Update on Biosimilars

By Jason Chen, PharmD Candidate 2016 and Craig Stern, PharmD, MBA, CSP

Introduction

In the past three decades, there has been an enormous penetration of biologic drugs into the U.S. market. Traditionally, these biopharmaceuticals were designed for orphan disease states, but the advent of specialty drugs such as Enbrel™ (etanercept) and Sovaldi™ (sofosbuvir) has revolutionized the treatment regimens for chronic diseases such as rheumatoid arthritis and hepatitis C. Many of the drugs have significant benefits over their small molecule counterparts, and have significantly improved quality of life and mortality for patients. Due to their high costs (yearly values can range from $15,000 to $150,000 per patient), they are either reserved for second-step therapy or for refractory or life-threatening situations.[1,2] The global biologics market was $170 billion in sales in 2012. The IMS report "The Global Use of Medicines: Outlook through 2017" estimates that spending will increase from $3 billion to $20-$25 billion in global developed markets. This report also estimates that biologics will represent 19 percent of global developed market value by 2017.[4]

Estimates from ***Generics & Biosimilars Initiative Journal Online*** (GaBI Online) are that $67 billion in biologics will lose patent protection by 2020.[5] As patents for blockbuster biologic drugs approach expiration in the U.S., drug manufacturers will attempt to capture a part of the growing biologic market by developing biosimilars, also sometimes referred to as biogenerics, which are follow-on biologic products that possess similar but not identical properties to currently FDA-approved biopharmaceuticals. The entry of biosimilars into the U.S. market will provide scope to therapeutic categories, leading to greater emphasis on substitution and formularies. In 2014 alone, Trastuzumab (Herceptin™) and Cetuximab (Erbitux™) will be subject to biogeneric substitution in Europe, presuming that no further actions are taken to extend these patents. In India, the first biosimilar version of Trastuzumab was approved in November 2013.[6] In the U.S., the FDA is reviewing Filgrastim (Neupogen™), manufactured by Novartis AG, as the potential first biosimilar approval. Interestingly, Sandoz, the generic division of Novartis, is already selling three biosimilars, including Filgrastim, in 60 countries. Closer to home, the PBM, Express Scripts, estimates that California represents 11 percent of the total national health care spend for specialty, making it a prime target for biosimilars for at least 11 of the most popular specialty biologic medications. The savings impact in California alone is estimated by Express Scripts to be $27.6 billion between 2014 and 2024.[7]

Biosimilars are expected to serve as a less expensive alternative to brand-name specialty drugs, but they will still be expensive. Management of biosimilars will be predicated on utilization management as well as cost control. However, the Federal Trade Commission (FTC) has concerns that biosimilars may not provide significant competition or savings to already marketed specialty medications. In a Federal Register brief, the FTC noted, "to compete against reference biologic products [biosimilars] will

depend on whether they are allowed to have the same nonproprietary name." The FTC's argument is that the lack of agreement on biosimilar nomenclature and state laws that prohibit substitution creates an uncertain influence on biosimilar effectiveness, leading to problems with pharmacy and formulary substitution, and free market competition.[8] To remove some of this uncertainty, and to ease the transition to interchangeability, the FTC requested comment on creating a book for biosimilars that is similar to the FDA's "Orange Book." The FTC is also soliciting comments on biosimilar competition outside of the U.S. to find out if, "… reference biologic manufacturers lowered their prices, offered discounts, engaged in enhanced marketing activities, or increased innovation or next-generation developments."[6]

Definition of Biosimilars and Interchangeability

In March 2010, the FDA passed the Biologics Price Competition and Innovation (BPCI) Act of 2009 as a part of the Affordable Care Act. The BPCI Act amends the Public Health Service (PHS) Act and provides an abbreviated approval pathway for biosimilars (also known as 351[k]). The BPCI Act defines a "biosimilar" as a biological product that is highly similar to an already FDA-approved biological product, i.e., the reference product. In addition, the biosimilar and reference product should possess no clinically significant differences in their "safety, purity, and potency."[9] In 2012, the FDA stated in a set of new guidance documents that it will use a "totality-of-the-evidence" approach to evaluate biosimilarity. Criteria for biosimilar approval include analytical, animal, and clinical studies to compare the safety, efficacy, immunogenicity, pharmacokinetics, and pharmacodynamics to the reference product.[10] The BPCI Act guarantees 12 years of market exclusivity to the reference product beginning from the date of its FDA approval, and during this period, a biosimilar application cannot be approved.[9]

The BPCI Act is analogous to the Hatch Waxman Act (i.e., Drug Price Competition and Patient Term Restoration Act of 1984), which amended the Federal Food, Drug, and Cosmetic Act to introduce an abbreviated process for the FDA approval of generic small molecule drugs.[11] Biosimilars are not defined as generic versions of specialty drugs. An important distinction between the two is that a pharmacist cannot automatically substitute a brand specialty drug with its corresponding biosimilar unless the biosimilar has demonstrated interchangeability. Generic small molecules on the contrary, can be interchanged directly because of demonstrated bioequivalency. Under the BPCI Act, a biosimilar is interchangeable only if its alternation with the reference product generates an identical clinical outcome with no reduction in efficacy or safety when compared to the repeated administration of the reference product.[9] The concept of interchangeability is important to allow for utilization and cost management at the pharmacy level.

Research and Development (R&D) Cost

Compared to small molecule generics, the approval of biosimilars will be limited due to a multitude of economic and regulatory factors. Biologics are much larger than small molecule drugs and possess complex molecular structures. Their mechanism of action for treating specific diseases and potential for immunogenicity is not only based on their molecular composition, but their protein folding and three-dimensional structures as well. Regulatory and development costs for biosimilar approval are estimated to range from $100 million to $200 million (versus $1 million to $5 million for small molecule generic drugs). In addition, the duration for biosimilar development could reach up to 10 years, which is double the time required for generic drugs.[12] These barriers will decrease the economic incentives for manufacturers to develop biosimilars, and discounted prices from brand specialty drug are expected to be modest at best when compared to generic discounts for small molecule drugs (20 percent versus 80 percent).[13] However, the high cost and utilization of biologic drugs means that the entry of biosimilars into the U.S. market can still result in large savings for patients, payors, and the entire U.S. health care system. The financial and regulatory obstacles for biosimilar approval may push drug manufacturers to develop "biobetters" by filing a full Biologics License Application. "Biobetters" are considered "improved" versions of the reference product with respect to properties such as potency, efficacy, and duration of action. Biobetter competition is expected to be driven more by quality than price, resulting in minimal or negligible cost savings from the original reference products.[14]

EU Experience

The European Union (EU) has been a leading body in developing standards for biosimilar approval since 2005. The European Medicine Agency (EMA), which is analogous to the FDA in the U.S., approved its first biosimilar, Omnitrope (somatropin), in 2008. Since then, 20 additional biosimilars have been approved for use in Europe (although two were withdrawn from the market), including two for the monoclonal antibody infliximab (Remsima from Celltrion and Inflectra from Hospira).[15] The EU relies heavily on post-marketing studies and pharmacovigilance to ensure that minute molecular differences between biosimilars and their reference products do not produce any unexpected changes in efficacy or safety.[13] The U.S. will most likely emulate this practice with the approval of its first biosimilar(s). The EMA has established no guidelines regarding interchangeability and does not encourage automatic substitution. France, on the other hand, in their 2014 budget, is the first European country to allow pharmacists to substitute less expensive biosimilar drugs for their branded biologics.

Although EMA's decision regarding automatic substitution is made on the

EXPIRATION DATES FOR TOP BIOLOGIC SPECIALTY MEDICATIONS

GENERIC NAME	BRAND NAME	APPROVED	U.S. EXPECTED EXPIRATION
Pegfilgrastim	Neulasta	June 31, 2002	2014
Insulin glargine	Lantus	April 24, 2000	2014
Glatiramer Acetate	Copaxone		2014
Insulin Aspart	NovoLog		2015
Ranibizumab	Lucentis		2016
Etanercept	Enbrel	Nov. 2, 1998	2028 (extended)
Adalimumab	Humira	Dec. 31, 2002	Dec. 31, 2016
Interferon beta-1a	Avonex / Rebif	Feb. 7, 2003	Expired
Enoxaparin sodium	Lovenox		Expired
Epoetin alfa	Epogen	June 1, 1989	Expired
Filgrastim	Neupogen	Feb. 20, 1991	Expired
Cetuximab	Erbitux	Nov. 26, 1997	Feb. 13, 2016
Bevacizumab	Avastin	Feb. 26, 2004	July 4, 2017
Trastuzumab	Herceptin	Sept. 25, 1998	June 18, 2019
Darbepoetin alfa	Aranesp	Sept. 17, 2001	May 15, 2024
Palivizumab	Synagis	Aug. 24, 1998	Oct. 20, 2015
Rituximab	Rituxan	Feb. 7, 2003	Sept. 22, 2016
Infliximab	Remicade	Sept. 17, 2001	Sept. 4, 2018

Reference: DrugStoreNews.com, March 17, 2014; IMS MIDAS, 06/2013, IMS Patent Focus

premise of potential safety concerns, e.g., immunogenicity, the inability to allow it, reduces the potential for cost savings.[13] Despite the entry of biosimilars into the European market, their success with regard to utilization and cost has not been consolidated. In 2011, biosimilar sales comprised less than 1 percent of all biologic sales in the European Union, and there was a high variability with regard to the market success of the biosimilars within different countries belonging to the European Union.[14,16] Spain may provide an indication of a cost savings trend in the EU. Article 93.7 of Act 29/2006 for Guarantees and the Rational Use of Medicines (Medicines Act) sets the prices of biosimilars by Spanish law at 30 percent below the price of the reference biological.

Expected Biosimilar New Entrants in the United States

Twelve biological products with global annual sales amounting to over $67 billion will lose patent protection by 2020, including Humira/adalimumab (December 2016), Remicade/infliximab (September 2018), and Rituxan/rituximab (September 2016).[5] The advent of the first biosimilars in the U.S. is expected to result in savings of over $10 billion for Medicare in the next decade.[17] However, the high cost of biosimilar development and strict regulatory restrictions will discourage smaller pharmaceutical companies from entering the biosimilars market. In addition, because biosimilars are not identical to their reference compounds, and there could be a higher potential for immunogenicity, biosimilar competition will not only be dependent on price but also on quality. This is a stark contrast to generic competition with small molecule brand-name drugs, which are assumed to be equivalent and are driven entirely by price. Factors dependent on quality, such as brand loyalty and manufacturer reputation, are expected to impact physician acceptance and uptake of biosimilars.[3,14] For biosimilars to succeed, pharmaceutical companies will need to invest in additional activities that are not required for small molecule generic companies. These include the enhancement of their research and development sectors, marketing strategies, and lobbying capabilities.[3]

The entrance of biosimilars into the U.S. is further complicated by naming conventions. The FDA has not yet issued any guidance regarding the naming of biosimilars in comparison to their reference products. Generic drugs share the same International Proprietary Name (INN) with their brand-name counterparts because they are bioequivalent, but biosimilars, not being identical to their reference products, cannot share the same INN.[18] Creating distinguishable INNs will promote the accurate reporting of biosimilar-associated adverse events, but could also cause confusion among physicians and other health care providers.[19] In addition, different INNs will discourage physician prescribing of biosimilars as well as prevent substitution at the pharmacy level.[19] To ensure the suc-

cess of biosimilars in the U.S. market, the FDA will need to implement an identification system that facilitates efficient post-marketing pharmacovigilance without jeopardizing the role of biosimilars as low-cost alternatives to expensive specialty medications.

Conclusion

Biosimilars present an opportunity for cost savings and substitution in an ever-growing biologic specialty market. The expectation is that the debate over biosimilar substitution as a cost-reducing methodology will be constantly scrutinized. Further, as biologics rival acute care hospital costs, emphasis will be placed on the marketing of these products as either biogenerics or competitor brands. Formulary product placement will determine if the savings potential for biosimilars will be realized. What is clear, however, is that traditional concepts of drugs as brands or generics are evolving.

Separate from the cost savings argument is the opportunity for treatments of diseases and conditions in ambulatory settings versus acute care. In addition, patients who have conditions that could not be treated in the past will have options that were unavailable just a few years before. The challenge for the health care system will be to develop rigorous selection, clinical management, and evaluation processes that are every bit as expert as the current acute care processes. The greater challenge is that these processes will have to be developed in a very short time frame.

About the Author

Jason Chen is a 2016 PharmD Candidate at the USC School of Pharmacy. He is currently working as a Pharmacy Intern at Huntington Memorial Hospital and was also a past Pharmacy Intern at Pro Pharma Pharmaceutical Consultants, Inc. At the USC School of Pharmacy, Jason is the current President of the Student Industry Association (SIA), an organization that is devoted to informing pharmacy students about the career opportunities within the pharmaceutical industry.

Craig Stern, PharmD, MBA, is President of Pro Pharma Pharmaceutical Consultants, Inc. and serves as the Chairperson of the CPhA Editorial Review Committee. Dr. Stern has no bias to report.

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