By Henry G. Grabowski, Rahul Guha, and Maria Salgado

ABSTRACT In March 2010 Congress established an abbreviated Food and Drug Administration approval pathway for biosimilars—drugs that are very similar but not identical to a reference biological product and cost less. Because bringing biosimilars to the market currently requires large investments of money, fewer biosimilars are expected to enter the biologics market than has been the case with generic drugs entering the small-molecule drug market. Additionally, given the high regulatory hurdles to obtaining interchangeability—which would allow pharmacists to substitute a biosimilar for its reference product, subject to evolving state substitution laws—most biosimilars will likely compete as therapeutic alternatives instead of as therapeutic equivalents. In other words, biosimilars will need to compete with their reference product on the basis of quality; price; and manufacturer’s reputation with physicians, insurers, and patient groups. Biosimilars also will face dynamic competition from new biologics in the same therapeutic class—including “biobetters,” which offer incremental improvements on reference products, such as extended duration of action. The prospects for significant cost savings from the use of biosimilars appear to be limited for the next several years, but their use should increase over time because of both demand- and supply-side factors.

The Biologics Price Competition and Innovation Act of 2009, which took effect in March 2010 as part of the Affordable Care Act, established an abbreviated pathway for the Food and Drug Administration (FDA) to use in approving biosimilars. Biosimilars are drugs that are manufactured from large-scale cultures of living cells and that are very similar—but not structurally identical—to older, more established drugs regarded as innovator or reference products.

Under the 2009 act, biosimilar manufacturers must provide evidence to the FDA that there are no meaningful differences between their product and the reference product in terms of safety, purity, and potency. The FDA is in the process of establishing specific regulatory requirements for biosimilar approval.

Competition between biosimilars and reference products is of particular interest to US policymakers and insurers because the United States has been the center of global biotech innovation and is the country with the largest expenditures on biological products. New biological entities have resulted in substantial improvements in survival, morbidity, and quality of life for patients with various cancers and autoimmune diseases. However, these entities can cost tens of thousands of dollars per course of treatment.

In this article we consider the economic opportunities for the manufacturers of biosimilars...
and the changes in regulations, insurance, physicians’ behavior, and patients’ characteristics that will shape the future of these products in the United States. We also consider how dynamic competition and incremental technological change can influence market outcomes and corresponding cost savings. We analyze some instructive US case histories and the experiences of biosimilar competition in Europe. In the final section of the article, we discuss potential costs savings from the use of biosimilars in the foreseeable future.

The US Market For Biologics And Biosimilars

The US market for biologics has been growing rapidly in recent years. Furthermore, many biologics are first-in-class and priority-review drugs for the FDA—products that are targeted for faster FDA review because they represent significant improvements over current therapies. More than six hundred biologic entities are in clinical pharmaceutical trials; together, they account for more than 40 percent of all such trials.

Seven of the twenty-one top-selling pharmaceuticals in 2011 were biologics. These blockbuster products, each with US sales in excess of $2.5 billion in that year, have approved uses for rheumatoid arthritis and other autoimmune diseases (Remicade, Enbrel, and Humira); anemia in dialysis and cancer patients (Epogen/Procrit); neutropenia, an infectious disease associated with low counts of white blood cells (Neulasta); or various oncology indications (Rituxin and Avastin). Furthermore, several other biological products had sales of approximately $1 billion or more in 2011 (Exhibit 1).

Many of these products could be subject to competition from biosimilars beginning in 2014, assuming regulatory approval from the FDA. However, it is important to recognize that there may be many subsidiary patents for the reference product that could delay biosimilars’ entry into the market. Such patents include those on the manufacturing process, which can be important in biotechnology. It is difficult to assess the strength and scope of these patents and the ability of biosimilars’ manufacturers to challenge or work around existing patents.

There is considerable uncertainty about the market entry dates for biosimilars. However, Exhibit 1 indicates that there are large potential commercial opportunities for companies with the resources to invest in biosimilar development and marketing.

Initial targets for biosimilar competition include the erythropoiesis-stimulating agents (ESAs) used to stimulate red blood cells for the treatment of anemia and the granulocyte-colony stimulating factors (G-CSFs) used to stimulate the growth of white blood cells to treat neutropenia. The first-generation products in these classes (Eprex and Neupogen, respectively) have already experienced competition from biosimilars in Europe for several years (Eprex is the recombinant erythropoietin product in Europe that corresponds to Epogen/Procrit in the United States). Monoclonal antibody products represent the largest potential commercial opportunity, but they are more complex molecules to develop and manufacture than ESAs and G-CSFs.

FDA Regulations And The Costs Of Developing A Biosimilar

The Biologics Price Competition and Innovation Act gives the FDA broad latitude to define the process and standards for approval of biosimilars. The extent of the evidence required by the FDA to gain approval will affect the costs of biosimilar market entry, the number of biosimilar entrants, and the degree of price and quality competition among biosimilars. Other FDA regulatory decisions about such points as the standards for interchangeability, naming conventions, and pharmacovigilance requirements could also play an important role in how competitive biosimilars become in the market.

The FDA has issued general draft guidelines for biosimilars that indicate that it will consider the totality of the evidence in granting biosimilar approval, including analytical data and the results of animal testing and clinical studies. The FDA is taking a flexible regulatory approach, given the possibility of significant technological changes in the ability to structurally characterize biological products—an approach described by the FDA as similar to fingerprinting that compares a large number of product attributes in two different products to quantify their similarity. These technological changes could reduce the need for expensive clinical trial data in the future.

However, clinical trials of biosimilars are expected to remain a prerequisite for gaining FDA approval for the foreseeable future. As a result, the costs and time to obtain FDA approval are likely to be dramatically higher for biosimilars than for generic drugs. Under the Hatch-Waxman Act of 1984, a generic manufacturer can obtain FDA approval through an Abbreviated New Drug Application demonstrating that the generic product is bioequivalent to the reference drug product and, as a result, relying on the reference drug’s clinical safety and efficacy data.

For complex biologics such as monoclonal
antibodies, developing a biosimilar could cost more than $100 million and take more than five years. This compares to a cost of $2–$5 million and a time span of two to three years for generic drugs. If the FDA will allow as evidence foreign clinical trial data for biosimilars that have already been approved in Europe, together with a bridging study that considers differences between US and European manufacturing and populations, the costs of US entry could be significantly reduced. In any case, the higher investment costs and longer times for biosimilar approval are likely to result in fewer entrants into the market and smaller discounts for biosimilars, compared to the situation for generic drugs.

Another major difference between biosimilars and generic drugs involves the issue of interchangeability. In the case of generic drugs, once a product receives an AB rating from the FDA—meaning that it is bioequivalent to its reference product—a pharmacist is allowed to automatically substitute the generic for the brand-name drug without physician approval, subject to state laws. For a biologic to be declared interchangeable with its reference product, section 7002 of the Biologics Price Competition and Innovation Act requires the manufacturer to show not only that its product is biosimilar to the reference product, but also that “it can be expected to produce the same clinical result as the reference product in any given patient.” The FDA has not provided guidance on the standard for interchangeability for biosimilars. However, it has signaled that the standard will likely involve much higher regulatory hurdles than those applying to biosimilarity alone, including postapproval data and potentially very expensive clinical studies. As a consequence, few if any biosimilar products are likely to be rated as interchangeable in the foreseeable future. Eventually, given technological advances, the FDA may be willing to accept that a biosimilar is both similar to and interchangeable with the reference product, based on a structural analysis that demonstrates the sameness of the two molecules.

The Roles Of Insurers, Physicians, And Patients

Large-molecule biological drugs are frequently either injected or infused in a hospital or clinical setting or self-injected at home. Many biological products are dispensed by a physician in a clinical setting where Medicare Part B is the primary payer. The strong incentives for physicians to use generics—fostered by Medicare Part B, where reimbursement is based on the average sales price of the brand-name drug and its bioequivalent generics—will not be present in the case of biosimilars if they are not rated as interchangeable with their reference products.

Congress anticipated the potential disincen-

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**EXHIBIT 1**

US Sales Of Leading Biological Products In 2011 And Earliest Reported Years Of Patent Expiry

<table>
<thead>
<tr>
<th>Product</th>
<th>Product type</th>
<th>Sales (millions of dollars)</th>
<th>Earliest reported year of key patent expiry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humira (adalimumab)</td>
<td>Monoclonal antibody</td>
<td>3,531</td>
<td>2016</td>
</tr>
<tr>
<td>Enbrel (etanercept)</td>
<td>Monoclonal antibody</td>
<td>3,507</td>
<td>---</td>
</tr>
<tr>
<td>Remicade (infliximab)</td>
<td>Monoclonal antibody</td>
<td>3,474</td>
<td>2018</td>
</tr>
<tr>
<td>Neulasta (pegfilgrastim)</td>
<td>G-CSF</td>
<td>3,316</td>
<td>2015</td>
</tr>
<tr>
<td>Rituxan (rituximab)</td>
<td>Monoclonal antibody</td>
<td>3,005</td>
<td>2016</td>
</tr>
<tr>
<td>Epogen or Procrit (epoetin alpha)</td>
<td>Erythropoietin</td>
<td>2,854</td>
<td>2013</td>
</tr>
<tr>
<td>Avastin (bevacizumab)</td>
<td>Monoclonal antibody</td>
<td>2,662</td>
<td>2019</td>
</tr>
<tr>
<td>Lucentis (ranibizumab)</td>
<td>Monoclonal antibody</td>
<td>1,767</td>
<td>2019</td>
</tr>
<tr>
<td>Herceptin (trastuzumab)</td>
<td>Monoclonal antibody</td>
<td>1,656</td>
<td>2019</td>
</tr>
<tr>
<td>Avonex (interferon beta-1a)</td>
<td>Interferon</td>
<td>1,558</td>
<td>2013</td>
</tr>
<tr>
<td>Rebif (interferon beta-1a)</td>
<td>Interferon</td>
<td>1,056</td>
<td>2013</td>
</tr>
<tr>
<td>Aranesp (darbepoetin)</td>
<td>Erythropoietin</td>
<td>986</td>
<td>2024</td>
</tr>
<tr>
<td>Neupogen (filgrastim)</td>
<td>G-CSF</td>
<td>945</td>
<td>2013</td>
</tr>
</tbody>
</table>

**SOURCE** Authors’ analysis of data from IMS Health and Securities and Exchange Commission 10-K filings for Epogen, Procrit, and Aranesp. **NOTES**

The earliest reported year of key patent expiry is based on a review of information disclosed in manufacturers’ financial reports, academic literature research reports, patent filings, and court documents. Other top-selling biological products—including the insulin products Humalog, Novolog, and Lantus—may lose protection from key patents by 2016. However, they were approved through new drug applications and are eligible for approval under an abbreviated pathway through the Hatch-Waxman process. G-CSF is granulocyte-colony stimulating factor. “Enbrel’s patent expiry was widely reported as 2012, but based on a patent issued in November 2011, Amgen now claims patent protection for it until 2028.”
tives for physicians to use less expensive biosimilars under Medicare’s average sales price approach. The Affordable Care Act mandated that Medicare Part B payment for a biosimilar product be based on the sum of its own average selling price plus 6 percent of the average selling price of the reference product. Hence, the law is designed to give physicians the same reimbursement, net of product costs, whether they dispense the biosimilar or the reference product.

The government and patients would benefit from lower biosimilar prices. However, this approach may not provide sufficient incentives for biosimilar use, given physicians’ experiences with, and brand loyalty to, the reference product. Medicare reimbursement will likely need to evolve to encourage the use of biosimilars, including such approaches as step therapy and bundled pricing.

In privately managed insurance plans, products dispensed by physicians have often been reimbursed under medical benefits instead of pharmacy benefits. Insurers have been reluctant to use strong cost control measures in the case of biologic products because they are often targeted at a life-threatening or disabling illness and frequently lack close substitutes.

However, as biologics account for an increasing proportion of expenditures on drug therapies, managed care organizations have begun to require prior authorization or step therapy for biologics, along with coinsurance payments in specialty drug tiers. Biologics that are used in the hospital setting and reimbursed under a bundled payment scheme, such as Medicare’s diagnosis-related groups, are likely to be most responsive to biosimilars’ price discounts relative to the reference products, particularly if a hospital’s pharmacy and therapeutics committee concludes that biosimilars are comparable to the reference product in therapeutic outcomes.

To the extent that biosimilars compete with the reference brand as therapeutic alternatives, their use is likely to be concentrated initially among treatment-naïve patients—that is, patients who have never used either the biosimilar or the reference product—instead of patients who are stable on the reference product. Another factor limiting biosimilar uptake will be the conservative approach of many physicians that makes them reluctant to switch patients who are stable on the reference product to a new therapy. The same is true of switches from one brand-name drug to another.

Other factors such as specialists’ brand loyalty and the conditions being treated will affect the rates of biosimilar uptake for existing patients as well as new ones. Relevant considerations in this regard include whether the disease or condition is life threatening, whether possible adverse reactions are perceived to be very serious, and whether the reference product and the biosimilar differ in ease of use and cost to the patient.

Over time, positive experiences with biosimilars and the provision of greater incentives by health plans for biosimilar use could lead providers and payers to increase their use of biosimilars, even if they are therapeutic alternatives instead of bioequivalent drugs. Biosimilar firms are also expected to need to do some traditional marketing and detailing—the industry term for direct encounters between pharmaceutical sales representatives and physicians. Such activities can help establish the reputation of biosimilars with hospital pharmacy and therapeutics committees and physicians as viable therapeutic options. This is also likely to add significant expense to the overall costs of biosimilars’ production and supply and to influence the number of entrants and the rate of biosimilar penetration in the market.

**Biosimilar Versus Generic Competition**

Because biosimilars require large investments of money before they can enter the market and are likely to be treated as therapeutic alternatives instead of equivalents, biosimilar competition will differ from generic competition for the foreseeable future. Generics rapidly penetrate the market, and generally provide large price discounts relative to reference brand-name drugs. In contrast, biosimilars’ ability to compete with reference products is likely to vary according to regulatory hurdles, therapeutic class, and disease indication. With fewer entrants into the market and a lack of interchangeability, competition between biosimilars and reference products is likely to resemble competition between brand-name drugs (which is based on differences in quality, price, and promotion) more than competition between a brand-name drug and a generic one (which is based primarily on price).

Another factor that will affect biosimilars’ market entry is the attractiveness of the option for a company to file a complete Biologics License Application instead of the abbreviated biosimilar application. This is the regulatory pathway—through section 351(a) of Biologics Price Competition and Innovation Act—used for new biological entities and improved formulations of existing molecules. A full Biologics License Application ostensibly would require more extensive clinical trial data. However, it could provide some strategic advantages in particular circumstances.

After passage of the Biologics Price Competi-
Biosimilars

price. with the reference product in areas other than the market of other biosimilars that compete may be delayed or discouraged by the entry into the way, the development of cost-saving biosimilars sponsors use the full Biologics License Application instead of following the biosimilars path-
sponsors engage in extra-cost requirements for biosimilars. Their products could in-
and would not be constrained by the require-
tions to multiple indications or wishes to seek an interchangeability rating.

In contrast, using a full Biologics License Application is more likely in product classes with an easy-to-prove end point and one prominent disease indication. Such an application may also be attractive when the innovator is developing a next-generation product that will divert sales from a first-generation biosimilar.

Sponsors using the full Biologics License Application pathway would likely seek to differentiate their products from the reference product and would not be constrained by the requirements of biosimilarity. Their products could incorporate deliberate differences from, or improvements to, the reference product, making the new products what are called “biobetters.” Marketing of these products also might focus on product quality, and the products may not offer significant (or even any) cost savings. Thus, if sponsors use the full Biologics License Application instead of following the biosimilars pathway, the development of cost-saving biosimilars may be delayed or discouraged by the entry into the market of other biosimilars that compete with the reference product in areas other than price.

The US Experience With Two Biosimilar-Like Drugs
To date, two biosimilar-like applications have been approved in the United States under the Hatch-Waxman regulatory regime. The first is the human growth hormone Omnitrope, whose reference product is Pfizer’s Genotropin. The second is m-enoxaparin sodium, an anticoagulant low-molecular-weight heparin whose reference product is Aventis’s Lovenox. Both cases involved some unique circumstances.

Omnitrope Omnitrope was approved by the FDA in October 2006 and launched on the market in January 2007. Human growth hormone drugs were legally subject to biosimilar competition under the Hatch-Waxman Act because the reference products were approved as New Drug Applications, which are used for small-molecule drugs, instead of as Biologics License Applications, which are used for biologics. This reflects the fact that reference recombinant products replaced previously approved human growth hormone drugs derived from natural sources. Omnitrope was not granted bioequivalent status to Genotropin by the FDA and was launched as a brand-name therapeutic alternative.

Omnitrope entered a mature human growth hormone market that already had several brand-name products, which were derived from recombinant somatropin (Exhibit 2). For several years Omnitrope struggled to gain market share. It was reported to have had a wholesale cost that was 30–40 percent less than that of its reference product, Genotropin, which was the leading biologic in this class. Nonetheless, Omnitrope’s share of somatropin use remained below 10 percent through 2010.

Omnitrope’s low market share in this period is attributable, at least in part, to the fact that its manufacturer, Sandoz, did not engage in substantive product differentiation strategies for Omnitrope. Competition in the human growth hormone market had occurred for many years on multiple dimensions, including price, promotion, and delivery devices (for example, a system using a cartridge and a pen). Omnitrope’s initial mode of delivery involved a lyophilized (freeze-dried) powder that had to be combined with a preservative. This put it at a competitive disadvantage compared to Genotropin and other human growth hormone products with more sophisticated delivery devices that used pens.

Eventually, Sandoz adjusted its market strategy to focus on support services and to include detailing by a sales force, and the company obtained FDA approval for a pen delivery system. Omnitrope has since increased its market share, claiming 19 percent of the somatropin market based on reports from November 2012.

m-enoxaparin sodium The second biosimilar-like product to be approved by the FDA is m-enoxaparin sodium (enoxaparin). Its reference product is Sanofi’s leading low-molecular-weight heparin drug product, Lovenox, which
is used to treat and prevent deep vein thrombosis. Enoxaparin’s Abbreviated New Drug Application was approved in July 2010.

Lovenox is a chemically synthesized product derived from natural sources (pig intestines) and has been described as a complex mixture of a chemical and biological entity. The FDA approved enoxaparin sodium with an AB rating, which allowed pharmacists to substitute it for Lovenox. The FDA approved Sandoz’s Abbreviated New Drug Application based on the analytical characterization technology developed by Sandoz’s manufacturer partner, Momenta, that demonstrated active ingredient sameness, taking into account the complexity of enoxaparin. Lovenox’s annual US sales exceeded $2.5 billion when enoxaparin entered the market.

**Market Dynamics**

The market penetration of enoxaparin (Exhibit 3) was very different from that of Omnitrope. Lovenox had steady growth in the period 2000–09 but then exhibited a familiar cliff-like drop in its sales after the introduction of enoxaparin in the fourth quarter of 2010, resulting from automatic pharmacy substitution and managed care formulary incentives to use enoxaparin. Enoxaparin earned over a billion dollars in its first year on the market and captured more than half of the market.

Enoxaparin’s market experience more closely resembles that of generics under the Hatch-Waxman Act. The formulary data on enoxaparin and Lovenox in January 2014 supports this conclusion. Enoxaparin was on tier 1 in almost 86 percent of the private health plans whose data are collected by Fingertip Formulary, whereas Lovenox was on tier 3 or not covered at all in close to 81 percent of those plans.

The formulary data for Omnitrope and Genotropin show a different picture. In January 2014 Omnitrope was on tier 2 in only 14 percent of private health plans, compared to 21 percent for Genotropin. Omnitrope’s favorable placement is slowly increasing over time, however.

These two products’ case histories appear to offer a key lesson: If the FDA does not determine that a biosimilar is bioequivalent to or interchangeable with the reference product, the biosimilar’s manufacturer may need to commit substantial resources after the product’s launch to educate providers about it. Interchangeability is likely to be much more important for self-administered biological products that are typically insured by third-party payers through their pharmacy benefit programs, than it is for drugs dispensed by physicians. A designation of interchangeability would likely incentivize these insurers to use typical pharmacy benefit management tools such as tiered formularies and step-therapy regimens (subject to state substitution laws that are now being enacted for biosimilars) to encourage the use of the biosimilar instead of the reference product. It could also allay some physicians’ and patients’ concerns about the products’ comparability.

In the case of biological products dispensed by physicians in hospitals or outpatient clinics, the interchangeability distinction would still be an important input to the decisions of the relevant hospital pharmacy and therapeutics committees regarding product usage. However, these committees are in a position to make informed and
binding judgments about product comparability even in the absence of an interchangeability designation. As noted above, hospitals are also likely to be most price sensitive of all providers and generally have very sophisticated pharmacy and therapeutics committees with the ability to implement strict formulary decisions.

**Biosimilar Insights From Europe**

In a recent article we examined the experience of biosimilars in five major European countries (Germany, Sweden, the United Kingdom, France, and Italy). In this section we provide a summary of our findings and their potential lessons regarding forthcoming US competition.

We examined market outcomes for biosimilars whose reference products were two major biologics, Eprex and Neupogen—as explained above, used to treat anemia in dialysis and cancer patients and neutropenia, respectively. Biosimilar competition in the European Union began for Eprex in 2007 and for Neupogen in 2008.

In addition, Amgen has introduced into the European Union second-generation products for anemia, Aranesp, and neutropenia, Neulasta, which are longer lasting than Eprex and Neupogen, respectively. The second-generation products have not had any biosimilars approved for sale in the European Union. These longer-acting agents require many fewer administrations per course of treatment, which has potential advantages for patients in terms of quality and convenience and for other segments of the health care sector in terms of cost.

Two major findings emerged in our analyses. First, the competitive performance of the two biosimilars relative to their reference products was mixed both within each country and across the five countries (Exhibit 4). Second, when we broadened the market segments to include the second-generation products, Aranesp and Neulasta, the biosimilars’ market shares were much smaller, reflecting the use of these longer-lasting products by patients for the same conditions (Exhibit 5).

Biosimilars for Neupogen generally had greater market shares in the five countries than biosimilars for Eprex did (Exhibit 4). Eprex’s biosimilars had less than 15 percent of the market in three of the five countries, with Germany and Sweden being notable exceptions. The higher market share for Neupogen’s biosimilars appar-
ently reflects, among other factors, the fact that it is used on a more short-term, acute basis than Eprex’s biosimilars and has greater patient turnover. In addition, in many countries it is subject to hospital purchase tenders—that is, a competitive bidding system by public hospital associations to obtain the best price. The lower sales of Eprex’s biosimilars also may be attributed to lingering concerns about product safety among physicians and other providers, given the adverse events experienced several years ago after a manufacturing change involving Eprex.17

Prices for biosimilars of Eprex and Neupogen are generally discounted by less than 25 percent relative to the prices of the reference products in all five of the European countries, based on audit data from IMS Health.15 This is consistent with survey data from the trade literature. However, caution is warranted in interpreting these prices, given the fact that manufacturers’ rebates are not included in audit data from IMS Health or other sources.

Germany and Sweden are the only two of the five countries in which biosimilars for both Eprex and Neupogen had high market shares (Exhibit 4). Germany in particular has provided strong incentives to use biosimilars, employing both reference pricing and requirements for minimum use of biosimilars by physicians and sickness funds (Germany’s insurance entities) that vary by region. Sweden has a history of encouraging the use of generic medicines and cost-effective therapies through reimbursement pricing policies and county council decisions on efficient health care delivery.15 County councils in Sweden are elected regional bodies that formulate therapeutic guidelines and regulate prices and levels of service offered by private providers.

It is difficult to generalize across health care systems. However, the systems in Germany and Sweden are arguably the closest to the US system. Both Germany and Sweden have a decentralized approach to drug use and reimbursement, a history of higher prices for innovative drugs relative to other European Union countries, and high use of generic drugs once brand-name products lose patent protection.

Using these countries as a benchmark, our analysis suggests that biosimilars for Eprex and Neupogen could also achieve substantial US market shares relative to their reference products after a phase-in period. This is, of course, subject to all of the institutional considerations discussed above, such as payment programs in multiple health care sectors and incentives for biological products in the United States.

However, a different picture emerges for the use of biosimilars when one considers the broader market segment that includes the longer-lasting products as well as the shorter-acting Eprex and Neupogen and their biosimilars. The market shares of biosimilars in the European countries were much smaller in this case—in several countries, less than 10 percent (Exhibit 5). These results suggest that even if biosimilars gained a substantial share of the reference product’s market, patients and providers could opt to use next-generation products instead of biosimilars.

There are a large number of commercial opportunities associated with the monoclonal antibodies used to treat various cancers, rheumatoid arthritis, and other life-threatening and disabling diseases, as discussed above (Exhibit 1). However, the introduction of biosimilar versions of these products may occur slowly and be moderated by the monoclonal antibodies’ scientific complexity, which could lead to higher development costs and biosimilar prices compared to erythropoietin and G-CSF recombinant molecules that have had biosimilar competition in Europe for several years.

The first monoclonal antibody biosimilar, whose reference product is Remicade, was approved as a treatment for rheumatoid arthritis by the European Union only in 2013. Some other monoclonal antibody biosimilars that are under development have encountered delays and requests by the European Union for additional clinical trials.15

It is also relevant that many manufacturers of leading monoclonal antibody biological products have next-generation products in development. In this regard, an advisory committee to the European Medicines Agency (the European Union’s equivalent to the FDA) has recently rec-

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**EXHIBIT 5**

**Shares Of Biosimilars In The Markets For Eprex And Neupogen And Their Second-Generation Alternatives In Five Countries, In Defined Daily Doses, 2009-11**

<table>
<thead>
<tr>
<th>Country</th>
<th>Eprex and second-generation alternative</th>
<th>Neupogen and second-generation alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td>28.9</td>
<td>31.9</td>
</tr>
<tr>
<td>Sweden</td>
<td>4.6</td>
<td>13.9</td>
</tr>
<tr>
<td>UK</td>
<td>1.0</td>
<td>2.3</td>
</tr>
<tr>
<td>France</td>
<td>0.8</td>
<td>1.9</td>
</tr>
<tr>
<td>Italy</td>
<td>0.2</td>
<td>2.4</td>
</tr>
</tbody>
</table>

**Source** Authors’ analysis of data from IMS Health and the World Health Organization (WHO). **Notes** Percentages were computed using IMS Health data on units by dosage strength and WHO information on the defined daily dose for these biological products. The second-generation alternative for Eprex is Aranesp. The second-generation alternative for Neupogen is Neulasta.

aMarket share is the doses of biosimilars as a percentage of the combined doses of the biosimilars, the reference branded product, and the second-generation branded product.
ommended the approval of a subcutaneous injection form of Herceptin, which is used to treat various cancers. The new form involves a less invasive type of administration that takes 2–5 minutes, compared to the 30–40 minutes required for the intravenous injection of the existing formulation.18

Also under development are a subcutaneous biologic formulation of Rituxan (marketed as MabThera in Europe), indicated for non-Hodgkin’s lymphoma, and a longer-acting version of Avonex, indicated for multiple sclerosis.15 Several manufacturers that are developing similar products also appear to be focusing on a “bio-better” strategy instead of a biosimilar one.

Conclusion
The primary objective of the Biologics Price Competition and Innovation Act, like the Hatch-Waxman Act before it, is to encourage price competition and realize savings for consumers while maintaining a favorable environment for innovation. Given the high costs of market entry for biosimilars—as well as the likelihood that the FDA will designate them only as biosimilar to, and not interchangeable with, their reference products for the foreseeable future—biosimilars’ competition with those reference products is expected to differ from current generics’ competition with brand-name drugs. In particular, fewer products and less-intensive price discounting are expected. Thus, as noted above, biosimilars will compete with reference products on the basis of quality and reputation as well as price.

The level of cost savings from biosimilars in the United States during the rest of the decade is likely to be below what was generally anticipated prior to the passage of the Biologics Price Competition and Innovation Act in March 2010.19 At this point, even the relatively moderate estimate by the Congressional Budget Office (CBO) of a cumulative $25 billion in total cost savings from the use of biosimilars over the first decade after the law’s passage (equivalent to roughly 0.5 percent of prescription drug spending) looks overly optimistic.20

The CBO estimate incorporated competitive scenarios including biosimilars’ market penetra-

Over a longer time frame, the economic opportunities for biosimilars can be expected to grow.

tion and prices that are reasonably consistent with what has occurred in the countries such as Germany and Sweden, which lead the European Union in use of biosimilars. However, the FDA is approving biosimilars much more slowly than the CBO anticipated. Four years have passed, and not one biosimilar has been approved; nor has any company announced that it has filed an application for such an approval.21

This delay apparently reflects caution on the part of the FDA, which has meant that manufacturers need a lengthy period of time to develop the evidence required for FDA approval. Furthermore, the existence of biobetters in the drug development pipeline and shifts to next-generation products on the part of patients and physicians could reduce the projected cost savings from the use of biosimilars.

Over a longer time frame, the economic opportunities for biosimilars can be expected to grow. For example, scientific advances could reduce the cost of developing biosimilars and allow their interchangeability to be demonstrated through structural analysis, or what the FDA calls “fingerprinting,” instead of through data from such sources as clinical studies. It is also likely that medical practices and reimbursement procedures will evolve to be more receptive to the use of biosimilars, assuming that experience with them is favorable. It took more than a decade after the passage of the Hatch-Waxman Act for generic products to produce substantial cost savings, and that is also a likely scenario for biosimilars.

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Notes


4. Under the Biologics Price Competition and Innovation Act, an abbreviated biosimilar submission cannot be approved for marketing until a twelve-year exclusivity period for the reference product has expired. However, the patent expiry date is the relevant factor for the products listed in Exhibit 1, given their respective introduction and patent expiry dates.


