

Primer: Biosimilars User Fee Act

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Introduction

The Patient Protection and Affordable Care Act (PPACA), signed into law by President Obama on March 23, 2010, amends the Public Health Service Act (PHS Act) to create an abbreviated licensure pathway for biologic products that are demonstrated to be “biosimilar” to or “interchangeable” with an FDA-licensed biologic product. This pathway is provided in the part of the law known as the Biologics Price Competition and Innovation Act (BPCI Act).

Under the BPCI Act, a biologic product may be demonstrated to be “biosimilar” if data show that, among other things, the product is “highly similar” to an already-approved biologic product.¹ Until President Obama signed the PPACA in March of 2010, there was no FDA approval process for biosimilars. In efforts to implement the BPIA, FDA and industry stakeholders have conducted meetings to develop a user fee system for the review of biosimilars and interchangeable products for fiscal years 2013 to 2017, to be named the 351(k) program. As such, this primer will provide an introduction to biosimilars and discuss the implications of the 351(k) program for the healthcare system and industry.

Biosimilars: The “Follow On” Biologic

Biologic products can include a wide range of products including vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and proteins. Unlike most traditional, small-molecule prescription drugs that are made through chemical processes, biologic products are generally made from human and/or animal materials. Biologic products are larger than and have a more complex structure than small-molecule prescription drugs. Figure 1 gives a scope of how much larger and more complex a biologic molecule, like the snake venom or

Key Takeaways

Similar but Different From Biologics

- Biologic drugs are made through the use of the cellular mechanisms of living organisms
- A biosimilar is highly alike to a U.S.-licensed reference biologic product notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences

FDA Instructed to Create Biosimilar Approval Pathway through BPCI

- The FDA recently drafted a user fee system for the review and approval of biosimilars
- A 12 year market exclusivity clause grants biotechnology innovators patent protection to recoup drug development costs and fees.

BUFA To Affect FDA and Industry

- The FDA is to gain \$150,000 for every year throughout the drug development process beginning with investigation and continuing through the pre-marketing and marketing phases
- Biosimilars would compete with brand name biologics reducing significant costs for consumers

Big BUFA Potential in the Near Future

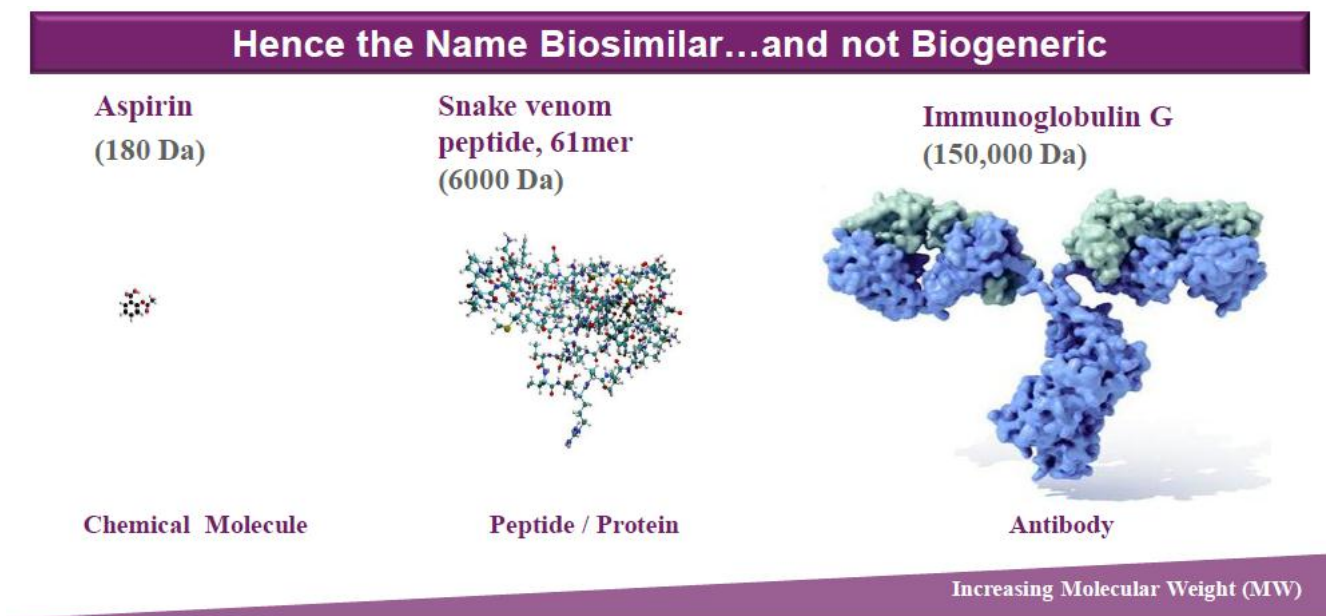
- Biotechnology manufacturers await new approval pathway before finalizing strategies to fully realize the tremendous growth opportunity in biosimilar market
- Minimal FDA regulations and fees will yield growth in employment and U.S. economy

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immunoglobulin molecule shown, is than a small molecular drug like aspirin and most other drugs. Biologic products may be manufactured through biotechnology, derived from natural sources, or, in some cases, produced synthetically.

A biosimilar is a biologic product that is highly similar to a U.S.-licensed reference biologic product aside from minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biologic product and the reference product in terms of the safety, purity, and potency. A biosimilar, also known as a follow-on biologic, is a copycat version of an innovator biologic. Because the production process of a biologic drug is complex and involves the extraction of a molecule from a living organism, it is nearly impossible to create a generic version that is identical to the original and is thus not considered a “generic.”¹

Figure 1: Complexity of Normal Drugs Versus Biologics



Source: Lonza M&I

The Biosimilar User Fee Act (BUFA)

The implementation of the Biosimilars User Fee Act (hereafter referred to as “BUFA”) is a topic of serious debate between consumers, industry stakeholders, biotech companies and the FDA. Its introduction on behalf of the Food and Drug Administration is aimed to create a fee structure to bring biosimilars to the market more quickly in order to benefit both consumers and biotech companies. Considering each innovator biologic costs the originator company an estimated \$1.2 billion from drug discovery to FDA approval, the proposed fee structure is consistent with that of the biologic drug approval process, which is likely to be just as time intensive and complex as reviewing clinical trial data for an original biologic.ⁱⁱ

¹ The word “generic” applies only to small-molecule drugs that are the same as, and bioequivalent to, an already-approved small-molecule drug regulated under the FD&C Act

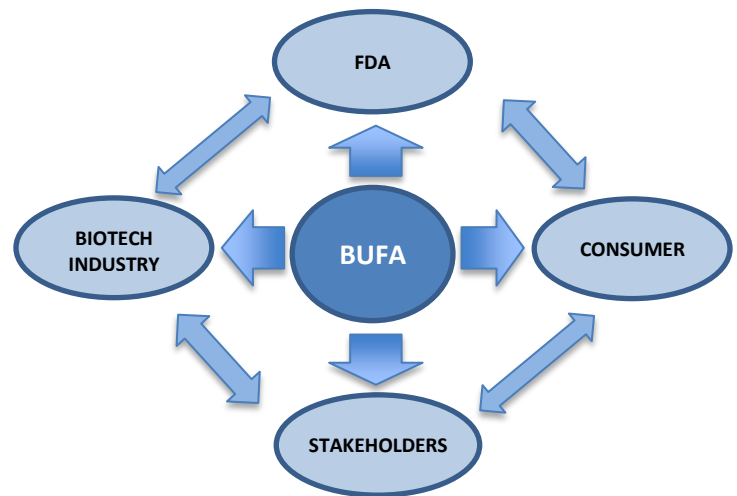
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Because the manufacturer of a biosimilar also must go through development and clinical trial period, biosimilar product development fees of \$150,000 due each year a product is being actively developed starting with submission of an investigational new drug application. The process would be in place for the first five years, at which point the FDA could reevaluate its approach. From discovery to approval, the average time it takes to produce a biosimilar is at least 8 years.ⁱⁱⁱ

The Effects of the BUFA on Biotechnology Companies, Consumers, Industry Stakeholders and the FDA

The implications and effects of the proposed fee structure of the BUFA are nuanced but will be widely felt by all parties with a hand in the healthcare system (Figure 2). Given the tremendous growth of the biosimilar market, biotechnology manufacturers await the FDA's guidance on the new approval pathway before finalizing strategies to fully realize the tremendous growth opportunity for biosimilar products. According to IMS Health statistics, biosimilar sales have doubled annually since 2006. In the U.S. alone, sales rose from \$10.6 million in 2007 to \$235 million in 2010. Future data projections predict the value of the global biosimilars market will grow from just \$243 million in 2010 to \$3.7 billion in 2015.^{iv}

Figure 2: Wide-Ranging Impact of BUFA



For consumers, the introduction of biosimilars would provide a cheaper alternative to innovator biologics, much like how generic drugs provide steep discounts to brand name pharmaceutical drugs. According to biotechnology industry experts, the development of biosimilars would decrease consumer costs between 20% to 30% and open access to new life saving medicines for a range of conditions and diseases.^v

Overall, industry stakeholders are likely to benefit due to increased regulatory clarity surrounding biosimilar development and approval. Yet concerns over “market fixing” have been raised in FDA hearings. The placement of a fee structure and market exclusivity clause can be viewed as molding the market. Small biotech companies, which lack significant resources, may not be able to compete with large biotech companies in biosimilar development and thus fail to earn protection under the “market exclusivity” clause.

However, given the projected growth numbers of the biosimilar market and the increasing demand for biologic drugs as the number of Medicare enrollees continues to climb, looming expirations of many blockbuster drug patents has prompted larger pharmaceutical companies to sign deals with smaller biotechnology companies to accelerate drug development. Larger companies provide smaller ones the resources to research develop the drug and also help in the distribution and marketing in return for a share of the revenue.^{vi}

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As is currently proposed, the FDA will gain \$150,000 for every year throughout the drug development process beginning with the application for investigation and continuing through the pre-marketing and marketing phases after FDA approval. The user-fee program for biosimilars includes fees to provide FDA with the extra resources needed to support development-phase meetings with sponsors of biosimilar biologic product candidates. Ultimately, this would decrease the review process significantly and bring the new drug to market faster, providing access to a greater variety of medicines to patients.

Legislative Issues and BUFA

Under the BPCI Act, the FDA is required to develop recommendations for a biosimilars user fee program for Fiscal Years 2013 through 2017. As part of this provision, the FDA consulted with a range of groups, including scientific and academic experts, health care professionals, representatives of patient and consumer advocacy groups, and industry stakeholders in developing the recommendations. Throughout the course of FDA meetings, two major legislative issues have surfaced: the constitutionality of BUFA and the safety of biosimilars.

Members of the biotechnology industry have questioned the constitutionality of the FDA review process. Genentech, one of the leading biotech manufacturers, suggested that agency reviewers cannot perform the rigorous scientific comparative assessment necessary to reach legitimate conclusions about the "similarity" or "sameness" of two products without first examining secret trade data concerning the manufacturing processes of the innovator, which is prohibited by law.^{vii} Moreover, such unauthorized reliance would violate not only section 505(b)(2) of the Food, Drug and Cosmetic Act (FDCA), but also the Trade Secrets Act and the United States Constitution.

Beyond legal issues, the scientific community has raised concerns over biosimilars and patient safety. This is, without question, the primary topic discussed throughout FDA meetings.^{viii} For decades, the FDA had taken the position that each biologic is unique and inexorably linked to the manufacturing processes used in its creation. Complex operational details of the manufacturing processes are central to and define the identity and unique molecular safety and effectiveness attributes of each biologic. A follow-on biologic manufacturer that uses different starting materials and a different process will produce a product that is different from the innovative product. The effects of the differences between a "follow-on" and its respective innovator product can only be determined by subjecting the follow-on biologic to substantial clinical testing in patients to prove that it is safe and effective.

Ensuring Fairness for Innovators: The Adoption of the 12 year Patent Protection Clause

In July of 2009, The House Energy and Commerce Committee, by a vote of 47 to 11, overwhelmingly adopted an amendment creating a regulatory pathway for biosimilars that will provide 12 years of market exclusivity for innovative biologics. The market exclusivity provisions included in this amendment will provide biotech companies with the protections they need to continue their search for new biomedical breakthroughs, providing increased hope to patients and their families that new therapies and cures will be discovered and made available. The 12 year exclusivity begins immediately following FDA approval.

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Outlook for Biosimilars

In efforts to implement the Biologics Price Competition and Innovation act of 2009, the FDA, industry stakeholders, biotech companies and members of the public have conducted meetings to develop a user fee system for the review of biosimilars and interchangeable products for fiscal years 2013 to 2017.

While all parties involved have come to a general agreement on the benefits of producing low cost biosimilars and the potential profitability of the biotechnology market, scientific and consumer groups have voiced strong concerns regarding the need to obtain sufficient preclinical and robust clinical data to ensure safety and efficacy for consumers. Meanwhile, the funding of FDA review on behalf of the innovator companies draws major ethical concerns surrounding the drug review and approval process. However, these ethical issues may prove inconsequential given the possibilities of producing new medical biosimilars to improve patient outcomes.

The ability to balance the conflicts of interest between all major parties is the greatest obstacle to overcome in drafting the legislation. Ultimately, BUFA must provide adequate review time for FDA reviews to satisfy safety concerns voiced by the scientific community and patient advocacy groups. For biotech industry stakeholders and companies the adoption of the market exclusivity clause is a step in the right direction by allowing companies to recoup the costs of development to bring the biosimilar to market.

At a time when the cost of medical care is escalating sharply, BUFA must not obscure the biotech industry's opportunity to innovate and grow with reduced risk. If so, not only will significant economic and job growth be abandoned but, more importantly, the development of effective, low cost medicines will be hindered.



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