically meaningful differences" from its reference product with regard to safety, purity, and potency, as supported by data from analytical, animal, and clinical studies. Applicants under 351(k) must demonstrate that the new product is biosimilar to the reference product, utilizes the same mechanism(s) of action for the proposed condition(s) of use, and has the same route of administration, dosage form, and strength. Interchangeability must be supported by data showing that the product is biosimilar to and likely to produce the same clinical results as the reference product. Interchangeable biosimilars must have the ability to be switched for or alternated with the reference produce in any given patient without introducing new risks in terms of safety and reduced efficacy. A product meeting interchangability standards may be substituted for the reference product without the authorization of the health-care provider (9).

In Feburary 2012, the FDA issued new guidance documents (10) to reflect input and questions from regulatory meetings on biosimilar product development. The guidelines describe a stepwise process required to demonstrate biosimilarity, beginning with comprehensive stuctural and functional analyses, followed by animal studies to assess toxicity and clinical studies on pharmacokinetics, pharmacodynamics, and immunogenicity. The draft guidance also suggests that the FDA may allow extrapolation across indications given sufficient scientific justification. The quality guidelines list physiochemical considerations that may be relevant to assessing biosimilarity, including manufacturing process, impurities, and product stability.

In the absence of product-specific guidance, drug developers will need to determine the analytical tools and study end points with which they can demonstrate similarity. New analytical technologies are currently in development to assess protein aggregation, post-translational modifications, and other product-related factors known to cause immunogenicity (11). However, only clinical studies will be able to account for the interplay between the potential immunogenicity of the drug itself and other factors such as mode of delivery, dosing, and patient characteristics (11).

The biosimilar industry

The pharmaceutical industry's biologics segment began in the 1980s with recombinant versions of endogenous human molecules (i.e., hormones and enzymes) and has evolved to develop more complex products such as mAb. Aptly named 'blockbuster

Table 2. European Medicines Agency-approved biosimilars[a]

Active substance and therapeutic areas	Product name	Authorization date	Manufacturer/company name
Epoetin alfa	Abseamed	28 August 2007	Medice Arzneimittel Pütter GmbH & Co KG
Anemia Cancer Chronic kidney failure	Binocrit	28 August 2007	Sandoz GmbH
	Epoetin alfa Hexal	28 August 2007	Hexal AG
Epoetin zeta	Retacrit	18 December 2007	Hospira UK Ltd
Anemia Autologous blood transfusion Cancer Chronic kidney failure	Silapo	18 December 2007	Stada R&D AG
Filgrastim	Biograstim	15 September 2008	CT Arzneimittel GmbH
Cancer Hematopoietic stem cell transplantation Neutropenia	Filgrastim Hexal	6 February 2009	Hexal AG
	Filgrastim ratiopharm	15 September 2008 (withdrawn 20 April 2011)	Ratiopharm GmbH
	Nivestim	8 June 2010	Hospira UK Ltd
	Ratiograstim	15 September 2008	Ratiopharm GmbH
	Tevagrastim	15 September 2008	Teva Generics GmbH
	Zarzio	6 February 2009	Sandoz GmbH
Somatropin	Omnitrope	12 April 2006	Sandoz GmbH
Pituitary dwarfism Prader–Willi syndrome Turner syndrome	Valtropin	24 April 2006	BioPartners GmbH

[a]Data collected 12 May 2011, updated 29 June 2012 (see ref. (23)).

drugs', mAbs have accounted for as much as 19% of the global pharmaceutical market and exceeded $140 billion in sales in 2011. The top 10 revenue-generating drugs in 2011 were Humira, Enbrel, Remicade, Rituxan, Avastin, Lantus, Herceptin, NovoLog, Neulasta, and Lucentis (12).

The development of biosimilars (also known as follow-on or subsequent entry biologics) was a consequence of the financial success of the biologic therapies and their inevitable "patent cliff"—a marked drop in sales as they near the expiration of their original patents. The complexity of the structure and the developmental process of biologics make their "patent cliff" different from that of chemically synthesized drugs (13). The BPCI Act provides for 12 years of non-patent market exclusivity for licensed reference products, and this may be extended by 6 months of pediatric exclusivity.

As a result of recent technological innovations, new regulations in the biopharmaceutical industry, and cost concerns, the idea of biosimilars has gathered support (14). In fact, efforts are already underway to develop a new class of follow-on biologics named "biobetters" or "biosuperiors", which go beyond mimicking the original biologic to provide improvements through changes in chemistry, alteration in the formulation, and innovative delivery (15).

The biosimilar industry in the United States has gained momentum more slowly than that in Europe (16). The EMA (European Medicines Agency) approved its first biosimilar in 2006, a biosimilar version of Amgen's Neupogen in 2010 (17), and the first mAb (Inflectra, a biosimilar of Remicade (infliximab)) in 2013 (18). The FDA has not yet approved a biosimilar under BPCI. However, several large biopharmaceutical companies including Merck BioVentures have intentions to market biosimilars (19).

Of the 14 or so true biosimilars licensed in Europe, nearly all fall into three biologic analogs: somatropin, epoetin alfa, and filgrastim (**Table 2**). Most drugs approved to date consist of relatively small molecules. The pharmaceutical industry, although excellent at manufacturing generic versions of small-molecule chemical drugs and small-molecule biosimilars, has demonstrated limited ability in creating large-molecule complex biosimilars that are a perfect copy of their reference product in terms of their size, molecular weight, and three-dimensional structure. This is bound to make regulatory authorities like the FDA put the complex biosimilars through prolonged and rigorous scrutiny. If this happens, it is likely to defeat the very reason why biosimilars were developed in the first place (20,21). The speed and integrity with which the biosimilar industry meets this challenge will decide its fate in the long run.

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CONFLICT OF INTEREST

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