

WHITE PAPER

WHAT YOU NEED TO KNOW ABOUT THE FOLLOW-ON BIOLOGIC MARKET IN THE U.S.: IMPLICATIONS, STRATEGIES, AND IMPACT

ANDREW F. BOURGOIN
andrew.bourgoin@thomsonreuters.com

JANUARY 2011



THOMSON REUTERS™

TABLE OF CONTENTS

INTRODUCTION	1
PATHWAY DESIGN	2
Exclusivity	2
Patent Litigation.....	3
Substitution	4
COMPETITIVE LANDSCAPE	5
Major Generics.....	5
Big Pharma.....	6
Emerging Market Players.....	6
STRATEGIC ALLIANCES	8
Trends	8
LOOKING FORWARD	9
APPENDIX 1: GENERAL U.S. REGULATIONS FOR FOLLOW-ON BIOLOGICS	10
REFERENCES	11

INTRODUCTION

The trend toward biologics development in the United States has been apparent. The total number of reported clinical trials with a biological intervention between 2000 and 2005 was 1,197. In the following five years, the total increased to almost 6,000. Additionally, as of November 2010, only 3 percent of reported Phase III candidates in U.S. clinical studies indicated a biological intervention. However, when considering Phase I biological candidates, this number grows to 15 percent.¹

With combined sales of the top 12 biologic products in the U.S. at around \$30 billion in 2010², incentive to develop these innovative therapies may be assumed. However, many of them demand substantial investment to manufacture due to the product complexity. In contrast to traditional, small-molecule products, biologics are developed using living organisms instead of synthesizing chemical compounds.

The high development cost of biologic products is often reflected in their price. While the average costs for biologic products are estimated around \$16,000 per year, some biologic treatments are much more expensive.³ For example, the costs for biologic therapies for treatment of colorectal cancer can cost as much as \$10,000 a month.⁴ With both federal and state programs, such as Medicare and Medicaid, covering many of these products, opportunities for cost savings are of interest to taxpayers as well as patients.

In March 2010, U.S. lawmakers passed legislation to promote competition in the biologic market. The Biologics Price Competition and Innovation Act (BPCIA) permits the approval and marketing of follow-on biologic drugs in the U.S. While the follow-on biologic market is not expected to generate the same cost savings as small-molecule generic drugs, it has been reported that potential cost savings could amount to more than \$300 billion by 2029.⁵ At the individual product level, reports are estimating that biosimilars may cost between 60 and 80 percent of the reference biologic therapy upon market entry.⁶

Entry of biosimilar therapies in the U.S. market is expected within the next few years due to loss of exclusivity and patent protection of the top-selling products. Understanding what to expect from the follow-on biologics market will be critical for successful competition, both in the U.S. and globally.

In this white paper, Thomson Reuters draws on the unique intelligence of Newport Premium™, IDRAC®, and Thomson Reuters Integrity™ to provide that understanding — by identifying the relevant U.S. regulation and its impact on competition, examining the strategies needed to gain a competitive advantage in the market, and presenting an alternative take on how the biosimilars market may evolve in years to come.

¹ What You Need to Know About The Follow-On Biologic Market in The U.S.

WHAT'S IN A NAME?

Correct usage of terms is imperative for effective communication in this growing market. U.S. regulations distinguish between different biologic products. **Follow-on biologic** products have a similar characterization to a pre-approved product on the market. Follow-on biologics that are proven to be “highly similar” to a reference product and meet the relevant regulatory requirements of safety, purity, and potency are considered **biosimilar** to the reference product. If the marketer of a biosimilar product can prove that there is no increase in risk or diminished efficacy when switching between the reference drug and the follow-on product (rather than when using only the reference product), the biosimilar product will be deemed **interchangeable**. Follow-on biologic products that receive approval via a biologics licensing application (BLA) should not be called a biosimilar or interchangeable. Approved products that have improved attributes of the original product are considered **biobetters**.

PATHWAY DESIGN

The BPCIA can be found under Subtitle VII of the Patient Protection and Affordable Care Act and amends the Public Health Service Act, creating the regulatory approval framework for follow-on biologics. Specific provisions of the BPCIA drew the interest of stakeholders from multiple business sectors during the creation of the bill and continue to receive attention. Although the bill has been enacted, further examination of the policy by the Food and Drug Administration (FDA) is expected, and thus, many of the most analyzed aspects of the BPCIA will be subject to ongoing debate.⁷

Rules regarding exclusivity periods, patent litigation standards, and substitution requirements will have a major impact on the business strategies of biologic companies.⁸ This section provides a general overview of the relevant regulation and its impact on competition. See Appendix 1 for additional information on the relevant regulations.

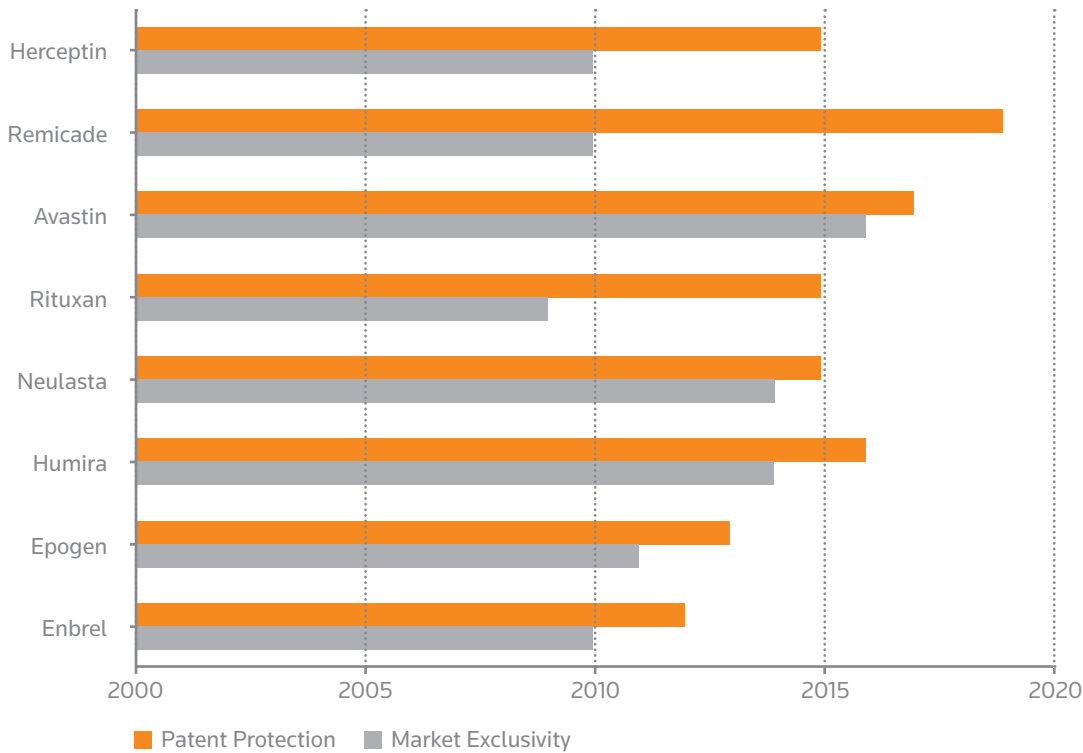
Exclusivity

The topic of data exclusivity has received a lot of scrutiny from invested parties. The revenue generated from commercially successful therapies during periods of market exclusivity is often used to pay for research and development, thus encouraging innovation.⁹ Recovering the investment required for regulatory approval of a biologic product is expected by marketers of the brand product, but the necessary time frame for adequate recovery is in question.

In 2008, the Biotechnology Industry Organization (BIO) asserted that data exclusivity has to be at least 14 years to provide companies with the certainty needed to stimulate innovation and recover investment.¹⁰

BIO's stance on 14-year data exclusivity was based on propositions from an analysis of biologic competition that suggested the breakeven point for reference products to be between 12.9 and 16.2 years of data exclusivity.¹¹ Opponents suggested a shorter time frame would still promote innovation.¹² The Generic Pharmaceutical Association (GPhA), advocating for consumer savings and patient access, also argued for a shorter time frame.¹³ The issue of exclusivity even drew the attention of the White House, which endorsed a time frame of seven years.¹⁴

FIGURE 1: Patent Protection and Market Exclusivity For Top Biologics Losing Patent Protection Prior to 2018.



A study undertaken by the Federal Trade Commission (FTC) discussed that, since high barriers to entry would limit the number of approved follow-on biologic products, market dynamics would not resemble the brand-generic competition common in the small-molecule market.¹⁵ The report concluded that a 12- to 14-year period of exclusivity was unnecessary to promote innovation, citing patent protection as another safeguard for reference products from competition.¹⁶ Since market and data exclusivity operate independently of any patent claims that protect a product, exclusivity periods may end up moot if patent protection exceeds the 12-year period the U.S. Congress adopted in the BPCIA. Critics of the FTC report contend if the assumptions regarding patent protection are wrong, the omission of an extended exclusivity period would inadequately incentivize future innovation.¹⁷ As seen in Figure 1, for the products losing patent protection before 2018, the patent period often exceeds any exclusivity period.

The 12-year exclusivity period will provide protection to reference product sponsors in the chance that constraining patents are proven invalid. While this provides incentive for innovation, it may also attract follow-on biologic manufacturers to seek approval through the BLA process instead of the abbreviated approval pathway.

Patent Litigation

Many differences exist between the intellectual property provisions in the BPCIA and the legislation covering the abbreviated pathway for small-molecule drugs, commonly referred to as the Hatch-Waxman Act.¹⁸ Perhaps the most notable difference is that the biosimilar legislation does not mandate a listing of relevant patents that reference sponsors claim protect approved products. Where generic small-molecule companies are able to reference patents in the Orange Book, biosimilar applicants will be forced to determine key patents on their own.¹⁹

The biosimilar legislation is unique in its approach to addressing issues of patent dispute. Notifications, actions, and procedures for patent infringement are regulated very differently in the biosimilar arena, as is the patent-resolution process. The patent-challenge process under the Hatch-Waxman Act is a well-established facet of the generic industry. Companies filing for an Abbreviated New Drug Application (ANDA) are only required to share information with New Drug Application (NDA) holders if filing a Paragraph IV challenge. Under the new legislation, follow-on sponsors must disclose their application to the reference product sponsor, along with additional information germane to the development process of the product, even if there isn't a patent dispute.²⁰

Companies seeking approval for a biosimilar or interchangeable product may have to navigate a new methodology of patent litigation that will require expertise and foresight. The strategies associated with patent challenges for small-molecule products may not apply. New strategies based on the regulations of the BPCIA will evolve in time. The unwillingness of follow-on biologic manufacturers to share sensitive information on production and development may result in alternative approaches to gain regulatory approval.

Substitution

Under the Hatch-Waxman Act model, generic products can frequently be dispensed by the pharmacist even if the prescription was for a branded product. This allows generic companies to compete without having to invest in marketing.

As identified in the BPCIA, if the marketer of a biosimilar product can prove that there is no increase in risk or diminished efficacy when switching between the reference drug and the follow-on product (rather than when using only the reference product), the biosimilar product will be deemed interchangeable. Once a product receives interchangeability status, it can be substituted for the reference product “without the intervention of the healthcare provider who prescribed the reference product.”²¹

The first approved interchangeable product is given one year of market exclusivity before any additional interchangeable products can enter the market. This market exclusivity could offset the additional costs associated with the required testing. Critics question if interchangeability provides the same incentive to companies in the biosimilar market as automatic substitution does to small-molecule generic competitors.

Companies seeking the first interchangeable product in a market will need to identify the costs and benefits inherent in the additional testing required for approval and granted market exclusivity. Acceptance of follow-on biologic products by patients, payers, and physicians will have a major effect on the substitution of products, the relationship between products deemed biosimilar and interchangeable, and the decision of manufacturers to seek approval for either.

PATHWAY DESIGN: WHAT YOU NEED TO KNOW

- Since the functionality of the pathway has yet to be tested, industry leaders and decision makers are left with uncertainty.
- Competitors in the follow-on biologics market may not be incentivized to use the abbreviated pathway due to issues regarding exclusivity, patent litigation, and substitution.

COMPETITIVE LANDSCAPE

Regulatory requirements for biosimilars have a direct effect on product development costs. In the EU, biosimilar applicants must prove safety and efficacy in studies that can cost developers up to \$30 million in U.S. dollars.²²

Companies looking to enter follow-on biologic competition in less-regulated markets can expect reduced development costs. In India, for example, follow-on biologic manufacturers can meet the lower regulatory standards with development costs 90 percent lower than in the EU. With lower development costs, follow-on biologic manufacturers in less-regulated markets are more common and able to offer products at a much more-reduced price than the original biologic product.²³ A shorter time to market entry, in addition to lower development costs, may attract major generic players to compete in these emerging markets to recoup investment for regulated market competition.

Development costs for biosimilars launched in the U.S. market will be as high as in EU, if not greater. Indeed, manufacturers seeking interchangeability will have even higher development costs due to the supplemental studies required for approval. Successful competition in the U.S. market may also demand additional investments from biosimilar developers. For example, post-marketing pharmacovigilance studies showing definitive evidence of comparability between a biosimilar and a reference product may be required to gain acceptance from physicians and patients.²⁴

Due to high development costs, biologics competition will not reflect the same model as the small-molecule market in the U.S., at least in the short term.²⁵ Companies that will pioneer the biosimilar market will likely have an established presence in the U.S. and share multiple attributes, such as biologic manufacturing capabilities, distribution, sales force, and marketing. With the regulatory landscape still taking shape, some uncertainties remain as to the exact strategies companies will employ to compete in the U.S. This section identifies companies expected to compete in the U.S. market during the short term and how development of biologic products in the global market may alter this scenario in the long run.

Major Generics

Competitors with prior biologic development experience in regulated markets, such as EU, Japan, or Canada, may be some of the first to gain approval under the BPCIA in the U.S. While all of the companies listed in Figure 2 have already demonstrated the ability to gain approval for a biosimilar in a regulated market, only Teva, Sandoz, Hospira, and Actavis are confirmed to be currently working toward launching biologic products in the U.S.

FIGURE 2: Launches of Biosimilars in Regulated Markets.

	EPOETIN*	FILGRASTIM	SOMATROPIN
Sandoz	EU		EU, JP, AUS, CAN
Teva	EU	EU	
Hospira	EU	EU, AUS	
Hexal (Sandoz)	EU	EU	
Actavis			EU, JP, AUS, CAN
CT Arzneimittel		EU	
Medice	EU		
Stada	EU		
Ratiopharm (Teva)		EU	

*The Epoetin Column Includes The Alfa, Zeta, and Theta Biosimilars.

Major generics started pursuing the U.S. biologic market even before the establishment of the biosimilar pathway. Currently, both Teva and Hospira have listed clinical trials for biologic products in the U.S. market. In late 2009, a BLA was filed by Teva for the granulocyte colony-stimulating factor (G-CSF) Neutroval™ and accepted by the FDA on February 2, 2010.²⁶ U.S. clinical trials of Hospira's biosimilar of the reference product Epogen™ entered Phase 1 in late July 2010.²⁷

Since the FDA may consider data requirements for biosimilar applicants on a case-by-case basis, the information and costs required to successfully complete the abbreviated pathway may remain uncertain, even after the first biosimilar product is approved in the U.S. In contrast, the costs associated with gaining approval for a BLA are clearer, as are the benefits. Drug sponsors choosing to file a BLA receive their own 12 years of exclusivity, if approved. Additionally, companies can file a BLA at anytime, whereas they have to wait four years after the reference product's first approval date before filing an abbreviated BLA. Major generic companies with an established experience with biosimilar development may opt to file a BLA even with the abbreviated regulatory pathway available.²⁸

Novartis' generic arm, Sandoz, a global leader in biosimilar development, has decided to pursue BLA approvals for U.S. biologic launches.²⁹ Sandoz has more biosimilar launches in regulated markets outside the U.S. than any other company. Omnitrope™ (recombinant human growth hormone) was the first biosimilar product to receive EU approval (2006) and is currently the only biosimilar product launched in Japan, Australia, and Canada.³⁰ Additional EU launches by Sandoz include Zarzio™ and Binocrit™, biosimilar products for filgrastim and epoetin alfa, respectively.

Major generic firms with regulatory and clinical experience with biosimilar products in regulated markets will most likely launch the first follow-on biologic products in the U.S. If major generic companies find more incentive to seek approval for follow-on biologic products through a BLA, market dynamics could be similar to competition in the same therapeutic class.

Big Pharma

Companies without a tradition in generic drug manufacturing are also expected to compete in the U.S. market with their own follow-on biologic products. In December 2008, Merck & Co. Inc. announced its intentions to compete in the biologics market through the formation of Merck BioVentures. The new business unit would be dedicated to research and development of innovative and follow-on biologic products. Also in December 2008, it was reported that Merck's pipeline would include follow-on biologic candidates, including a version of Neulasta™ (pegfilgrastim).³¹ After the FDA requested additional clinical data on MK-2578, a pegylated erythropoietin, Merck decided to discontinue development of the project in the spring of 2010.

A major licensing deal with India's Biocon has positioned Pfizer Inc. in the insulin market. It is expected that generic launches of recombinant human insulin products Glargine, Aspart, and Lispro will first occur in emerging markets and that the products will eventually compete in the U.S.³² Generic versions of insulin products listed in the Orange Book would not be considered biosimilars. While reports have suggested Pfizer will compete in the U.S. biosimilar market, it is unclear if the company will develop these products on its own.

Companies with major investment in biologic products, such as Amgen and Roche, may also become involved in the follow-on biologics market. With years of experience in the manufacturing of novel biologic products, both companies may either seek opportunities internally for biosimilar development or look to partner with other global manufacturers, just like Pfizer.

Many of the traditional innovator companies have the most to lose from competition in the follow-on biologics market. Conversely, companies with established sales and marketing forces in the U.S. will have an advantage against competition void of such attributes.

Emerging Market Players

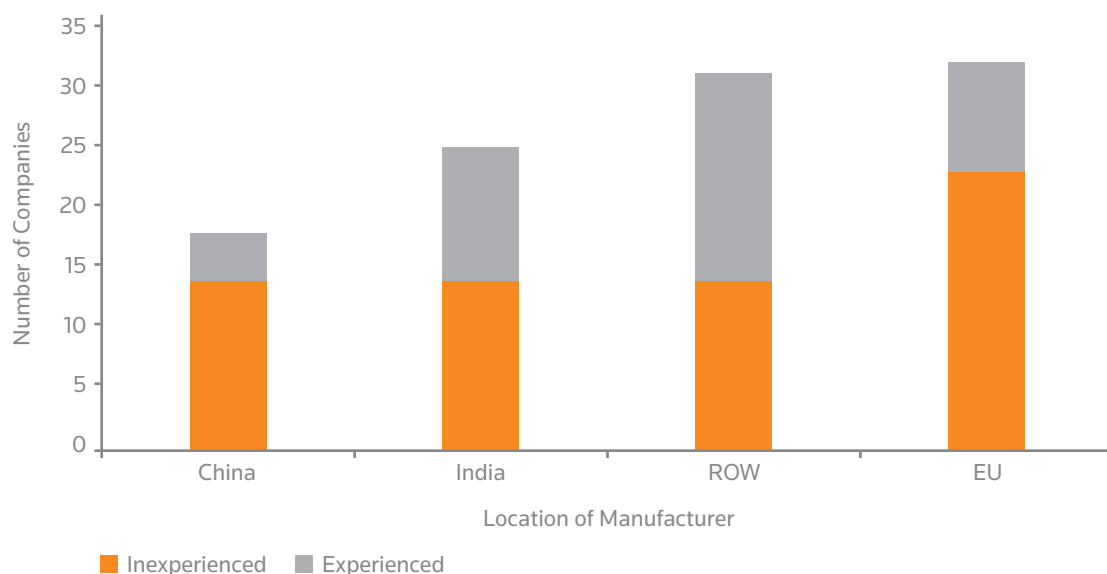
Follow-on biologics launched in less-regulated markets may provide additional insight as to potential players in the U.S. market. Reditux™, Dr. Reddy's Laboratories Ltd.'s version of rituximab, is currently marketed in seven countries worldwide, and Dr. Reddy's will reportedly seek approval in both the EU and U.S. Dr. Reddy's has been marketing Reditux in India for over three years, gaining both experience and scientific evidence that could prove beneficial in meeting the requirements of approval in regulated markets. Dr. Reddy's launched a version of darbepoetin alfa named Cresp® in the Indian market in September 2010 and expects additional biologic product launches in early 2011.³³

Generic companies in India, such as Cipla and Wockhardt, are also focusing on biosimilar development, as are major Chinese companies, such as Shandong Xinhua Pharmaceutical Group. Some of the most competitive development has been taking place in South Korea, where companies, such as Celltrion, have multiple MAb biosimilars currently in development.³⁴

While biologic competition in emerging markets is increasing, many of the companies with domestic product launches do not have the same international experience as Dr. Reddy's. In fact, many of the companies associated with follow-on biologic product development in emerging markets are without experience in regulated markets, leaving industry leaders certain that a significant presence of emerging market players (similar to the small-molecule industry) will not likely develop in the U.S. market in the near future.

As shown in Figure 3, nearly half of the companies currently manufacturing or developing active substances for follow-on biologic manufacturers outside of the U.S. and EU have no prior experience with supplying active ingredients to regulated markets and lack manufacturing sites that meet good manufacturing practice (GMP) standards.

FIGURE 3: Number of Companies Currently Manufacturing or Developing Active Substances For Follow-on Biologics



Due to the size of the domestic market in China, there is plenty of opportunity for growth in the local follow-on biologic industry. High drug prices and limited competition in the domestic market will act as an incentive for local manufacturers to generate follow-on biologic products. Companies in China that gain experience in the growing domestic market will likely compete in regulated markets like the U.S. in the long term.³⁵ It is worth noting that in China, development of MAb products is currently limited due to the high technical barriers. Delayed progress in manufacturing these complex products is a function of difficulty of scale-up technology and a low number of novel products.

Opportunities for follow-on biologic development in India may also provide incentive for regional growth. Regulatory requirements in India are not as strict as those in the U.S. and provide domestic manufacturers with the ability to manufacture follow-on products at a lower cost. Additionally, approved biosimilars are substituted automatically in India, which generates incentive similar to the small-molecule market in the U.S. The difference in required investment for regulatory approval in India and the U.S. may result in Indian generic companies initially focusing product launches in unregulated and semi-regulated markets only.³⁶

Global development of follow-on biologics will continue with the increasing demand for the lower-cost therapies and increased patient access. Due to financial opportunity in local markets and the high cost of regulatory requirements in the U.S., most manufacturers in emerging markets will not likely compete in the U.S. follow-on biologic market in the near term. This is likely to change as international competitors gain more experience in the development and technology associated with biologics.

COMPETITIVE LANDSCAPE: WHAT YOU NEED TO KNOW

- Short-term competition is likely from major generic players. Depending on the regulatory strategies employed by these companies, a trend toward gaining approval through the BLA process instead of the new pathway may be established.
- Big Pharma will meet follow-on biologics competition with increased innovation but could also participate in biosimilar development due to available capital and experience.
- In addition to follow-on biologics, Big Pharma companies will also look to develop “me too” biologics.
- Emerging markets will have more local competition than regulated markets.
- Follow-on biologic manufacturers in emerging markets achieving success domestically will likely compete in the U.S. in the long term.

STRATEGIC ALLIANCES

Companies unable to develop cost-effective, high-quality biologic therapies in-house will need to develop new strategies to remain competitive in the biosimilar market.³⁷ Small and large competitors may focus on internal strategies, such as process optimization, to mitigate manufacturing inefficiencies and reduce excess developmental costs.³⁸ Gaining significant revenue in the biosimilar market can also be achieved by exploring external opportunities. Acquiring a competitive advantage through dealmaking is a common strategy in the biologics landscape.³⁹

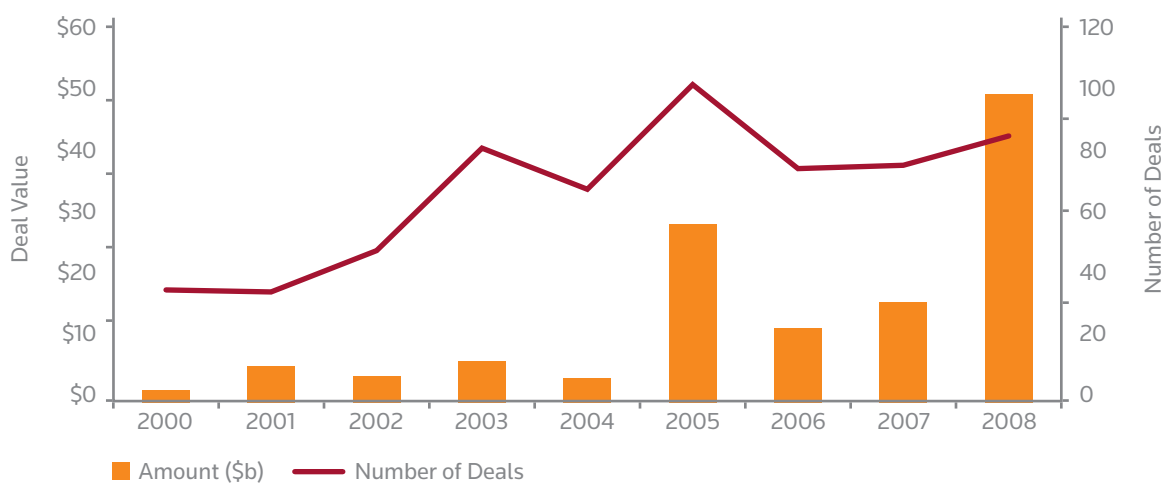
This section highlights trends related to biologic deals and provides insight to the strategic moves that may create a competitive advantage for companies in the U.S. market.

Trends

Since 1995, merger and acquisition transactions have highlighted the many barriers to entry required to compete with biosimilars in regulated markets. Due to costly process and manufacturing requirements, many companies have based investment decisions on the complexity of targeted products. Thus far, the majority of biologic-related deals have been associated with product development, technological innovation, and marketing/distribution.⁴⁰

As seen in Figure 4, companies associated with manufacturing follow-on biologic products are making deals more so now than ever before. The number of deals made by companies associated with follow-on biologic development has tripled since 2000. In 2008, the total number of deals first announced was 86, which had a combined value of about \$50 billion. As competition increases in this market, it is expected that deals by companies developing follow-on biologics will continue to grow.

FIGURE 4: Deal Activity by Companies Associated With Follow-on Biologic Development



Over the past two decades, deals associated with product development reveal an interesting trend. Prior to 2006, most deal activity related to biologic development involved recombinant protein products. This first wave included major deals by leading generic companies, such as Teva, Hospira, and Ratiopharm.

After 2006, deals based on monoclonal antibody development became more common. This second wave of deals associated with biologic production underscores the shift toward MAb development by major companies. Many of the same companies associated with protein-related deals also competed for investment in MAb development.

A third wave of deals based on complex product development has emerged in the vaccine market. Due to high sales in the U.S., it is expected that deals based on vaccines, MAbs, and recombinant proteins will continue to increase.⁴¹

One attribute of successful competition in the U.S. follow-on biologics market will be effective design and implementation of product development strategy. As business leaders manage the costs and requirements to create successful follow-on biologics, areas that will delay progress will be identified. These gaps in relevant experience and technology will create opportunity for biotech companies to generate innovative solutions and incentivize additional competition. Companies unable to develop products internally will look to gain a competitive advantage by making strategic deals with innovative companies based on new and proven technologies.

Protein expression and purification technology is a major component in biological product development. Biotech companies will develop systems with high yields and enhanced solubility to attract manufacturers without these processes in place. Expression systems that mitigate development costs will also draw attention from follow-on biologic competitors. Additionally, novel expression techniques, such as plant cell systems, offer an alternative approach to established cell expression techniques, such as E. coli and yeast.

A closer look at recent deals by Teva provides insight into the strategies other competitors may employ as well to gain an advantage in follow-on biologics development.

- The 2004 purchase of the U.S. company SICOR, with a biologics facility in Lithuania, gave Teva capacity to manufacture biologic products. This move came directly after biosimilar regulations were passed in the EU.
- Teva purchased the Chinese interferon product market leader Tianjin Hualida in 2005.
- In 2006, Teva entered a Collaboration and Licensing Agreement with the Israeli company Protalix Biotherapeutics for the development of products with Protalix's novel protein expression system, ProCellEx™. This plant cell-based expression technology at Protalix has also attracted Pfizer, which entered into an arrangement with Protalix in December 2009 to develop and commercialize the product taliglucerase alfa.⁴²
- In 2008, Teva purchased CoGenesys, a biotech company involved in the development of albumin-fusion technology. This strategic investment presented Teva with an opportunity to apply the albumin-fusion technology to extend the half-life of protein products.⁴³
- In January 2009, Teva formed an alliance with Lonza, one of the world's most established contract biomanufacturers, to develop follow-on biologic products. The companies formed the joint venture to develop complex biologic products, such as monoclonal antibodies.

The emergence of biosimilar products in the U.S. market will benefit contract manufacturing organizations, too.⁴⁴ Outsourcing can provide smaller companies with resources and capacity that may be too expensive to develop in-house. More-established businesses will look to outsource aspects of the manufacturing process to reach capital efficiency. Furthermore, companies aiming to improve an existing biologic product may seek specialized expertise of a contract manufacturer to help provide an advantage in the market.⁴⁵

Current strategies for companies investing in follow-on biologic development focus on novel technologies and manufacturing experience. Improved efficacy and safety of products that employ these new technologies and manufacturing practices will increase incentive for innovative process development. Strategic deals will focus on additional solutions that will provide a competitive advantage in the follow-on biologic market in the U.S. and globally.

LOOKING FORWARD

Over the past 25 years, provisions of the Hatch-Waxman Act have dramatically changed the pharmaceutical industry and created major cost savings within the healthcare sector. Due to the infancy of the follow-on biologic market, and the expectation of further amendment to the relevant legislation, it is uncertain if the abbreviated regulatory approval pathway for biosimilars will create the same impact as the Hatch-Waxman Act. While industry leaders develop business strategies relating to follow-on biologic manufacturing with some uncertainty, we believe the following can be expected:

Regulatory requirements for follow-on biologic products in the U.S. are likely to change.

- Pressure from policymakers and industry leaders to reform the legislation remains, and the demand for price reduction and increased patient access is increasing. If follow-on products can meet or exceed safety and efficacy requirements, additional pressure will be put on policymakers to amend the current legislation to make it easier to get interchangeable products to market.

Although the global follow-on biologics market is still nascent, it is growing rapidly and eventually will produce competition in the U.S.

- Companies manufacturing follow-on biologics outside of regulated markets will gain experience by meeting local demand. The manufacturers achieving success in emerging markets will obtain the necessary experience over time to either attract the attention of major regulated-market players interested in strategic partnering or to compete in the U.S. market on their own.

Technological advancements will attract collaboration and, in the long run, drive down the cost of follow-on biologics manufacturing.

- Competition in the biologic market has increased dramatically over the past decade. As the number of biologic-based deals continues to grow, biotech companies are incentivized to create more cost-effective technologies.

Cost savings in the U.S. will be significant due to follow-on biologics entry but will not be as dramatic as in the small-molecule market.

- Competition in the U.S. will occur. However, it will probably be similar to the injectable generic market in the U.S., which until recently was less crowded than the oral solids market. In the longer term, due to global development and the drop in manufacturing costs in the U.S., the follow-on biologics market will be more reflective of the small-molecule market.

APPENDIX 1: GENERAL U.S. REGULATIONS FOR FOLLOW-ON BIOLOGICS

APPROVAL REQUIREMENTS: GENERAL	<p>Applicant can only be evaluated against one reference product.</p> <p>Mechanism of action(s), condition(s) of use, route of administration, dosage form, and strength of applicant product must be the same as the reference product, to the extent that it is known.</p> <p>FDA may waive additional requirements on a case-by-case basis.</p>
APPROVAL REQUIREMENTS: BIOSIMILAR	<p>Products deemed “biosimilar” must meet general requirements.</p> <p>Biosimilar applicants must show through analytical studies that it is “highly similar” to a reference product. Additional animal studies and clinical studies will be required to provide data demonstrating the product’s “safety, purity and potency.”</p>
APPROVAL REQUIREMENTS: INTERCHANGEABLE	<p>Products deemed “interchangeable” must meet all of the requirements of the biosimilar product and also prove that there is no increase in risk of safety or diminished efficacy when switching between the reference drug and the follow-on product verses the risk of using only the reference product.</p>
EXCLUSIVITY: REFERENCE PRODUCT	<p>FDA can accept applications for follow-on products four years after the reference product was first approved.</p> <p>FDA can approve follow-on biologic products 12 years after the reference product was first approved. Both time frames may be prolonged by six months if the reference product is granted a pediatric extension.</p>
EXCLUSIVITY: INTERCHANGEABLE	<p>FDA cannot determine any additional follow-on products interchangeable with the reference product until one year after the first interchangeable product is approved.</p>
AUTOMATIC SUBSTITUTION	<p>Products receiving approval for interchangeability are able to be substituted with the reference product “without the intervention of the healthcare provider who prescribed the reference product.”</p>

REFERENCES

- ¹ clinicaltrials.gov
- ² *Newport Premium*
- ³ Shapiro, Robert J., et al., "The potential American market for generic biological treatments and the associated cost savings," February 2008.
- ⁴ Szabo, L., "Cost of cancer drugs crushes all but hope," *USA Today*, July 2006.
- ⁵ Shapiro, 12.
- ⁶ Congressional Budget Office, *Cost Estimate: S.1695, Biologics Price Competition and Innovation Act of 2007*, June 2008.
- ⁷ Holman, Christopher M., "Maintaining incentives for healthcare innovation: A response to the FTC's report on follow-on biologics," *Minnesota Journal of Law, Science & Technology*. 2010;11(2):755-800.
- ⁸ Tam, J. W. Y., "Biologics revolution: the intersection of biotechnology, patent law, and pharmaceutical regulation," 98 *Georgetown Law Journal* 535, 540 (2010).
- ⁹ Congressional Budget Office, *A CBO study: How increased competition from generic drugs has affected prices and returns in the pharmaceutical industry*, July 1998.
- ¹⁰ Biotechnology Industry Organization, *A follow-on biologics regime without strong data exclusivity will stifle the development of new medicines*, 2007.
- ¹¹ Grabowski, H., "Data exclusivity for new biological entities," Duke University Department of Economics Working Paper, June 2007.
- ¹² Brill, A., "Proper duration of data exclusivity for generic biologics: A critique," November 2008.
- ¹³ Generic Pharmaceutical Association, *Statement on BIO's flawed data exclusivity white paper*, January 2009.
- ¹⁴ "Richwine, L., "White House: 7 years enough to shield biotech drugs," *Reuters*, June 2009.
- ¹⁵ Federal Trade Commission Report, *Emerging health care issues: follow-on biologic drug competition*, June 2009.
- ¹⁶ *Ibid*
- ¹⁷ Holman, 786.
- ¹⁸ "Drug Price Competition and Patent Term Restoration Act," P.L. 98-417, September 1984.
- ¹⁹ Newport Research, 2010.
- ²⁰ *Ibid*
- ²¹ "Icelandic drugmaker Actavis up for sale", *Reuters*, January 8, 2009.
- ²² Mody, R., Varshney, B., and Patankar, D. "Understanding variations in biosimilars: Correlation with risk and regulatory implications," *The International Journal of Risk and Safety in Medicine*, 22 (2010), 27-40.
- ²³ *Ibid*
- ²⁴ Roger, Simon D. "Biosimilars: current status and future directions," *Expert Opinion on Biological Therapy*, July 2010.
- ²⁵ Federal Trade Commission Report, *Emerging health care issues: follow-on biologic drug competition*, June 2009
- ²⁶ Habib-Valdhorn, S., "Teva delayed in biogenerics," *Globes*, October 2010.

²⁷ Hospira.com

²⁸ McCaughan, M., "Follow-on biologics: is there a pathway?" *invivoblog.blogspot.com*, May 2010.

²⁹ Ibid

³⁰ Note that Omnitrope is also approved in the US, but through the New Drug Application process.

³¹ EP Vantage, "Merck's ditching of aranesp biosimilar highlights follow-on-biologics pitfalls," *seekingalpha.com*, May 2010

³² Ahmed, R., Becker, N., "Pfizer, Biocon in insulin licensing deal," *Wall Street Journal*, October 2010.

³³ "Reddy's plans to file regulated biosimilars," *Generics Bulletin*, November 2010.

³⁴ "Newport Research , 2010.

³⁵ Chen, C., "Challenges and opportunities of monoclonal antibody manufacturing in China," *Trends in Bio/Pharmaceutical Industry*, 5(3), 2009.

³⁶ Ariyanchira, S., "The opportunity for India in the global biosimilars market," *pharmaphorum.com*, June 2010.

³⁷ Fernandez, P., "The changing landscape for biosimilars," *Pharmaceutical Technology Europe*, 22 (8), August 2010.

³⁸ Sinclair, A. and Monge, M. "Influence of process development decisions on manufacturing costs," *BioProcess International*, 8 (8), September 2010.

³⁹ Carroll, J. "Novartis biosimilars point to a blockbuster future," *fiercebiotech.com*, October 2010.

⁴⁰ Newport Research, 2010.

⁴¹ Ibid

⁴² protalix.com

⁴³ "CoGenesys' \$55M financing makes HGS spinout official," *BIOWORLD*, June 2006.

⁴⁴ Puppe, J., "A positive outlook for outsourcing biologics," *Next Generation Pharmaceutical*, 3, March 2007.

⁴⁵ Ibid



REUTERS/Petr Josek

BIOLOGICS

ONE OF OUR NEW OPTIONAL MODULES

Follow-on biologics are fast becoming a reality in global pharmaceutical markets. The passing of the 2010 Healthcare Reform Act defines the framework and exclusivity rules concerning biosimilars in the US, and is expected to fuel increased activity in this important area for generics, traditional small-molecule focused innovators, and biotech companies.

The *Newport Biologics Module* contains unique manufacturing process data covering biologic drugs. Companies considering pursuing biosimilar opportunities can analyze multiple potential bio-manufacturing processes for each drug, genetic sequences, process steps, starting materials, and equipment required, as well as review related patents and literature references. Also included is US BLA (Biologics License Application) data for drugs approved through this regulatory route.

HOW TO SUBSCRIBE

The *Newport Biologics Module* is an optional subscription module that may be added to your *Newport Premium™* subscription for an additional annual charge.

To get a quotation, contact your account manager or visit interest.science.thomsonreuters.com/forms/newport_biologics_module

Also available to enhance your subscription are modules covering *Generic Deals*, *Phase III Drugs* and *US Market Share*.



To sign up to our *Pharma Matters* range of publications visit:
science.thomsonreuters.com/info/matters

THE ONES TO WATCH

Focuses on the latest phase changes in the pharmaceutical pipeline.

MOVERS AND SHAKERS

Unravels the most significant game-play in the U.S. generics market.

WHO IS MAKING THE BIGGEST SPLASH

Reviews the leading sources of information on medical research.

ABOUT NEWPORT PREMIUM

Newport Premium is the critical product targeting and global business development system from Thomson Reuters, the industry authority on the global generics market.

Created specifically for generic pharmaceutical companies and strategic API manufacturers, it can help you to identify and evaluate product opportunities worldwide, ensuring you'll be first to find the generic product and niche opportunity, first to make the deal, and first to get to market.

ABOUT THOMSON REUTERS PHARMA

Thomson Reuters Pharma brings together the best pharmaceutical data owned by Thomson Reuters in a single comprehensive solution containing millions of pieces of information. And it's not just data. *Thomson Reuters Pharma* extends and deepens its knowledge with unique abstracts, commentaries and analysis prepared by our team of industry experts. You can link at a click between different types of content. No other data source puts so much information at your fingertips.

In place of your legacy indexing systems, multiple interfaces, and complex data sources, imagine how *Thomson Reuters Pharma* can simplify your information needs, justify and speed your decision-making, and keep you abreast of the market.

ABOUT THOMSON REUTERS

Thomson Reuters is the leading source of intelligent information for professionals around the world. Our customers are knowledge workers in key sectors of the global economy. We supply them with the intelligent information they need to succeed in fields that are vital to developed and emerging economies such as law, financial services, tax and accounting, healthcare, science and media.

Our knowledge and information is essential for drug companies to discover new drugs and get them to market faster, for researchers to find relevant papers and know what's newly published in their subject, and for businesses to optimize their intellectual property and find competitive intelligence.

NOTE TO PRESS:

To request further information or permission to reproduce content from this report, please contact:

Paul Sandell
Phone: + 44 20 7433 4704
Email: paul.sandell@thomsonreuters.com

For more information, please visit:

go.thomsonreuters.com/newport
go.thomsonreuters.com/thomsonpharma

HEALTHCARE & SCIENCE

REGIONAL OFFICES

North America

Philadelphia +1 800 336 4474

+1 215 386 0100

Europe, Middle East, and Africa

London +44 20 7433 4000

For a complete office list visit:

science.thomsonreuters.com/contact

