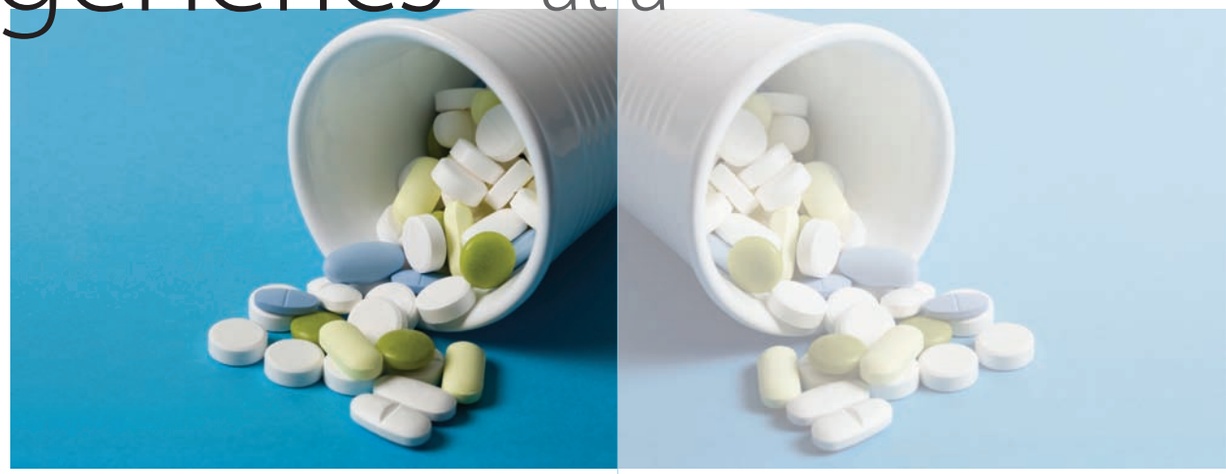
BY CYNTHIA BORDA

Biogenerics at a CROSSROAD



ALTHOUGH THERE ISN'T A CLEAR REGULATORY PATHWAY FOR BIOSIMILAR PRODUCTS, some companies are forging ahead and forcing regulators and legislators to reconsider how biologics reach the market.

Over the past few years, several forces have begun to converge that will likely shift the entire biomarket's dynamics. Patents of top-selling biotechnology products have lost or will lose patent protection in the next half dozen years (see chart on page 46 for more information). A variety of legal and legislative moves are focusing on the regulation of biogenerics. And companies at the forefront of these changes are creating the pathways that others could follow.

In June 2007, the Senate approved the Biologics Price Competition and Innovation Act of 2007 (S. 1695), which would establish a pathway for the licensure of biosimilar biological products. This follows an effort in the U.S. House of Representatives by Henry Waxman in late September 2006, who introduced H.R. 1038, the Access to Life-Saving Medicine Act, which would allow abbreviated biogeneric applications based on BLA-registered reference products. The bill was reintroduced in February 2007 as an amendment to the PHS Act, which would provide two regulatory designations for biogenerics: "comparability" or "interchangeability."

Biosimilars are protein products that are manufactured using biotechnology or derived from natural sources that are intended to be similar to a product already approved and the applicant relies, in part, on certain scientific knowledge about the approved products to demonstrate safety and effectiveness.

Because follow-on biologics drugs are developed through biological processes rather than manufactured in the traditional sense, they pose special difficulties for approval and safe use.

Last year, two companies made history when they received European approval for their biosimilar products. In April 2006, Sandoz was the first company to receive European approval for such a medicine, the human growth hormone Omnitrope. U.S. approval was granted in May 2006. In its regulatory applications, Omnitrope referenced Pfizer's Genotropin. That same month, BioPartners' hGH biosimilar, Valtropin, received EU approval for Turner's syndrome and human growth deficiency in children. Valtropin is a biosimilar of Eli Lilly's Humatrope.

The four classes expected to play the largest role in the biologic market

1. Erythropoiesis stimulating proteins (ESPs)
2. Granulocyte colony stimulating factors (G-CSFs)
3. Insulin and insulin analogues
4. Human growth hormone (hGH)

Biogeneric sales in the United States of these four classes are expected to top $2.2 billion by 2015.

— Decision Resources

STEVEN BRUGGER
Momenta Pharmaceuticals

Each follow-on protein product needs to be evaluated individually. Any legislation should allow the FDA the discretion to review products on a case-by-case basis.

In June 2007, Sandoz also received a positive opinion from the European Medicines Agency (EMEA) for approval of epoetin alfa biosimilar. The recommendation supports the use of epoetin alfa for use in treating patients with renal anemia as well as those receiving chemotherapy.

Despite these few successes, the development of biosimilars is complicated by several factors. Experts say one of the biggest obstacles is a lack of a regulatory foundation in the United States for evaluating similar biologics.

"Policymakers, patients, and the industry must work together to develop a science-based pathway for biosimilars that is fair and reasonable, that applies consistent and appropriately high regulatory standards to all biologics, that ensures that patients will have greater access to safe and effective medicines, and that promotes competition while continuing to encourage innovation by respecting legitimate intellectual property rights," states Ajaz Hussain, Ph.D., VP and global head of biopharmaceuticals development for Sandoz, the generic division of Novartis.

REGULATORY **ISSUES**

U.S. regulatory authorities have claimed that the current law does not address how to review abbreviated applications for biosimilar products that reference biologics already approved, and the agency is being cautious. In fact, when approving Sandoz's Omnitrope, the FDA described it as "comparable to," but not equivalent to, Pfizer's Genotropin.

WILLIAM SCHULTZ, Zuckerman Spaeder

The question is should the FDA be given the discretion to require additional clinical studies for follow-on biologics, or should there always be the requirement of additional clinical studies even if the FDA would conclude they are not necessary.

In a posting on its Website, the FDA emphasized that Omnitrope does not establish a pathway for approval and that Congress must still act to give the agency authority to address future biogeneric applications.

"Legislation must allow each product individuality and allow the FDA discretionary review on a case-by-case basis," says Steven B. Brugger, senior VP of strategic business operations at Momenta Pharmaceuticals Inc. "In the short term, developing truly interchangeable generic versions of biologic drugs will be difficult, due to the challenges in characterizing these complex biomolecules. But as the characterization science advances from companies like Momenta and others, approval of interchangeable follow-on biologics will become a reality. Therefore, we don't want to stifle innovation through legislation."

It is unlikely that legislation will be enacted this year, although it's not impossible, says William B. Schultz, a partner at Zuckerman Spaeder LLP.

"There needs to be a general recognition by Congress of the critical importance of the legislation before a bill will move forward," he says. "The question is should the FDA be given the discretion to require additional clinical studies for follow-on biologics, or should there always be the requirement of additional clinical studies even if the FDA would conclude they are not necessary."

Europe has been more proactive on this issue. The EMEA has issued several documents, including a number of guidances on the development of biosimilar products. A draft guidance was issued in November 2004 by the Committee for Medicinal Products for Human Use (CHMP). It was adopted in September 2005.

In a June 2007 question-and-answer document, the European authority pointed out that because of the complex method of production of biological medicines, the active substance may differ slightly between the biological reference and the biosimilar medicine. Therefore, studies comparing the two medicines have to be carried out. These studies involve a step-by-step process starting with a comparison of the quality and the consistency of the medicinal product and of the manufacturing process.

"Europe has set forth testing guidelines to be required on a case-by-case basis, which we support," says Audrey Phillips, Ph.D., executive director, biopharmaceutical public policy, Johnson & Johnson. "The testing is substantial, although the process allows for an abbreviated pathway."

Eight top-selling biologic agents will have lost patent protection by 2014, making this period a likely inflection point in the uptake of biogenerics and erosion of branded biologic revenue. Of the blockbuster biologics, Epogen and Procrit are likely to become the most popular targets for early biogenerics.

— Decision Resources

SAFETY **ISSUES**

Experts agree that the science of producing a follow-on biologic is different from producing a generic for a small-molecule agent.

The standard generic approach (demonstration of bioequivalence with a reference medicinal product by bioavailability studies) is normally applied to chemically derived medicinal products. Experts agree that because of the complexity of biological/biotechnology-derived products the generic approach is scientifically not appropriate for these products.

Another issue is understanding the mechanism of action of the biologic. In some cases, such as insulin or growth hormone, the action is well understood, while for others the mechanisms of action are not well-understood.

Immunogenicity is the ability of the body to stimulate an immune response or adverse event due to recognizing a foreign body or, in

TROY HAMPTON, Campbell Alliance

Depending on the pricing, **payers are likely to take a tier-based approach to biosimilars.**

DR. AJAZ HUSSAIN, Sandoz

U.S. policymakers, patients, and the industry must work together to develop a science-based pathway for biosimilars that is fair and reasonable and that applies consistent and appropriately high-regulatory standards to all biologics.

this case, a biologic. Therefore, biologics can cause the body to produce antibodies to neutralize or fight the foreign substance. This reaction is important to patient safety and can be induced by the individual patient, the disease, or the product.

"The potential for an immunogenic response makes automatic switching between similar products very dangerous because tracing adverse events to a specific product would be difficult," Dr. Phillips says.

Two generics companies — Sandoz (with Omnitrope) and BioPartners (with Valtropin) — made history in spring 2006 by fielding the first two approved biosimilars in the European Union; Omnitrope has also gained FDA approval.

— Decision Resources

Johnson & Johnson learned firsthand how a slight change in a product could induce an immunogenic response. About a decade ago, European authorities requested that the company remove human serum albumin (HSA) as the stabilizer in its erythropoietin product, Eprex, because of a concern about Mad Cow disease. Johnson & Johnson replaced HSA with Polysorbate 80. This simple change caused an interaction between uncoated rubber stoppers used in some prefilled syringes and the new stabilizer, resulting in an increased incidence of antibody-mediated pure red cell aplasia (PRCA). PRCA is a rare but serious condition in which the bone marrow stops making red blood cells.

"It took $100 million and more than 100 scientists over a four-year period to correct the situation," Dr. Phillips says. "This is an example of how even a slight change can affect patient safety."

Any biogeneric company must have extensive knowledge of the product and manufacturing process and should be held to the same high standards as the branded product, Mr. Brugger says.

"Ensuring patient safety must be our No. 1 priority," he says. "From a scientific perspective, we are now advancing our technology platform to be able to characterize the complex protein products by going all the way back to the cell line to build an understanding of the key ingredients and process."

Momenta Pharmaceuticals is founded on technology developed at the Massachusetts Institute of Technology (MIT). The company partnered with Sandoz in 2003 and submitted an ANDA in 2005 for its generic version of the low-molecular weight heparin enoxaparin, which is sold as Lovenox by Sanofi-Aventis.

Momenta and Sandoz extended their collaboration in 2006 to develop four complex generic and follow-on protein products.

THE MARKETPLACE

The biotechnology field has grown dramatically and is one of the fastest growing segments of the pharmaceutical industry, according to a 2006 report from Decision Resources. IMS Health estimates from 2005 indicate a 17.1% increase in sales, which translates into more than $50 billion. Biologics represent almost one-third of the clinical products in development.

According to Decision Resources, there are various factors that will impact biogenerics on the biologics market, including launch date, price competitiveness, and adoption by the physicians and payers.

The four classes expected to play the largest role in market share will be the erythropoiesis stimulating proteins (ESPs), granulocyte colony stimulating factors (G-CSFs), insulin and insulin analogues, and the human growth hormone (hGH). Biogeneric sales in the United States of these four classes are expected to top $2.2 billion by 2015, according to Decision Resources.

U.S. payers expect to incorporate biogeneric agents into their formularies quite rapidly; about 90% of U.S. payers surveyed predict that their formularies will include biogeneric products within one year of their availability.

— Decision Resources

Within the payer market, several topics are being discussed, says Troy Hampton, senior practice executive, managed markets practice, at Campbell Alliance.

"Some issues being considered include: how biogenerics will be defined, how they will be evaluated, and how they will be managed," he says. "Many of the managed-care market decision makers offer that there is less likelihood of a therapeutic interchange in the short-term. At this point, biosimilars will likely have a full review by payers. Abbreviated reviews will occur based on guidance from the FDA. Managing products will likely be a tier-based approach, but will be directly impacted by where the pricing falls."

The main driver for biosimilar acceptance will be the cost savings, he says.

A Decision Resources survey of U.S. pharmacy directors reveals that biogenerics should expect a warm welcome from payers and rapid adoption upon their approval if they are priced at a significant discount to their branded counterparts. Pharmacy directors are expected to encourage adoption through standard managed care pharmacy benefit strategies, such as preferred placement for biogenerics on formularies and reduced costs to patients.

Specifically, U.S. payers intend to place

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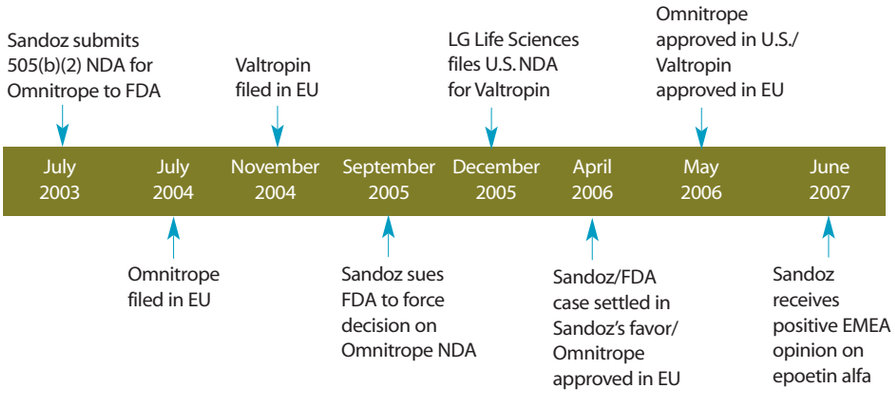
TIMELINE OF **BIOGENERICS COMMERCIALIZATION MILESTONES**



Source: Decision Resources Inc., Waltham, Mass. For more information, visit decisionresources.com.

PATENT AND EXCLUSIVITY EXPIRATIONS **OF KEY BIOLOGICS**

Drug	2006 Global Sales	United States	France	Germany	Italy	Spain	United Kingdom
Enbrel	$2,879	2012	2014	2014	2014	2014	2014
Remicade	$3,013	2014	2014	2014	2014	2014	2014
Rituxan	$2,882*	2015	2013	2013	2013	2013	2013
Epogen	$2,511	2013	2007	2004	2007	—	2004
Procrit/Eprex	$3,180	2013	2007	2004	2007	—	2004
Aranesp	$4,121	—	2014	2014	2014	2014	2014
Neupogen	$3,923**	2013	2006	2006	2006	2006	2006
Neulasta	$3,923**	2015	2017	2015	2017	2017	2017
Betaseron	$737	2007	2008	2008	2008	2008	2008
Avonex	$1,707	2013	2005	2005	2005	2005	2005
Rebif	$1,451	2013	2013	2013	2013	2013	2013

Notes: Dollars are in millions. Sales data are from individual companies.
* Genentech recognizes all U.S. sales of Rituxan of $2.07 billion; Biogen Idec recognizes worldwide sales of $811 million.
** Amgen reports combined sales for Neulasta and Neupogen.

Source: Patent expirations from Decision Resources Inc., Waltham, Mass. For more information, visit decisionresources.com.

biogenerics on lower tiers than originator brands, and they may opt to drop formulary coverage of branded agents. Many will employ step-therapy techniques to encourage use of biogenerics before branded comparators and second-generation branded agents.

Respondents believe that biogenerics should be priced at a discount of about 35% relative to the branded agent as a way to encourage physicians to prescribe them. U.S. payers expect to incorporate biogeneric agents into their formularies quite rapidly; about 90% of U.S. payers surveyed predict that their formularies will include biogeneric products within one year of their availability.

A Decision Resources survey of 160 oncologists and endocrinologists in the United States, France, and Germany reveals that physicians are receptive to the arrival of biogenerics and expect to incorporate these products into their treatment practices.

Specialists in all three countries identify efficacy and safety as the most important attributes for regulators to scrutinize when evaluating biogeneric products. They expect to adopt biogeneric agents rapidly. In fact, 80% of U.S. respondents expect to prescribe them within their first year on the market. European physicians expect a slightly more conservative adoption rate, but 80% to 90% of these specialists believe they will begin prescribing biogenerics within two years. ✦

PharmaVOICE welcomes comments about this article. E-mail us at feedback@pharmavoice.com.

Experts on this topic

STEVEN B. BRUGGER. Senior VP, Strategic Business Operations, Momenta Pharmaceuticals Inc., Cambridge, Mass.; Momenta is a biotechnology company specializing in the detailed structural analysis and development of complex mixture drugs. For more information, visit momentapharma.com.

TROY HAMPTON. Senior Practice Executive, Managed Markets Practice, Campbell Alliance, Raleigh, N.C.; Campbell Alliance is a management consulting firm specializing in the pharmaceutical and biotech industries. For more information, visit campbellalliance.com.

AJAZ S. HUSSAIN, PH.D. VP and Global Head of Biopharmaceuticals Development, Sandoz Pharmaceuticals, Princeton, N.J.; Sandoz is a division of Novartis Pharmaceuticals that develops, manufactures, and markets off-patent medicines, as well as pharmaceutical and biotechnological active ingredients. For more information, visit sandoz.com.

AUDREY PHILLIPS, PH.D. Executive Director, Biopharmaceutical Public Policy, Johnson & Johnson Pharmaceutical Services LLP, New Brunswick, N.J.; Johnson & Johnson is a comprehensive and broadly based manufacturer of healthcare products, as well as a provider of related services, for the consumer, pharmaceutical, medical-device, and diagnostics markets. For more information, visit jnj.com.

WILLIAM B. SCHULTZ. Partner, Zuckerman Spaeder LLP, Washington, D.C.; Zuckerman Spaeder is a law firm whose FDA practice represents individuals, generic, and small biotechnology companies, state governments, associations, and advocacy organizations before the courts, government agencies, and Congress. For more information, visit zuckerman.com.