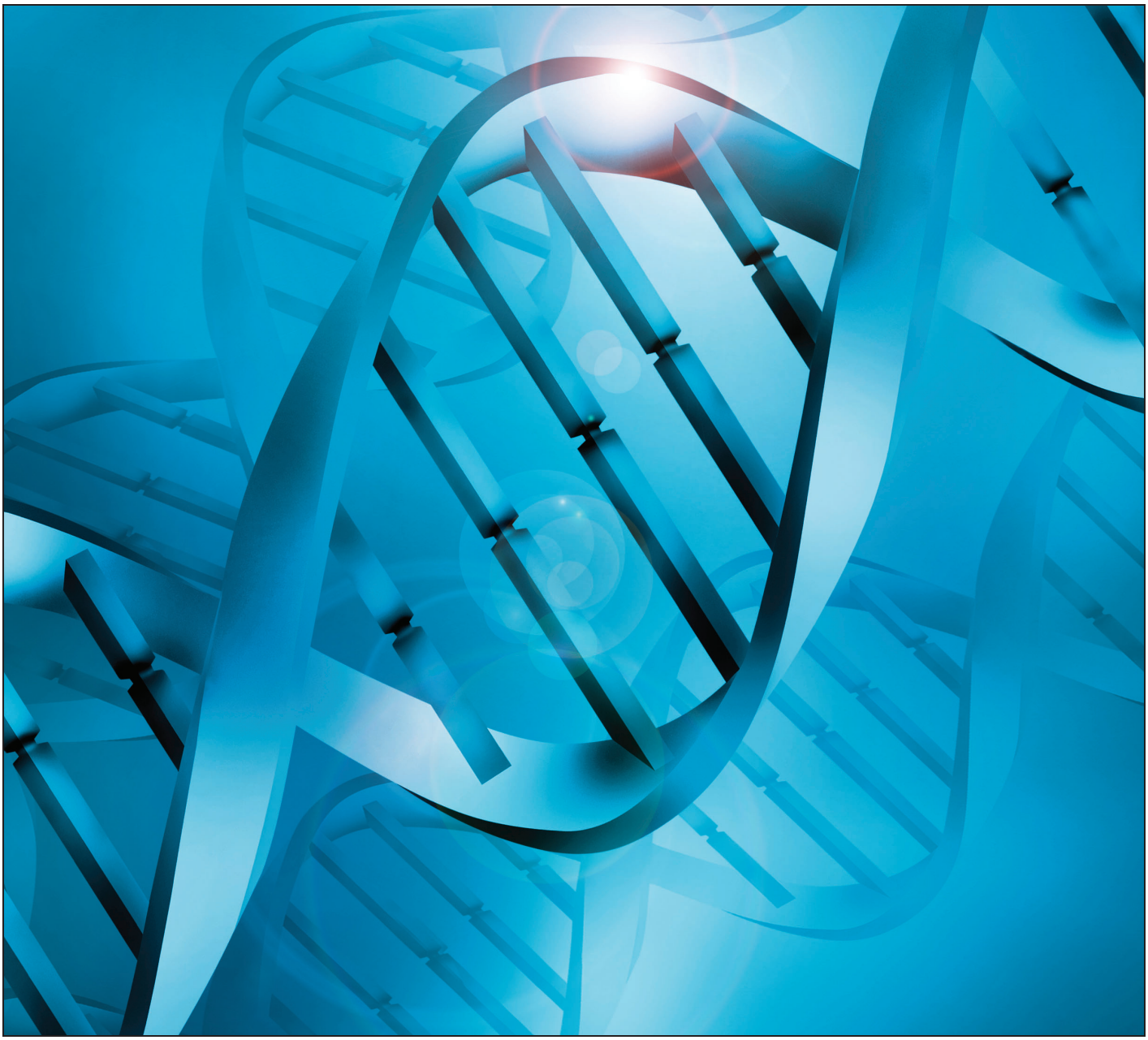

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The Potential American Market for

Generic Biological Treatments and the Associated Cost Savings

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The Potential American Market for Generic Biological Treatments and the Associated Cost Savings[1]

INTRODUCTION

The availability and cost of biological medical treatments has become a critical issue for the United States as these therapeutic agents derived from living sources have claimed an increasingly important role in the American pharmaceutical market. More than 150 biopharmaceuticals are currently available in the United States, including therapeutic serums, antitoxins, vaccines and biological therapeutics that induce immunity in infectious diseases.[2] Furthermore, the number of new biologics is growing at twice the rate of new small-molecule pharmaceuticals, and more than 500 biologic products worldwide are in various stages of clinical trials.[3] Recently, the expanding role of biologic treatments and their high costs have stimulated serious congressional interest in creating a new regulatory pathway for the approval and marketing of generic or "follow-on" versions of biological treatments that no longer have patent protection.

Before Congress can create regulatory procedures for the use of generic biologics, complex issues of safety, effectiveness and intellectual property rights have to be resolved. These issues will be especially important and challenging if, as expected, the new regulations adopt a standard of effective "similarity" to the original biologic instead of precise "bioequivalence" as part of an approval process that, like the one for traditional generic pharmaceuticals, does not require that "biogeneric" producers conduct their own extensive clinical trials. In addition, Congress will have to evaluate the potential savings likely to follow from the introduction of these "follow-on biologics."[4] This study examines the potential U.S. market for biogenerics over the next 10 and 20 years and concludes that the savings for patients and the health care system would be very large: Our analysis found that generic versions of the top 12 categories of biologic treatments with patent protections that have expired or are due to expire in the near future could save Americans, in net present value, $67 billion to $108 billion over the first 10 years and $236 billion to $378 billion over 20 years. Moreover, these estimates almost certainly understate the savings, because they could not take full account of a number of factors likely to reduce the price of biogenerics and further expand their use in the United States. Today, biogenerics are used across the European Union and the major countries of Asia, because biologics are the best way to treat many grave medical conditions, and biogenerics are the least expensive way to provide those treatments. The United States has led the world in developing biologics, and when the U.S. Congress approves a regulatory pathway for biogenerics, the United States very likely will quickly become the world's largest market for follow-on biologics.

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1 The research for this study was supported by Insmed Corporation. The analysis and conclusions are solely those of the author and co-authors.
2 www.buildingipvalue.com/05_NA/135_138.htm.
3 Grabowski, Henry, Iain Cockburn, and Genia Long, "The Market for Follow-On Biologics: How Will It Evolve?," *Health Affairs* 25.5 (2006).
4 In the United States, generic forms of biologic products are commonly called "follow-on biologics," "follow-on protein products" and "biogenerics," while European usage favors "similar biological medicinal products" or "biosimilars."

BIOLOGICS AND HEALTH CARE

The Food and Drug Administration (FDA) approved the first biologic product in 1982, Eli Lilly's Humulin, a form of insulin made in a recombinant DNA, genetic-engineering process. The biotechnology industry expanded rapidly in the 1990s when a number of science-based enterprises working on recombinant therapeutics figured out how to manufacture a number of critical treatments by genetically manipulating a single-cell organism such as bacteria or yeast, including insulin, growth hormone, interferon, and treatments for Gaucher's disease and cystic fibrosis. By 2002, the FDA had approved 36 new biologics, followed by 37 more in 2003, another 40 in 2004 and 39 more in 2005. By 2006, the leading category of biologic treatment, the red blood cell enhancer recombinant erythropoietin (EPO), generated $14 billion in sales revenues, or 40 percent more than the best-selling traditional pharmaceutical, Lipitor.[5] IMS Health reports that the U.S. biologics market reached $52 billion in 2005 and has been growing about 17 percent a year, faster than any other portion of the pharmaceuticals market.[6] Worldwide, revenues from biologics have been growing at an average annual rate of about 20 percent since 2000, and this rising demand for biologics will likely accelerate further in coming years. For example, more than 300 therapeutic antibodies currently are in clinical development and trials, compared to just 13 that already are widely available.[7] One industry observer, Federico Polliano from BioGeneriX, has forecast that biologics will account for half of all approved pharmaceutical treatments by 2010.

The biotechnology industry expanded rapidly in the 1990s when a number of science-based enterprises working on recombinant therapeutics figured out how to manufacture a number of critical treatments by genetically manipulating a single-cell organism such as bacteria or yeast, including insulin, growth hormone, interferon, and treatments for Gaucher's disease and cystic fibrosis.

U.S. government regulation of biological-based products is more than a century old: In 1902, Congress passed the Biologics Control Act after 22 children died from contaminated diphtheria and smallpox vaccines. That act created the Center for Biologics Evaluation and Research (CBER) to regulate biological products for safety, which became part of the National Institutes of Health in 1944 and then part of the FDA in 1972. Today, the FDA evaluates and approves biologics mainly under the Public Health Safety Act, although a small number have been approved under the Food, Drugs and Cosmetic Act.

Congress created an accelerated regulatory process for FDA approval of generic pharmaceuticals in 1984, under the Hatch-Waxman Act,[8] but the law covers only traditional, small-molecule pharmaceuticals and not biologics. Under this act, a pharmaceutical producer can secure FDA approval to market a generic version of an original drug no longer under patent protection without having to conduct lengthy and expensive safety and effectiveness studies and clinical trials, by demonstrating that the generic is the "bioequivalent" of the original drug. The process involves the approval of an "Abbreviated New Drug Application" (ANDA), which rests on a certification that the original patent has expired or is invalid, and that the dosage and active ingredients of a generic are identical to those in the original treatment.

Creating this accelerated process produced a sharp increase in the number of generic products and producers. Eleven of the 13 top-selling drugs with patents that expired from 1990 to 1993 attracted generic versions, compared to two of the top 13 from 1976 to 1982, before the ANDA regulatory path was created,[9] and by 1994, consumers saved, in 2007

5 See www.techconfidential.com/archives/biotechpharma/the-epo-plot-thickens.php, and www.bio-medicine.org/medicine-news/British-Authorities-Seize-Spurious-Drugs—4130-1/.

6 "Beyond Borders: Global Biotechnology Report 2005," Ernst and Young, www.ey.com/global/content.nsf/International/Biotechnology_Library_Beyond_Borders_2005; see also data from IMS Health.

7 Tufts Center for the Study of Drug Development, "Outlook 2004," www.csdd.tufts.edu/InfoServices/OutlookPDFs/Outlook2004.pdf.

8 Also referred to as the Drug Price Competition and Patent Restoration Act. The provisions of Hatch-Waxman are described by John R. Thomas in "Authorized Generic Pharmaceuticals: Effects on Innovation," Congressional Research Service Report for Congress, 8 August 2006.

9 Cook, A. "How increased competition from generic drugs has affected prices and returns in the pharmaceutical industry," Congressional Budget Office, 1998; Caves, R., M. Whinston, and M. Hurwicz, "Patent expiration, entry and competition in the US pharmaceutical industry," Brookings Institution, Brookings Papers on Economic Activity: Microeconomics 1-66, 2001.

dollars, an estimated $11.2 to $14 billion a year.[10] The Kaiser Family Foundation reports that generics accounted for half of all prescriptions dispensed in the United States in 2004 and two-thirds by 2006, producing very large savings for patients and the health care system.[11] The extent of the savings from the availability and use of generics depends on the level of their price discount compared to branded versions, which in turn depends on the number of generic producers competing in a particular market. An FDA analysis of drug prices from 1999 to 2004 found that the discount from generic competition was just 6 percent with one generic competitor, but jumps to 48 percent with two generic competitors, 56 percent with three, 61 percent with four and 67 percent with five generic producers in a market.[12] More generic competitors will enter a market if the drug is a large seller and the fixed investments required to produce a generic version are relatively low. For example, within two years of the expiration of the patent for the popular drug Zantac in mid-1997, generic versions accounted for 90 percent of the treatment's total sales, and the price for patients was about 10 percent of its pre-generic price.[13] In recent years, this displacement by generic producers has occurred very quickly: Eli Lilly's Prozac lost 80 percent of its market share within two months of losing its patent protections in August 2001.[14]

Recently, legislation has been introduced in Congress to create a comparable, accelerated pathway for generic or follow-on biologics. A handful of these biogenerics are available in the United States—mainly early versions of biosynthetic insulin and human growth hormone produced with recombinant DNA technologies—after being grandfathered in by Hatch-Waxman under the U.S. Food, Drug and Cosmetic Act. The FDA has never officially certified these biogenerics as therapeutically equivalent to the original versions, insisting that legally they are not biogenerics at all, but proteins,

> . . . intended to be sufficiently similar to a product already approved or licensed to permit the applicant to rely for approval on certain existing scientific knowledge about the safety and effectiveness of the approved protein product.[15]

The Kaiser Family Foundation reports that generics accounted for half of all prescriptions dispensed in the United States in 2004 and two-thirds by 2006, producing very large savings for patients and the health care system.[11]

Moreover, most biologics in the U.S. are regulated under the Public Health Service Act, which has no provision for biogenerics.

Biologics present greater challenges for generic producers than most small-molecule drugs, because biologics are much more complex and therefore much more difficult to replicate. While most traditional pharmaceuticals are composed of small organic molecules containing 20 to 100 atoms in well-defined structures, most protein-based biologic treatments involve highly complex molecules with 5,000 to 50,000 atoms, many with complicated folding structures. Moreover, because biologic treatments are derived from unique biological materials and are affected by the particular manufacturing process, follow-on versions generally cannot establish the precise bioequivalence required for generic versions of small-molecule drugs. Consequently, current proposals would authorize the Secretary of Health and Human Services to determine on a case-by-case basis the necessary studies required to establish "comparability." A comparable biogeneric would have to have principal structural features comparable to the original treatment, the same mechanism of action (if it is known), and the same means of administration, dosage form and strength. Under these proposals, a biogeneric producer also could elect to establish "interchangeability" with an original product, indicating that the follow-on version would be expected to produce the same clinical results as the original drug.

The economic and medical benefits from generic

10 In 1994 dollars, consumers saved some $8 to $10 billion. Congressional Budget Office, "How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry," July 1998.
11 Seigel, Jeff, "Momentum Builds for Generic Producers," 20 August 2007, www.pharmaceuticalcommerce.com/frontEnd/main.php?isSection=668.
12 FDA, Center for Drug Evaluation and Research, "Generic Competition and Drug Prices," www.fda.gov/CDER/ogd/generic_competition.htm.
13 Brendt, E.R., "The U.S. Pharmaceutical Industry: Why Major Growth in Times of Cost Containment?," *Health Affairs* 20.2 (2001).
14 Harris, Gardiner, "For Drug Makers, Good Times Yield to a New Profit Crunch," *Wall Street Journal* 20 April 2002.
15 Quoted in Jeff Siegel, op. cit.

biologics should be as great as or perhaps even greater than those from generic forms of traditional pharmaceuticals. As noted, the role of biologic treatments in health care is increasing rapidly and sharply. Moreover, the potential savings from the discounted prices that generics provide will be larger with biogenerics, because original biologics are so much more expensive than other traditional, brand pharmaceuticals. Providing one person with Interferon Beta to treat multiple sclerosis for a year costs more than $10,000, a three-month course of Serostim (somatropin) to treat lipodystrophy in AIDS patients costs about $21,000, and cancer biologics such as the antibody Herceptin can cost $20,000 to $30,000 for one course of treatment. Similarly, a year of biologic treatments for severe arthritis will cost from $17,000 (for Enbrel) to $35,000 (for Remicade), a year's supply of Gleevec to treat leukemia costs $28,000, and Cerezyme for Gaucher's disease costs $200,000 per year.[16] Across all treatments, biologics cost an average of $45 per day or $16,425 per year, more than 20 times the $2 per-day and $730 per-year cost of traditional pharmaceuticals.[17]

As noted, the role of biologic treatments in health care is increasing rapidly and sharply.

The challenges to the development and use of biogenerics on a large scale are well known. As noted earlier, issues of biogeneric safety and effectiveness arise from the complexity and variability of their composition and manufacture.[18] Biologics are developed from living organisms, and, unlike chemical compounds, no two proteins or enzymes are precisely identical. Further, slight changes in the production process can produce subtle variations in the final product. Some analysts argue that these factors dictate that the approval of generic versions of biologics should require independent and extensive clinical trials, which would substantially increase the time and costs required to develop and market them. The result would be fewer biogeneric competitors in each market, which in turn would limit the price reductions and consequent savings, as well as the numbers of people using the treatment.

The complexity of the biologic manufacturing process also will impose significant investment costs on biogeneric producers, which will limit the number of competitors. While small-molecule drugs are generally manufactured in labs using chemical synthesis, the production of most biologics requires cell-culture facilities that can take three to five years to build, using materials 20 to 100 times more expensive than those for facilities used to manufacture molecule-based drugs, at a cost of $200 million or more. These factors also could extend the process of approval for many biogenerics, with one analyst estimating that developing a generic biologic, producing it and gaining FDA approval could take five to eight years: One to two years to carry out the cell biology, one year for process analysis, two to four years for new clinical trials and one year for final approval.[19] However, it also could take as little as two years, if the cell biology occurs before the patent expires, extensive clinical trials are not required and the manufacturing is subcontracted to an approved facility. Finally, some analysts posit that doctors and patients will resist generic biologics, being more wary about using a generic alternative for conditions such as cancer or multiple sclerosis than for allergies, high cholesterol or erectile dysfunction. However, purchasing managers and insurance companies are likely to take serious account of the cost-effectiveness of biogenerics, and one recent study found that cost pressures will drive payers and pharmacy benefits managers to move quickly to encourage the use of follow-on biologics.[20]

These challenges have not stopped the development and use of scores of biogenerics, especially in developing-nation markets that are less strictly regulated than the United States for both "comparability" and intellectual property rights. A recent worldwide survey reported 30 producers of biogenerics in just five treatment areas, including 32 instances in which the treatments are now being marketed and sold. (See Table 1, next page.)

16 Lloyd, Linda, "Opening a Path for Biotech Generics," *Philadelphia Inquirer* 19 September 2006; Stephen Hauser, "Shire Drug Gets FDA Approval," *Boston Globe* 25 July 2006.
17 Himchlor, Ben, "FDA Rebuffs Novartis Over Delay to Biogeneric Drug," *Reuters News* 15 November 2005.
18 For a detailed outline of the issue of fixed costs for biologics, including clinical trials, capital costs and manufacturing, see Grabowski, Henry, D.B. Ridley, and K.A. Schulman, "Entry and competition in generic biological," Duke University, 2007; and Grabowski, Henry, Statement to the House Oversight and Government Reform Committee, 26 March 2007.
19 Cook, *op cit*.
20 Ahlstyrom, Alexis, Roland King, Ruth Brown, Jen Glaudermans, and Don Mendelson, "Modeling Federal Cost Savings from Follow-On Biologics," Avalere, April 2007.

Moreover, the European Union (EU) has created a new regulatory pathway for follow-on biologics, which became national law in member states in November 2005 with a standard approval process administered by the European Agency for the Evaluation of Medicinal Products (EMEA) in London.[21] The EMEA has produced new procedures for establishing a biogeneric's similarity or comparability with an original biologic in quality, safety and effectiveness; specific guidelines for the necessary studies for generic versions of biotherapies that contain insulin, somatropin (human growth hormone), granulocyte-colony stimulating factor (G-CSF) and erythropoietin; and an abbreviated approval process for those meeting those standards.[22]

Table 1

Approved and Marketed (M) Biogeneric Products, by Treatment Area and Manufacturer, September 2007[23]

	EPO	HGH	Insulin	G-CSF	Interferons
Anhui Anke Biotech		Yes M			
Barr Pharma.				Yes	
Biocon			Yes M	Yes	
BioGeneriX	Yes				
Biopartners		Yes M			Yes[24]
Bioton			Yes M		
Cangene		Yes		Yes[25]	
Cell Therapeutics	Yes			Yes	
CIGB	Yes			Yes	Yes M
Cipla					
CJ Corp	Yes M			Yes M	Yes M
Dr. Reddy's Labs				Yes M	
Dongbao Pharma.			Yes M	Yes M	
Dragon Pharma.	Yes M			Yes M	
GeneMedix	Yes	Yes	Yes	Yes	Yes
GeneScience Pharma.		Yes M		Yes M	Yes M
Inno Biologics	Yes	Yes	Yes	Yes	Yes
Intas Biopharma.	Yes M			Yes M	Yes M
LG Life Sciences	Yes	Yes		Yes	Yes
Pliva	Yes M			Yes	
Ranbaxy Laboratories				Yes	
Sandoz	Yes M	Yes M			
Scigen	Yes	Yes M	Yes M	Yes	Yes
3SBio	Yes M				Yes M
Shenzhen-Kexing		Yes M	Yes M		Yes M
Stata Arzneimittel	Yes[26]			Yes	
Teva Pharma./Sicor		Yes M		Yes M	Yes M
Viropro	Yes			Yes	Yes
Wockhardt	Yes M		Yes M	Yes	Yes
Zenotech		Yes		Yes M	

21 Directive 2003/63/EC, Annex 1 on "similar biological medicinal products."
22 Guidelines on comparability, www.emea.europa.eu/pdfs/human/biosimilar/043704en.pdf.
23 "Biosimilars: A market coming of age?," Espicom Business Intelligence Report, October 2007.
24 Alpheon was rejected by the EMEA in June 2006; interferon b was recently submitted.
25 Currently in Phase III clinical trials.
26 Currently in Phase III clinical trials.

European patents on biologic treatments began to expire in 2000, and in April 2006, Sandoz and Biopartners received EMEA approval for the first European biogenerics, two products containing human growth hormone. Moreover, in June 2007, the EU Committee for Medicinal Products for Human Use issued positive findings that three biogenerics are comparables for Ortho Biotech's Eprex/Eryp, a form of epoetin alfa, which is the world's largest selling biologic treatment.[27] It is too early to know the extent of the price discounts with three competitors, but Biopartners has announced that it will offer its Valtropin growth hormone biogeneric at a 20 percent to 25 percent discount, and Sandoz says it will sell its generic EPO for 30 percent less than the original.[28] These examples are only the beginning: By the end of this decade, EU patent protection will end for a substantial number of growth hormones, alpha, beta and gamma-interferons, human insulins, epoetin alpha, interleukin 2; G-CSF, follitropin, streptokinase and tissue plasminogen activators.

27 The three EPO biogenerics are Binocrit from Sandoz, epoetin alfa Hexal from Hexal and Abseamed from Medice.
28 Moran, Nuala, "Fractured European market undermines biosimilar launches," *Nature Biotechnology* 26.1 (January 2008).

THE POTENTIAL SAVINGS FROM BIOGENERICS: PREVIOUS STUDIES

Several previous studies have attempted to analyze the prospects for the biogeneric market in the United States and the dimensions of its potential savings. Henry Gabrowski of Duke University and his colleagues, for example, estimate the U.S. biogeneric market over a one-year horizon, assuming high fixed costs for development, clinical trials and production.[29] Their study assumes such high costs to enter the market that few biogeneric competitors would emerge, which would keep biogeneric prices relatively high and produce limited savings: The study estimates that a generic version of a biologic with a $500 million U.S. market would sell at an 18 percent discount compared to the original, versus an average first-year discount of 44 percent for the generic versions of traditional drugs. Other researchers have estimated larger savings. An analysis by the consultant Everett Ehrlich concludes that biogenerics would produce savings of $43.2 billion over 10 years or an average of more than $4 million per year.[30] Two other recent studies examine the potential savings for the Medicare program from biogenerics, and estimate savings there that would range from $3.6 billion to $14 billion over 10 years.[31]

Our review of these studies found that they all tend to underestimate the size of the likely market for biogenerics and the consequent potential savings, much as the early estimates of the market for generic versions of traditional drugs and their associated savings were a fraction of what eventually occurred. While forecasts for markets that do not yet exist can be neither verified nor fully refuted, the assumptions used in those previous studies are problematic in ways that all tend to reduce their savings estimates.

First, most of these studies assume that the price of the original drug remains unchanged despite competition from lower-priced biogenerics. Yet, in India, for example, a biogeneric version of recombinant human insulin reduced the price of the original brand version by a reported 40 percent. Evidence from traditional generics suggests that the price response from U.S. makers of original biologics would be less, but some price adjustment would almost certainly occur. Since biologics are much more expensive than traditional drugs—on average 22.5 times more costly for a daily dose—even a relatively modest percentage reduction in the prices of the original versions would produce substantial dollar savings. Previous studies also generally adopt a static view of the potential market for biogenerics, assuming that their introduction would shift some users from the brands to the generic version, but not increase the total number of users. Unsurprisingly, the availability of lower-priced generic versions of traditional drugs has increased the numbers of people using those treatments, because more insurers will cover them and more patients can afford them. While this effect could be more limited in the case of biogenerics, the number of users almost certainly will increase beyond trend as the price falls.

An analysis by the consultant Everett Ehrlich concludes that biogenerics would produce savings of $43.2 billion over 10 years or an average of more than $4 million per year.[30]

While biogeneric producers can forgo most R&D costs, which average $530 million for each new original biologic, and do not have to bear the costs of failed development projects, they will face the high costs of building the manufacturing facilities to produce the biogenerics. Those costs are essential elements of any analysis of the potential market for biogenerics, and previous studies focus on how these high costs will discourage biogeneric producers from entering many markets, limiting the size of the eventual price discounts. However, none of those studies takes account of factors that are likely to reduce those costs, especially the near-certain prospect that biogeneric producers in China, India and other lower-cost developing nations will compete in the U.S. market, and that U.S. biogeneric producers will build many of their facilities in those lower-cost developing nations or subcontract with existing production opera-

29 Grabowski, H.G., Statement to the House Oversight and Government Reform Committee, 26 March 2007; Grabowski, Henry, et al., "Entry and competition in generic biological," *op cit*.

30 Ehrlich, Everett, and Elizabeth L. Wright, "Biogenerics: What They Are, Why They Are Important, and Their Economic Value to Taxpayers and Consumers," Citizens Against Government Waste, Policy Briefing Series, May 2007.

31 Ahlstyrom, *et al., op. cit*; and "Report to the Pharmaceutical Care Management Association," Engel & Novitt, LLP, 2 January 2007.

For the first five to 10 years of that market, almost all biogenerics coming to the United States from developing nations will be produced in the Asian, Latin American or Eastern European facilities built and operated by Western biologic manufacturers.

tions there or in the United States. Any foreign biogeneric production facility would have to be certified by U.S. regulators, as they do today for foreign facilities that produce original and generic versions of traditional pharmaceuticals for the American market. In 2007, 3,249 offshore production facilities were certified by the FDA to produce drugs for the U.S. market, including 299 establishments in India and 566 facilities in China.[32] And Indian companies accounted for more than 20 percent of all applications for generics–43 of 186—approved by the FDA from January to May 2007.[33]

There are many foreign biologic facilities capable of producing biogenerics for the American market on a contract basis or on their own. As noted earlier, there are at least 30 foreign biogeneric producers operating today in developing nations. Even more important, Western companies with Asian manufacturing bases that have already said they are prepared to enter Western markets include Dragon Pharmaceuticals, a U.S.-based company with production facilities in China; GeneMedix, a British-based company with manufacturing alliances in Malaysia and India; and the world's largest generics producer, Teva, based in Israel with facilities in India and Latin America. These and other biogeneric companies have focused thus far on producing for developing country markets. SICOR, part of Teva, markets a generic version of Intron A in Lithuania, Mexico and other emerging markets; GeneMedix, headquartered in Vancouver with Chinese production facilities in Nanjing and Datong, markets G-CSF in China, India and Malaysia; Savient, a U.S.-based producer, sells generic forms of human growth hormone in Eastern Europe; and Dr. Reddy's Laboratories markets the anti-cancer biogeneric Grastim in India. All of these companies will almost certainly try to enter the U.S. market once the regulatory pathway for biogenerics is in place.

Developing a cell line and producing biologics that are entirely pure remains very high-end science, and many of the current biologics producers in developing nations could not today meet the standards of the United States and European Union to produce biogenerics for their markets. Consequently, biologic producers in the United States, Europe, Japan, Israel and South Korea initially will have an important edge in a new American market for biogenerics. For the first five to 10 years of that market, almost all biogenerics coming to the United States from developing nations will be produced in the Asian, Latin American or Eastern European facilities built and operated by Western biologic manufacturers. But the high-end technologies and expertise can be transferred to developing economies, especially through alliances between Western and Asian biologic enterprises. A similar process occurred with small-molecule generics: Indian and other developing-nation producers could reproduce the active ingredients of many traditional drugs, but needed transfers of Western control and release technologies before they could enter the American and European markets.

In addition, some U.S. producers of biologics have idle production facilities that could be refitted to produce new biogenerics themselves or could subcontract from others, at a much lower cost than required to build a new U.S. facility. Insmed, for example, has FDA-certified production facilities in Boulder, Colorado to produce cGMP proteins, as does Althea Technologies in San Diego, California. The participation of these companies in the U.S. biogenerics market, along with producers with foreign production facilities, would increase competition for biologics coming off patent, suggesting again substantially greater savings for U.S. patients and the health care system than contemplated or estimated by previous studies.

In addition, some U.S. producers of biologics have idle production facilities that could be refitted to produce new biogenerics themselves or could subcontract from others, at a much lower cost than required to build a new U.S. facility.

32 Crosse, Marcia, Director, U.S. Government Accountability Office, Statement before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, U.S. House of Representatives, 1 November 2007.
33 Siegel, *op. cit*.

The prospect of significant numbers of foreign and domestic producers of generic biologics competing in the U.S. market is increased by recent technological advances that will make it easier to replicate some biologics. For example, recent advances have reduced the cost of producing a number of proteins created through microbial fermentation in E. Coli, and with high purity and reliability. This category includes the major classes of biologics treatments targeted by foreign biogeneric producers, including insulin, human growth hormone, many forms of interferon, Filgrastim and other forms of granulocyte-colony stimulating factors (G-CSF) that increase production of white blood cells.

The likelihood of significant numbers of foreign and domestic biogeneric producers competing in the U.S. market is also enhanced by the prospective increases in demand for biologics in general and for less expensive versions in particular. In the United States and most other countries, the numbers of elderly people will rise sharply over the next two decades, and they compose the majority of patients with conditions currently treated with biologics, including cancers and kidney disease. These demographic changes, along with fast-rising costs of medical care everywhere, could make the rapid introduction of biogenerics a priority for health authorities and payers. In July 2005, for example, Britain's National Institute for Clinical Excellence (NICE) cited a cost of 5,000 British pounds per course of treatment in recommending that erythropoietin drugs no longer be used routinely to treat chemotherapy-induced anemia. These cost pressures will increase demand for all cost-saving generics, which in turn may attract more biogeneric producers and potentially larger price discounts from their competition.[34]

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Finally, previous studies underestimate the number of biologics that will lose patent protection once Congress creates a regulatory pathway for biogenerics. Under the current regulation of traditional generic drugs, generic makers can file "Paragraph IV" challenges to patents of original drugs, alleging that the patent is invalid in some respect, and if they prevail, they are granted 180 days during which no other generic producer can enter the market. From 1998 to 2002, 31 new generics were approved following Paragraph IV challenges, or 20 percent of all new generics certified in those years.[35] Current proposals to create a pathway for biogenerics would apply Paragraph IV provisions to biologics, and there is no reason to expect those challenges will be less common or less successful than with traditional drugs.

34 Strong demand for biogenerics in not only the United States and other advanced countries, but also many developing or transition economies in Asia, Latin America, and Eastern and Central Europe should enable biogeneric producers to achieve greater economies of scale and consequent lower prices.

35 Brendt, E.R., R. Moetimer, and A. Parece, "Do authorized generic drugs deter paragraph IV certifications? Recent evidence," Working Paper, The Analysis Group, 2007.

A NEW ESTIMATE OF THE POTENTIAL SAVINGS FROM BIOGENERICS IN THE U.S. MARKET

Table 2 Global Sales of Biologics by Category, 2005 ($ billions)[36]

Product Category	Global Sales
Erythropoietins	$10.9
TNF Blockers	$7.6
Insulin & Insulin Analogs	$7.2
Cancer Antibodies	$6.8
Interferon Beta	$3.8
G-CSF (granulocyte-colony stimulating factors)	$3.8
Human Growth Hormone	$2.3
Recombinant Coagulation Factors	$2.2
Interferon Alfa	$2.1
Enzyme Replacement	$1.3
Antiviral Antibodies	$1.1
Follicle-Stimulating Hormones	$1.0
Total	**$50.0 billion**

We focus on the products with the largest expected future markets and profits, which should experience the most rapid and extensive entry by biogeneric producers—12 categories of treatments with markets of at least $1 billion.

We derive a new estimate of the potential savings from Congress approving a new pathway for biogenerics in the United States, as follows. First, we identify biologics with patents expired or due to expire over the next 20 years, drawn from the FDA's Approved Drug Products (the "Orange Book").[37] Next, we collect data on the expected size of the market for these biologics between 2010 and 2029, based on past price and utilization data from the Department of Health and Human Services.[38] We estimate price discounts and the share of the market likely to be captured by biogenerics for each product. The savings are calculated based on differences between prices of the original drug and prices of competing biogenerics, times the projected number of users of the biogenerics. (For a technical description of this analysis, see Appendix 1.) We focus on the products with the largest expected future markets and profits, which should experience the most rapid and extensive entry by biogeneric producers—12 categories of treatments with markets of at least $1 billion. These drugs accounted for 75 percent of global biologic sales in 2005. The treatment categories are presented in Table 2 (above).

Next, we estimate the U.S. markets for these classes of treatments using a number of assumptions. These assumptions are consistent with those used by leading analysts of the market, including Datamonitor.

- The product's sales grow 11 percent a year prior to the introduction of biogenerics;
- Those sales grow much more slowly after the introduction of biogeneric competition—an estimated 4 percent a year—as the biogenerics reduce the price.
- 80 percent of the future market of "high-value" users and their insurers will pay the brand price, while 20 percent ("low-value" users) will only pay a lower price and are drawn into the market by biogeneric competition;
- The price discount for the high-value users is 35 percent; the price discount for the low-value users is half that, or 17.5 percent.
- We convert the stream of savings over the next 20 years into net present value using a 3.9 percent

36 "Biologic Drug Report," www.biologicdrugreport.com.
37 FDA, "Electronic Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations," www.fda.gov/cder/ob; Purvis, Leigh, and Lee Rucker, "Top 20 Biologics (2006) and Approximate Annual Treatment Costs," AARP Public Policy Institute, 2007.
38 www.cms.hhs.gov/NationalHealthExpendData/downloads/proj2006.pdf.

discount rate, based on the 2007 yields of 10-year and 30-year U.S. government bonds.

The most critical variable in the forecast is the price discount, which we estimate will be about 35 percent over a 10- and 20- year period. This estimate is greater than those used in previous analyses, which range from 10 percent to 30 percent,[39] but those analyses disregard the series of factors described above, which all will tend to raise the discount by drawing more competitors into the biogeneric market. A 35 percent discount is considerably less than those reported by the FDA in markets for traditional drugs with generic competition, of 48 percent with two generic competitors, 56 percent with three competitors and 67 percent with five generic producers.[40] We can expect the discount from generic competition to be smaller with biologics than with traditional pharmaceuticals, because the competitive forces may be dampened by physician and patient resistance to the alternatives and by the fact that many biologics are administered by physicians or in specialized facilities. Our estimate of a 35 percent discount also corresponds to the forecast for the U.S.

The most critical variable in the forecast is the price discount, which we estimate will be about 35 percent over a 10- and 20- year period.

biogeneric market developed by a leading industry forecasting platform, Datamonitor—and its analysts also note that competition from two or three biogeneric competitors should produce discounts of 40 percent to 50 percent.[41] The estimate of just under 4 percent growth in revenues following the introduction of biogenerics reflects the price discount (11 percent growth x 0.35 = 3.8).

While a number of factors suggest that the ultimate discount may be greater than 35 percent, especially for the most widely used treatments, such as EPO and cancer antibodies—including competition from U.S. producers with facilities in low-cost countries, from producers who subcontract production to idle U.S. or European facilities, and later from foreign biogeneric producers and U.S. producers subcontracting to them—we also provide a savings estimate assuming only a 25 percent discount. The analysis shows very large savings: $67.0 billion to $107.7 billion

Table 3

Estimated U.S. Savings from Biogeneric Competition by Product Class, 2010-2029 ($ billions)

Product Class (Year Introduced)	25 Percent Discount		35 Percent Discount	
	2010-2019	2010-2029	2010-2019	2010-2029
Erythropoietins (2017)	$14.39	$62.67	$23.07	$100.45
TNF Blockers (2011)	$14.48	$30.72	$23.21	$49.23
Insulin and Insulin Analogs (2020)	-	$24.68	-	$39.55
Cancer Antibodies (2015)	$12.86	$38.76	$20.61	$62.13
Interferon Beta (2010)	$7.00	$14.08	$11.23	$22.56
G-CSF (2017)	$6.48	$28.22	$10.39	$45.23
Human Growth Hormones (2010)	$3.60	$7.18	$5.71	$11.51
Recombinant Coagulation Factors (2012)	$3.36	$7.48	$5.36	$12.16
Interferon Alfa (2021)	-	$5.80	-	$9.29
Enzyme Replacement (2012)	$2.80	$6.38	$4.53	$10.23
Antiviral Antibodies (2017)	$1.29	$5.60	$2.07	$8.97
Follicle-Stimulating Hormones (2017)	$0.93	$4.00	$1.47	$6.41
Total	**$67.19**	**$235.67**	**$107.65**	**$377.72**

39 See, for example, the review of discount levels in Ahlstyrom, Alexis, *et al., op. cit*.
40 FDA, "Generic Competition and Drug Prices," *op. cit*.
41 "Biogenerics," Datamonitor, October 2005.

over the decade from 2010 to 2019, for the 25 percent and 35 percent discount levels, respectively, and $235.7 billion to $377.7 billion over the 20 years from 2010 to 2029 (Table 3, previous page). These estimates assume that a biogeneric pathway is approved in 2008, and those products already off patent (and often produced in biogeneric form for other markets) could be approved for the U.S. by 2010. In other cases, the timing depends on the year of patent expiration, assuming two years from patent expiration to biogeneric introduction. (For more detailed projections, see Appendix 2.)

These estimates assume the relatively rapid introduction of biogenerics following the patent expirations of the original biologics, based on a regulatory process much like the EU's, the entry of foreign biogeneric producers in the U.S. market and the use of subcontracted manufacturing facilities. If the introduction of biogeneric competition occurs more slowly, it will affect the timing of these savings but not affect their dimensions. Moreover, competitive pressures on the pricing of these treatments could be even greater than assumed here, because the prices of original biologics have been so high. A report in the *Technology Review* of the Massachusetts Institute of Technology found that industry participants anticipate larger discounts in the major biologic treatment classes: Phage Biotechnology predicts price discounts of 30 percent to 50 percent for generic growth hormone treatments, Cangene expects 40 percent price declines across a range of biogeneric treatments, and Duramed Research forecasts price cuts of up to 50 percent for self-administered biogenerics such as insulin.[42]

Even if the initial price discounts should be substantially less, the industry experts at Datamonitor see initial discounts that start as low as 20 percent rising to 40 percent to 50 percent within a few years as competition increases. And even at relatively modest price discounts, biogenerics can still produce large savings for the U.S. health care system by capturing large market shares. Research conducted by the German biologic and biogeneric producer BioGeneriX, for example, found that American oncologists are very cost-conscious and say that a price discount for biogenerics of just 10 percent to 20 percent would be sufficient to shift their prescriptions for new patients.

Moreover, competitive pressures on the pricing of these treatments could be even greater than assumed here, because the prices of original biologics have been so high.

42 Erika Jonietz, "Generic Biotech," *Technology Review*, December 2004, www.technologyreview.com/Biotech/13970.

CONCLUSION

Over the last 30 years, scientific progress has created a new and powerful class of biological medical treatments, and within a generation, these biologics will likely dominate pharmaceutical use in the United States and other advanced countries.

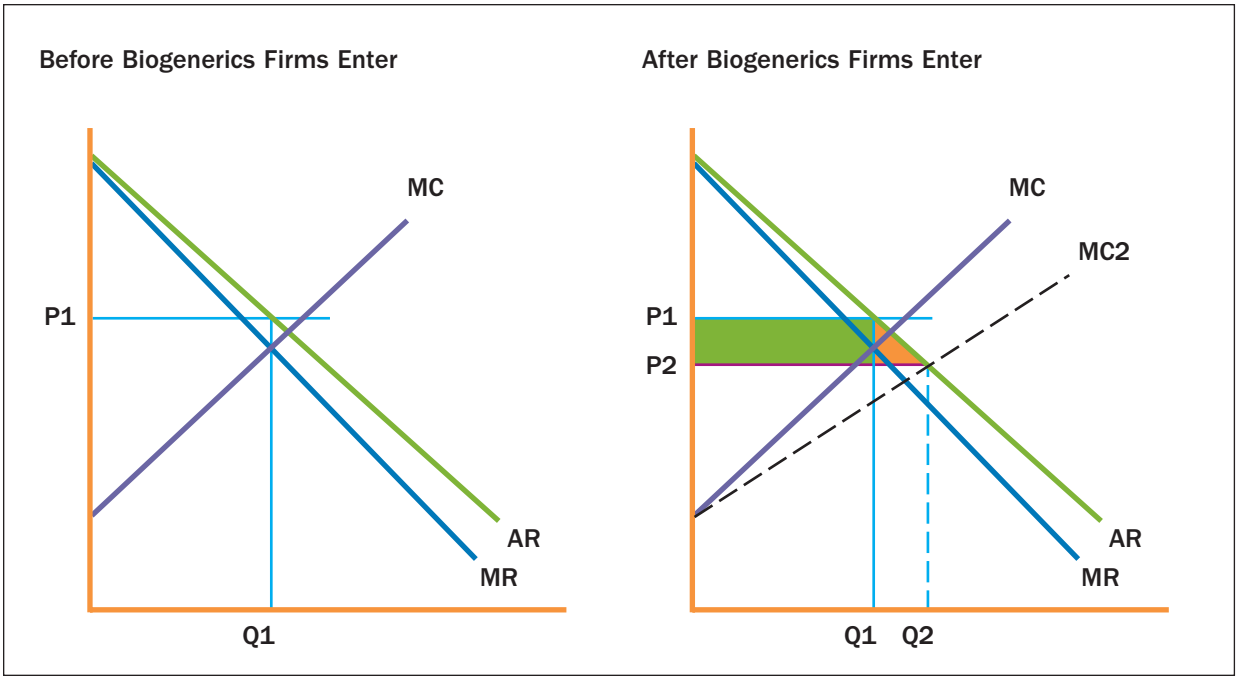
These treatments have been very costly to develop and produce, and a daily dose of a biologic costs patients and their payers, on average, 22 times as much as a daily dose of a traditional pharmaceutical. As biologic treatments become central to health care, pressures to drive down their prices will inevitably increase—or many patients will not have access to them. The safest and most certain way to reduce the price of scores of critical biologic drugs would be to create competition by establishing a regulatory process for approving safe and effective generic versions of biologics once their patents have expired.

This study has analyzed the potential U.S. market for biogenerics and the associated potential savings over the next 10 and 20 years. We find that generic versions of the top 12 categories of biologic treatments with patent protections that have expired or are due to expire in the near future should save Americans, in net present value, $67 billion to $108 billion over the first 10 years and $236 billion to $378 billion over 20 years. We expect that the actual savings may well be considerably greater, because these estimates do not take full account of several factors that would further reduce the price of biogenerics in the United States. Creating a pathway for the approval of biogenerics raises other issues that Congress will have to address. Once they are resolved, the United States can expect very substantial savings and health benefits from a strong biogenerics market.

APPENDIX

Our expected cost savings from biogenerics are represented graphically in the following way:

Appendix 1



The shaded area in the figure represents consumers' savings from biogenerics in one period. P1 on the Y-axis represents the cost of a biologic per year (price) to a consumer. We assume that each consumer uses the same amount of drugs each year. The Q1 on the X-axis represents the number of consumers in the market and the amount of drugs sold in the market. We assume that prior to the entry of generic firms, there exists a monopoly market and price for the drugs, which sets the price P1 that consumers are charged. Following the entry of generic producers, the drug's price falls to P2, and the quantity sold in the market increases to Q2. The fall in price results in a cost savings to the consumers, which is represented by the shaded area. We divide consumers into two groups depending on the extent of the cost savings. Initially Q1 amount of drugs are sold in the market—high-value consumers who can afford the drugs at price P1 purchase these drugs. This group of consumers will save (P1-P2)*Q1 amount of money. The remainder of the consumers cannot afford to purchase the drugs at price P1 and will enter the market only after the entry of the biogeneric producers, which sell the drug at a discount from the price of the original. As shown in the figure, cost savings for individuals is not equal within the two groups. We assume that the average price of the second group is equivalent to ½*(P1-P2). And therefore, the cost savings for the second group is equivalent to (½*(P1-P2))*(Q2-Q1).

From this model, the cost savings to the consumers in one period is defined as:

$$CS = (P1-P2)*Q1 + [½*(P1-P2)]*(Q2-Q1)$$

Appendix 2A

Estimated Savings from Biogeneric Competition by Treatment Category
35 Percent Average Price Discount, 2010-2029, $ billions

	Erythropoietins	TNF Blockers	Insulin & Insulin Analogs	Cancer Antibodies	Interferon Beta	G-CSF (granulocyte-colony stimulating factors)	Human Growth Hormone	Recombinant Coagulation Factors	Interferon Alfa	Enzyme Replacement	Antiviral Antibodies	Follicle-Stimulating Hormones	Total
2010					1.12		0.57						**1.69**
2011		2.57			1.12		0.57						**4.26**
2012		2.57			1.12		0.57	0.67		0.56			**5.50**
2013		2.57			1.12		0.57	0.67		0.56			**5.50**
2014		2.58			1.12		0.57	0.67		0.56			**5.51**
2015		2.58		4.11	1.12		0.57	0.67		0.57			**9.63**
2016		2.58		4.12	1.12		0.57	0.67		0.57			**9.64**
2017	7.68	2.58		4.12	1.13	3.46	0.57	0.67		0.57	0.69	0.49	**21.96**
2018	7.69	2.59		4.13	1.13	3.46	0.57	0.67		0.57	0.69	0.49	**21.98**
2019	7.70	2.59		4.13	1.13	3.47	0.58	0.67		0.57	0.69	0.49	**22.00**
2020	7.70	2.59	3.94	4.13	1.13	3.47	0.58	0.67		0.57	0.69	0.49	**25.96**
2021	7.71	2.59	3.94	4.14	1.13	3.47	0.58	0.68	1.03	0.57	0.69	0.49	**27.02**
2022	7.72	2.60	3.95	4.14	1.13	3.48	0.58	0.68	1.03	0.57	0.69	0.49	**27.04**
2023	7.73	2.60	3.95	4.15	1.13	3.48	0.58	0.68	1.03	0.57	0.69	0.49	**27.07**
2024	7.73	2.60	3.95	4.15	1.13	3.48	0.58	0.68	1.03	0.57	0.69	0.49	**27.10**
2025	7.74	2.60	3.96	4.15	1.13	3.49	0.58	0.68	1.03	0.57	0.69	0.49	**27.12**
2026	7.75	2.61	3.96	4.16	1.14	3.49	0.58	0.68	1.03	0.57	0.69	0.49	**27.15**
2027	7.76	2.61	3.96	4.16	1.14	3.49	0.58	0.68	1.03	0.57	0.69	0.50	**27.17**
2028	7.76	2.61	3.97	4.17	1.14	3.50	0.58	0.68	1.04	0.57	0.69	0.50	**27.20**
2029	7.77	2.61	3.97	4.17	1.14	3.50	0.58	0.68	1.04	0.57	0.69	0.50	**27.23**
Total	**100.45**	**49.23**	**39.55**	**62.13**	**22.56**	**45.23**	**11.51**	**12.16**	**9.29**	**10.23**	**8.97**	**6.41**	**377.72**

Appendix 2B

Estimated Savings from Biogeneric Competition by Treatment Category
25 Percent Average Price Discount, 2010-2029, $ billions

	Erythropoietins	TNF Blockers	Insulin & Insulin Analogs	Cancer Antibodies	Interferon Beta	G-CSF (granulocyte-colony stimulating factors)	Human Growth Hormone	Recombinant Coagulation Factors	Interferon Alfa	Enzyme Replacement	Antiviral Antibodies	Follicle-Stimulating Hormones	Total
2010					0.70		0.36						**1.05**
2011		1.60			0.70		0.36						**2.66**
2012		1.60			0.70		0.36	0.42		0.35			**3.43**
2013		1.61			0.70		0.36	0.42		0.35			**3.43**
2014		1.61			0.70		0.36	0.42		0.35			**3.44**
2015		1.61		2.57	0.70		0.36	0.42		0.35			**6.01**
2016		1.61		2.57	0.70		0.36	0.42		0.35			**6.01**
2017	4.79	1.61		2.57	0.70	2.16	0.36	0.42		0.35	0.43	0.31	**13.70**
2018	4.80	1.61		2.57	0.70	2.16	0.36	0.42		0.35	0.43	0.31	**13.72**
2019	4.80	1.62		2.58	0.70	2.16	0.36	0.42		0.35	0.43	0.31	**13.73**
2020	4.81	1.62	2.46	2.58	0.70	2.16	0.36	0.42		0.35	0.43	0.31	**16.20**
2021	4.81	1.62	2.46	2.58	0.70	2.17	0.36	0.42	0.64	0.35	0.43	0.31	**16.86**
2022	4.82	1.62	2.46	2.58	0.71	2.17	0.36	0.42	0.64	0.36	0.43	0.31	**16.87**
2023	4.82	1.62	2.46	2.59	0.71	2.17	0.36	0.42	0.64	0.36	0.43	0.31	**16.89**
2024	4.83	1.62	2.47	2.59	0.71	2.17	0.36	0.42	0.64	0.36	0.43	0.31	**16.91**
2025	4.83	1.62	2.47	2.59	0.71	2.18	0.36	0.42	0.64	0.36	0.43	0.31	**16.92**
2026	4.83	1.63	2.47	2.59	0.71	2.18	0.36	0.42	0.64	0.36	0.43	0.31	**16.94**
2027	4.84	1.63	2.47	2.60	0.71	2.18	0.36	0.42	0.65	0.36	0.43	0.31	**16.95**
2028	4.84	1.63	2.48	2.60	0.71	2.18	0.36	0.42	0.65	0.36	0.43	0.31	**16.97**
2029	4.85	1.63	2.48	2.60	0.71	2.18	0.36	0.42	0.65	0.36	0.43	0.31	**16.99**
Total	**62.67**	**30.72**	**24.68**	**38.76**	**14.08**	**28.22**	**7.18**	**7.58**	**5.80**	**6.38**	**5.60**	**4.00**	**235.67**

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