

INSIGHTS**Biopharmaceutical Generics: A Complicated Issue***The Issues Surrounding Biosimilar Development*

“Is there a generic drug available?” Many patients ask their pharmacist or physician this question, wanting to know if a generic version of a brand name drug is available, if it is as safe and effective as the brand name drug, and if it saves them money.

To be considered a generic, a drug must be identical in dose, strength, route of administration, safety, efficacy, and intended use to the brand name chemical-based drug counterpart. These criteria have been used for 25 years to bring hundreds of generics to the marketplace. But, this only applies to “traditional” chemical-based drugs.

Traditional pharmaceutical drugs are small molecule, chemical-based, and relatively simple to manufacture; biologics, also called biopharmaceuticals, on the other hand, are large molecule, protein-based, and rather difficult to manufacture. Biologics have had a profound impact on many medical fields, including rheumatology and oncology. These drugs have added major therapeutic options for the treatment of many diseases, including some for which no effective therapies were available, and others where previously existing therapies were clearly inadequate. Therefore, biologics are seen as a replacement for traditional chemical-based drugs. They are considered to be the therapies of the future, but they have no generic versions in the US.

This insights paper will explore the many reasons why the US doesn't have generic biopharmaceuticals in the marketplace and offers advice to the pharmaceutical industry on how to best address the issue.

“Biologic drugs are cutting-edge medicines created from living cells instead of the chemicals used to develop traditional pharmaceuticals. Though vastly more expensive than their chemical cousins, there are no generic equivalents on the market.”



INSIGHTS **Biosimilar Development**

Generic biopharmaceuticals, or the other way around, biopharmaceutical generics, are also called biosimilars, follow-on proteins, copycat biologics or anything similar to those names. For your convenience, a terminology section can be found at the end of this document.

Different needs and wants in the industry

Biopharmaceutical generics present a complicated issue. The US clearly lags in this area because the innovator companies, the generics makers, the patients, the FDA and the Obama Administration aren't all in agreement. Let's review the needs of each.

The innovator companies (companies like Amgen, Genzyme, and Biogen Idec) are seeking basically two things:

- 1 Significant intellectual property protection. This sounds fancy, but it is merely a long period of market exclusivity or monopoly (depending on who you ask) to recoup their investments on their brand name drugs and ensure innovation to fund their pipeline to develop new drugs. The innovator companies are asking for up to 14 years.
- 2 Safe biosimilar drugs. The innovator companies want to ensure that the FDA enforces a science-based process for approval of the biosimilars. Because biosimilars are not identical to the original drugs, any undetectable differences in impurities and/or breakdown products could have serious health implications. To alleviate this, it requires rigorous testing, which includes clinical trials for the generics makers.

The public, especially the patients, wants safe drugs, cheaper drugs and more novel drugs. They are anxious to reduce health care costs, so they want generic biologics sooner rather than later in hopes of spending less on prescription drugs. They also desire new cutting edge protein-based drugs to treat those now untreated diseases.

Generics makers (companies like Momenta, Sandoz, and Teva) are anxious to begin manufacturing generic biopharmaceuticals. They want guidance from the FDA, but, so far the FDA has provided none. This leaves generics makers with no regulatory pathway to get generic biopharmaceuticals approved in the US.

Although they do not have access to the originator's molecular clone or original cell bank, nor to the exact fermentation and purification process, generics makers are eager to make even better versions of the existing biopharmaceutical drugs.

And lastly, the FDA is at the mercy of Congress. Even though the FDA has drafted the guidelines, the guidelines can't be finalized until legislation is approved by Congress.

All these players have different needs and wants, but none are willing to compromise at this point. That partially answers the question of why no generic biologics?, but, there is more. Before we get into the legislation (see section entitled: Bills, bills and more bills?) and before we get into the reason why there are already generic biologics abroad (see section entitled: Biosimilars abroad), let's ponder some numbers.

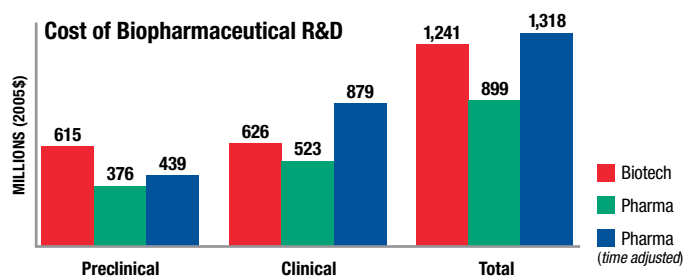


Figure 1: Pre-approval capitalized cost per approved molecule

The costs of biopharmaceuticals

A review of some figures will help us understand the cost of drug making.

- Figure 1 shows the costs of preclinical work, clinical trials, and the total costs of an approved drug. In addition to high costs for drug development, the timelines are also lengthy. The time it takes for clinical development and approval is 97.7 and 90.3 months respectively for biotech and pharma drugs.²
- Current pricing for biosimilars in the European Union (EU) is approximately 20% less than the branded biologics; and, "generic biologics are expected to cost 10 to 30% less than traditional biotech drugs"³. This is interesting, especially if the cost to bring them to market is nearly equivalent.



INSIGHTS **Biosimilar Development**

- The average clinical trial costs \$1.2 billion:¹ obviously not apples to apples with Figure 1, but making the point that clinical trials are high priced, and if required (or not) make a big difference to the generics makers.
- The pharmaceutical industry has spent over \$300 million to lobby Congress in the past two years.¹ This is mainly to advocate a longer market exclusivity time.
- An estimated \$25 billion worth of biologics will lose patent protection by 2016, creating a significant market opportunity for biosimilars. Monoclonal antibodies (mAb) such as Herceptin and Rituxan/Mabthera are among a number of major biologics going off-patent during this period.⁴ The clock is ticking.

All in all, costs are exorbitant to develop biopharmaceuticals, whether brand name or generic. The requirement of a clinical trial for a generic biologic makes a big difference in the time and the cost in getting a generic approved. Looking at these costs, it is understandable why we don't have generic biopharmaceuticals yet, because it is a huge investment and without any rules in place, no one wants to get started. But the clock is ticking and innovator drugs have patents expiring. Let's move on and look at the legislation.

Bills, bills and more bills?

First, let's review the 1984 Hatch-Waxman Act which established a new market for generic versions of branded pharmaceuticals (the chemical-based drugs). That act contained two sets of changes. First, it eliminated the duplicative testing requirements necessary to obtain approval for a generic copy of a previously approved innovator drug. Second, it established patent-term extensions for innovator drugs. By extending patents on brand name drugs while making it easier for generic drugs to enter the market after patents expire, the Hatch-Waxman Act aimed to benefit consumers by increasing the supply of generic drugs while preserving drug companies' incentive to invest in research and development.⁵

This act enabled companies such as Teva, Sandoz, and Ranbaxy to become leaders in generics production. Thus over the years the US has seen numerous generics come to market covering a wide range of therapeutic areas from antibiotics (i.e., amoxicillin) to anti-hypertensives/beta blockers (i.e., propranolol HCl), to antidepressants (i.e., paroxetine) and beyond. According to the Generic Pharmaceutical Association (GPhA), an industry trade group, generics represent 69% of the total prescriptions dispensed in the US but only 16% of all dollars spent on prescription drugs.

Now let's look at recent legislation for generic biopharmaceuticals.

While prior attempts at approving biosimilars legislation have failed, the push for cost-saving measures thrives under the Obama Administration. Avowed to enact sweeping reforms throughout the medical, pharmaceutical, and biotech industries, the Obama Administration has thrust generics into the headlines, seemingly polarizing drug manufacturers, healthcare providers, and the general public. Ever-increasing healthcare costs, the Administration's preference to limit "evergreening" (the practice of reformulating branded drugs to increase patent exclusivity), and the impending end of market exclusivity for several biologic drugs have contributed to a renewed urgency. Three issues have emerged as key points of concern:

- **Product interchangeability:** A product found by the FDA to be interchangeable that can be safely substituted for the original product if state law permits.
- **Regulatory guidance:** The need for formal regulatory guidance to delineate the regulatory process for each category of protein drugs prior to the approval of the first biosimilars including the clinical trial requirements.
- **Market exclusivity:** The amount of time an innovator biologic may essentially control the market until a generic competitor may begin to compete.

INSIGHTS Biosimilar Development

Moving Toward a Biosimilars Pathway: The Lines are Drawn in Congress

Provision	Waxman Bill (H.R. 1427)	Eshoo Bill (H.R. 1548)	Hatch-Waxman Act
Exclusivity	New product: 5 years New indication: 3 years Pediatric applications: additional 6 months	New product: 12 years ¹ New indication: 14 years ² Pediatric applications: additional 6 months ³	New product: 5 years ¹ New indication: 3 years ² Pediatric applications: additional 6 months ³
New clinical trials required?	No	Yes	No
Interchangeability with branded drug?	Yes	No, except in limited circumstances	Yes
First-to-file exclusivity	1 year	2 years	180 days
Patent notification	<ul style="list-style-type: none"> Biosimilar applicant or prospective applicant may send written request to approval holder for patent information at any time. Approval holder has 60 days to provide patent information to biosimilar applicant. Approval holder must update patent information for 2 years from date of first request. Biosimilar applicant may provide notice of application to approval holder at any time; must include certification that product will not infringe or that patent claims are invalid. Approval holder and/or patentee have 45 days from notice to sue biosimilar applicant for infringement. 	<p>The FDA would provide a copy of a biosimilar application to the reference product approval holder, who would then be required to:</p> <ul style="list-style-type: none"> Provide the biosimilar applicant with a list of patents that purport to cover the product or its use, and Explain in writing to the biosimilar applicant why the reference product approval holder believes the biosimilar product would infringe one or more patents on that list. 	<ul style="list-style-type: none"> Patents covering product or use must be listed by approval holder in the Orange Book. Generic applicants must certify at time of filing of generic application that product will not infringe or that patent claims are invalid. Generic applicant must notify patentee/approval holder of ANDA submission, and explain reasons for certification(s). Approval holder and/or patentee have 45 days from notice to sue generic applicant for infringement.
Naming of generic	Biosimilar has same official name as reference product.	Biosimilar must have distinct official name from reference product.	Generic product has same official name as reference product.

1. Measured from date of first approval of new product using a given biologic.
2. Measured from date of first approval of new indication.
3. Added to the end of exclusivity period provided for new product or indication.

Figure 2: A comparison of key provisions of the biosimilars bills and the Hatch-Waxman Act⁶

Responding to the urgency, US lawmakers have sprung into action by introducing two bills designed to allow generic biologic drugs, or biosimilars, to become a reality for American patients. The first bill, H.R. 1427, the Promoting Innovation and Access to Life Saving Medicine Act, was introduced on March 11, 2009 by Representatives Henry Waxman (D-CA), Frank Pallone (D-NJ), Nathan Deal (R-GA), and Jo Ann Emerson (R-MO). A second bill was introduced the following week. H.R. 1548, the Pathway to BioSimilar Act, was introduced on March 17, 2009 by Representatives Anna Eshoo (D-CA), Jay Inslee (D-WA), and Joe Barton (R-TX). Figure 2 shows a comparison of the two bills along with the original Hatch-Waxman Act.

These bills do not come without controversy. The biotech industry group BIO has indicated its preference for H.R. 1548, stating that the first bill (H.R. 1427) would sacrifice industry growth and innovation as well as patient safety for the sake of saving money. On the other hand, the Generic Pharmaceutical Association (GPhA) lauds the possibilities outlined in H.R. 1427 as a means for “huge savings for payers and insurance companies, patients, and state and local governments as well as federal programs,” as therapy options and price point competition would increase with shorter patent exclusivity periods for the branded biologics⁷.



INSIGHTS **Biosimilar Development**

And more recently, on July 31, 2009, the House Energy and Commerce Committee approved an amendment that would give brand name makers of biologic drugs 12 years of market exclusivity and would also allow evergreening. The amendment was added to the broader health-care legislation making its way through Congress and was introduced by Representatives Anna Eshoo (D-CA) and Jay Inslee (D-WA).

Again we ask, why don't we have generic biopharmaceuticals? It could be because legislation for generic chemical-based drugs that has worked for the last 25 years is not applicable to biologics, and because the requirements are still being negotiated to create a regulatory pathway for generic biopharmaceuticals.

Let's see what we can learn from the EU.

Biosimilars abroad

The US market is currently lagging behind the EU, where currently five biosimilar drugs have received marketing approval. In 2004 the EMEA established a rigorous biosimilar approval framework, which includes:

- Specifically distinguishing between biosimilars and generic drugs. The EMEA recognized that "due to the complexity of biological/biotechnology-derived products the traditional generic approach is scientifically not appropriate for these products."
- Protecting and fostering innovation by providing ten years of data exclusivity for innovator drugs and biologics against generics, hybrids, and similar biological products with a one-year extension grantable for certain new indications.
- Recognizing the importance of patient safety and the need to minimize the risk to the patient by establishing a regulatory framework that will require extensive testing before approval in order to ensure that biological therapies are safe and effective.
- Recognizing there may be safety and efficacy differences between seemingly similar products. Accordingly, the EMEA has taken a case-by-case approach to similar biological products, and has said that any "differences between the

similar biological medicinal product and the reference (innovator) medicinal product will have to be justified by appropriate studies on a case-by-case basis." Safety data must be collected and clinical trials may be requested.

- Recognizing the potential for a biosimilar to exhibit immunogenicity problems that were not detected in clinical trials and do not occur with the innovative product. This requires that biosimilars undergo post-marketing monitoring like that required for new innovative biologics.

There is no doubt that Europe is leading the way in the biosimilar space, but it is interesting to note that a number of biosimilars are being developed and sold in less regulated Asian markets. And just recently, Japan has approved their first generic biotech drug.

Despite the measures being in place in the EU, the Europeans have been slow to adopt biosimilars as viable therapeutic solutions. However, as Europe's population ages, the opportunities increase for biosimilars in the marketplace; and, with Europe and India leading the charge into Asia, again the opportunities increase. The US is going to lose a substantial amount of money (not to mention market share) if it doesn't move fast in filling this pipeline. Therefore, it is possible that the US doesn't have biopharmaceutical generics because they are waiting on more data to see if the EU approval framework is suitable.

“Europe is leading the way in the biosimilar space, with a rigorous biosimilar approval framework, and five biosimilar drugs with marketing approval.”



INSIGHTS **Biosimilar Development**

Guidance for biopharmaceutical generics issue resolution

Clarkston Consulting had the opportunity to talk with Dr. Jeffrey Leighton, Founder & CSO at Maine Natural Health LLC, about his views on biosimilars. He has a wealth of knowledge on the subject, from the chemistry of the molecules, to the sensitivity of the manufacturing processes, to the regulatory considerations, and to the market implications. He provides a common sense approach to working through the biopharmaceutical generics issues. We have summarized his advice to industry.

Advice for biosimilar developers

Choose the smaller proteins. Choose the right protein to go after in terms of pursuing a biosimilar version. The larger the protein, the more complicated the folding patterns, etc. The longer the protein, the greater the difficulty in reproducing it and thus the greater the number of impurities. Biosimilar companies should focus on a small protein (small amino acid sequence) that will have the highest probability of success.

Focus on the right markets. Choose a market where the regulatory requirements are well defined and where there are fewer barriers to entry. For instance, a drug for liver cancer where the market is 18,000 patients in Europe and the Far East would be a good choice.

Count the cost. The premise that a protein-based product that is off patent can be copied and sold at a lower price point quickly is not realistic. The cost to generate a drug is not cheap and the cost of a biosimilar may be 0.9 to 1 of the cost of the innovator product. There will need to be a substantial investment in technology to prove safety, efficacy, and bioavailability. So because of the large price tag, the biosimilars market would be more appealing to big pharmaceutical companies than small companies.

Build in adequate development time. It is going to take some time to find the right biosimilar. For instance, to prove efficacy, phase 2 studies will have to be conducted which will involve hundreds of patients over several years costing \$20-50K per patient.

Dr. Jeffrey Leighton, PhD, is currently Founder & CSO at Maine Natural Health LLC. Previously, he has held the positions of Co-Founder, Chairman of the Board at ICAgen Pharmaceuticals, and Director at Drug Royalty Corporation.

He has 30 years of experience in the pharmaceutical and biotechnology industry. After studying chemistry, natural product isolation, pharmacology and medicine at the University of Virginia, Dr. Leighton joined Burroughs Wellcome Company, eventually rising to the position of Principal Scientist for the Corporation. Later, he joined Glaxo Pharmaceuticals (now GlaxoSmithKline) as V.P. of Pharmacology and worldwide Group Director for cardiovascular and metabolic disease. Later he embarked on a career of forming and taking public or merging start-up biotech companies such as Genesis (a chemistry company), Inspire Pharmaceuticals (a dry tissue/pulmonary medicine company) and ICAgen (an ion channel science-based company).

Advice for innovator drug companies

Protect your patents. Every route into the final drug product is patented. Smart companies continually refine their process and then register the new process to protect the patent. For example, Amgen's blockbuster anti-anemia drug EPOgen (EPO) was approved in 1989, but the drug has numerous patents for composition-of-matter, medical use, process, and formulation, with each patent having an expiration date. So even though Amgen's EPO patent will run out soon, the process to make it won't run out until sometime in 2020-2030 because Amgen will extend the patent.

Challenge the biosimilar products. There are so many ways to prove that biosimilars are materially different and very few ways to show that they are materially similar. Challenge the patent structure. Put up roadblocks. Require the biosimilar manufacturer to prove that the product is as safe and effective as the innovator product. Using Amgen's EPO again for an example, Amgen would make the argument that small changes in chemical structure could have a big impact on drug activity.



INSIGHTS **Biosimilar Development**

Manufacture your own biosimilars. This issue is a matter of politics and marketing. When the innovator companies start making biosimilars and especially when all big pharma companies start making biosimilars, the FDA will likely relax the rules because arguing the difference (between the innovator drug and the biosimilar) will be next to impossible.

Not “if” but “when”

With regard to generic biopharmaceuticals in the US, it is no longer a question of “if” but “when”. Unfortunately the innovator companies and the generic manufacturers have struggled between their respective needs and wants. Patients are feeling the pressure of rising drug costs and the FDA is feeling the pressure to create a regulatory pathway for approval of the much desired generic biopharmaceuticals. The precedents that have been set with the Hatch-Waxman Act and with the EU guidelines just don’t seem to apply. So the issue, as complicated as it is, lies within Congress. It most likely will be a couple years before the legislation is finalized. And then there is the issue of what to call them: biosimilars, biogenerics, follow-on proteins, follow-on biologics, generic biotech drugs, copycat versions, or interchangeable biological products? It will be an interesting couple of years to watch this story unfold, and no doubt will end with a workable solution for the FDA review and licensing of biosimilars, ultimately maximizing the interests of the public, innovator companies and the generics makers.

How can Clarkston help?

Clarkston Consulting has subject matter experts with vast industry experience to keep life sciences companies up to date on biosimilars and other industry impacting issues. In addition, Clarkston offers services and tools to assist these companies, including the following:

- Regulatory and Compliance
- Quality Systems
- Strategy
- Supply Chain
- Human Capital Management

Our many success stories, consistently high rate of repeat business, and unparalleled customer satisfaction rating all mean one thing: our knowledge, coupled with our dedication, is a winning formula for results.

Terminology

Biosimilar and interchangeable: The term biosimilar makes the distinction that two complex chemical entities (the innovator drug and the generic biologic drug) will never be identical because of the sensitivity of the manufacturing processes. The term biosimilar was created to distinguish between follow-on biologics from generic chemical-based drugs. Interchangeable describes complete interchangeability of a reference drug for a biosimilar drug, i.e. substitution at a pharmacy level of the biosimilar as being equivalent to the branded drug.

Evergreening: The practice by pharmaceutical companies of making minimal adjustments to their drugs, such as creating extended-release versions, as a way to lengthen their monopoly. In other words it is a way that brand name drug makers reformulate existing products to extend the life of their market exclusivity.

Generics: Generic drugs are identical or within an acceptable bioequivalent range to the brand name chemical-based drug counterpart with respect to pharmacokinetic and pharmacodynamic properties. Therefore, generics are considered by the FDA to be identical in dose, strength, route of administration, safety, efficacy, and intended use.

Patents and exclusivity: Patents and exclusivity work in a similar fashion but are distinctly different from one another. Patents are granted by the patent and trademark office anywhere along the development lifeline of a drug and can encompass a wide range of claims. Exclusivity is exclusive marketing rights granted by the FDA upon approval of a drug and can run concurrently with a patent or not. Exclusivity was designed to promote a balance between new drug innovation and generic drug competition. Patents are generally granted for 20 years.

About the author

Wylene Lengel is a director with Clarkston Consulting's life sciences practice. With over 25 years of in-depth industry experience, she is passionate about improving quality systems.

For more information, visit: www.clarkstonconsulting.com or contact Rob Klein 877-362-3649 / rklein@clarkstonconsulting.com

References

- ¹ "The High Cost of Biologics, How long will it take for generic versions?" by Tamara Lytle, AARP Bulletin Today, July 17, 2009. http://bulletin.aarp.org/yourhealth/policy/articles/the_cost_of_biologics.html
- ² "The Cost of Biopharmaceutical R & D: Is Biotech Different?" DiMasi and Grabowski, 2007 John Wiley & Sons, Ltd. <http://ideas.repec.org/a/wily/mgtdec/v28y2007i4-5p469-479.html>
- ³ Cost-control plan: generics, "Drug Makers may lose – or gain – if copying pricey treatments for rare illnesses is made easier", by Todd Wallack, Globe Staff, March 3, 2008, The Boston Globe. http://www.boston.com/business/healthcare/articles/2008/03/03/cost_control_plan_generics/
- ⁴ "The Top 10 Biosimilars Players", Business Insights, May 2009. <http://www.globalbusinessinsights.com/content/rbhc0225m.pdf>
- ⁵ "How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry", Congressional Budget Office, July 1998. <http://www.cbo.gov/ftpdocs/6xx/doc655/pharm.pdf>
- ⁶ "Moving Toward a Biosimilars Pathway: The Lines are Drawn in Congress", July 1, 2009 by Brian J. DelBuono, PhD, BioPharm International. <http://biopharminternational.findpharma.com/biopharm/GMPs%2FValidation/Moving-Toward-a-Biosimilars-Pathway-The-Lines-are-/ArticleStandard/Article/detail/608685>
- ⁷ "Generic-Drug Makers Hail Obama Budget Proposal" by Alicia Mundy, Wall Street Journal, February 25, 2009. <http://online.wsj.com/article/0,,SB123561281773277865,00.html>

Additional resources

- "US House Panel Backs Exclusivity for Biologic Drugs" by Alicia Mundy, The Wall Street Journal, August 1, 2009. <http://online.wsj.com/article/SB124917341780899303.html>
- "How has Europe Approached Biosimilars?" <http://bio.org/healthcare/followonbkg/Europe.asp>
- "Japan approves first generic biotech drug", by Sam Cage, June 25, 2009. http://www.boston.com/news/science/articles/2009/06/25/japan_approves_first_generic_biotech_drug/
- "Who's Who in the Biosimilar Space?" May 12, 2008. <http://www.biojobblog.com/2008/05/articles/ideas-and-indulgences/whos-who-in-the-biosimilar-space/>



Headquarters
Research Triangle Park
1007 Slater Road, Suite 400
Durham, NC 27703
Phone: 800-652-4274
Fax: 919-484-4450

www.clarkstonconsulting.com

Copyright © 2009 Clarkston Consulting. All rights reserved.
0339_0909

About Clarkston Consulting

Clarkston Consulting is a different kind of management and technology consulting firm. We deliver a unique experience for market leaders within the Consumer Products and Life Sciences industries. Considering professionalism, expertise, and value as prerequisites, we take service a step further through our unyielding commitment to the success of people as individuals, both our clients and our employees. By combining integrity, adaptability, and a whatever-it-takes attitude, we have achieved an extremely high rate of referral and repeat business and a 7-year average client satisfaction rating of 97%.