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Biologics and Biosimilars: Background and Key Issues

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September 30, 2016

Congressional Research Service
7-....
www.crs.gov
R44620

CRS REPORT
Prepared for Members and
Committees of Congress

Summary

A biological product, or biologic, is a preparation, such as a drug or a vaccine, that is made from living organisms. Compared with conventional chemical drugs, biologics are relatively large and complex molecules. They may be composed of proteins (and/or their constituent amino acids), carbohydrates (such as sugars), nucleic acids (such as DNA), or combinations of these substances. Biologics may also be cells or tissues used in transplantation.

A biosimilar, sometimes referred to as a follow-on biologic, is a therapeutic drug that is similar but not structurally identical to the brand-name biologic made by a pharmaceutical or biotechnology company. In contrast to the relatively simple structure and manufacture of chemical drugs, biosimilars, with their more complex nature and method of manufacture, will not be identical to the brand-name product, but may instead be shown to be highly similar. The Food and Drug Administration (FDA) regulates both biologics and chemical drugs.

Biologics and biosimilars frequently require special handling (such as refrigeration) and processing to avoid contamination by microbes or other unwanted substances. Also, they are usually administered to patients via injection or infused directly into the bloodstream. For these reasons, biologics often are referred to as specialty drugs. The cost of specialty drugs, including biologics, can be extremely high.

In April 2006, the European Medicines Agency (EMA) authorized for marketing in Europe the first biosimilar product, Omnitrope, a human growth hormone. The EMA has authorized a total of 21 biosimilars for the European market. The introduction of biosimilars in Europe has reduced prices for biologics overall, in some cases by 33% compared with the original price of the brand-name product. For one drug in Portugal, the price reduction was 61%.

In contrast, the pathway to marketing biosimilars in the United States has had several barriers. FDA approved Omnitrope in June 2006, following an April 2006 court ruling that the FDA must move forward with consideration of the application. At the time Omnitrope was approved, FDA indicated that this action "does not establish a pathway" for approval of other follow-on biologic drugs and stated that Congress must change the law before the agency can approve copies of nearly all other biotech products.

Four years later, in March 2010, Congress established a new regulatory authority for FDA by creating an abbreviated licensure pathway for biological products demonstrated to be "highly similar" (biosimilar) to or "interchangeable" with an FDA-licensed biological product. The new authority was accomplished via the Biologics Price Competition and Innovation Act (BPCIA) of 2009, enacted as Title VII of the Affordable Care Act (ACA, P.L. 111-148). In addition, Congress authorized FDA to collect associated fees via the Biosimilar User Fee Act of 2012 (BsUFA, P.L. 112-144). The five-year biosimilars user fee authority will sunset on October 1, 2017. FDA held meetings with industry during March through May 2016 to renegotiate the user fee agreement. The draft BsUFA agreement on FDA performance goals and procedures for FY2018 through FY2022 was posted on the FDA website in September 2016. The public will have an opportunity to express its views on the draft during a public meeting on October 20, 2016, and a 30-day comment period after which the agreement will be presented to Congress.

FDA has approved four biosimilars for marketing in the United States: Zarxio (filgrastim-sndz) in March 2015, Inflectra (infliximab-dyyb) in April 2016, Erelzi (etanercept-szzs) in August 2016, and Amjevita (adalimumab-atto) in September 2016. The entry of such products on the U.S. market may result in price reductions similar to those that have occurred in Europe.

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Introduction

A biologic or biological product is a preparation, such as a therapeutic drug or a vaccine, made from living organisms, either human, animal, yeast, or microorganisms. Biologics are composed of proteins (and/or their constituent amino acids), carbohydrates (such as sugars), nucleic acids (such as DNA), or combinations of these substances. Biologics may also be cells or tissues used in transplantation.

A biosimilar, sometimes referred to as a follow-on biologic, is a therapeutic drug that is similar but not structurally identical to the brand-name biologic made by a pharmaceutical or biotechnology company. The brand-name product is sometimes referred to as the innovator or reference product.

In contrast to biologics, most commonly used drugs—over-the-counter drugs and most prescription drugs—are synthesized via a chemical process. A generic drug is chemically identical to its reference brand-name drug. The molecular structure of a commonly used chemical drug is much smaller than a biologic and therefore less complicated and more easily defined. For example, **Table 1** shows that the chemical drug aspirin contains nine carbon atoms, eight hydrogen atoms, and four oxygen atoms while the biologic drug Remicade contains over 6,000 carbon atoms, almost 10,000 hydrogen atoms, and about 2,000 oxygen atoms. Inflectra, which is biosimilar to Remicade, was approved by FDA in April 2016.

Table 1. Relative Size of Chemical and Biologic Drugs

Drug (nonproprietary name)	Molecular formula
chemical drugs	
aspirin	$C_9H_8O_4$
Tylenol (acetaminophen)	$C_8H_9NO_2$
Sovaldi (sofosbuvir)	$C_{22}H_{29}FN_3O_9P$
small biologic drugs	
Lantus (insulin glargine)	$C_{267}H_{404}N_{72}O_{78}S_6$
Epogen (epoetin alfa)	$C_{809}H_{1301}N_{229}O_{240}S_5$
Neupogen, Zarxio (filgrastim)	$C_{845}H_{1339}N_{223}O_{243}S_9$
growth hormone (somatropin)	$C_{990}H_{1528}N_{262}O_{300}S_7$
large biologic drugs	
Enbrel, Erelzi (etanercept)	$C_{2224}H_{3472}N_{618}O_{701}S_{36}$
Remicade, Inflectra (infliximab)	$C_{6428}H_{9912}N_{1694}O_{1987}S_{46}$

Source: Drugs @FDA and Drugs.com.

Notes: The nonproprietary name of a drug product is used in drug labeling, drug regulation, and scientific literature to identify a pharmaceutical substance or active pharmaceutical ingredient. C, carbon; H, hydrogen; O, oxygen; N, nitrogen; F, fluorine; P, phosphorus; S, sulfur.

The Food and Drug Administration (FDA) regulates both biologics and chemical drugs. The Center for Biologics Evaluation and Research (CBER) within FDA regulates what are often referred to as traditional biologics, such as vaccines, blood and blood products, allergenic

extracts, and certain devices and test kits.[1] CBER also regulates gene therapy products, cellular therapy products, human tissue used in transplantation, and the tissue used in xenotransplantation—the transplantation of non-human cells, tissues, or organs into a human.[2]

The FDA Center for Drug Evaluation (CDER) regulates prescription brand-name and generic drugs, over-the-counter drugs, and most therapeutic biologics; this last responsibility was transferred from CBER to CDER in 2003.[3] See **Appendix A** for further details. Examples of types of therapeutic biologics regulated by CDER are briefly described in the list below.[4]

- Monoclonal antibodies—proteins that bind to a specific substance in the body or a specific cell. A monoclonal antibody may carry a drug or toxin. An example of a monoclonal antibody product is infliximab, used to treat Crohn's disease, ulcerative colitis, rheumatoid arthritis, and psoriasis.
- Cytokines—proteins that control (stimulate or slow down) the immune system and are used to fight cancer, infections, and other diseases. Examples include interleukins, interferons, and colony-stimulating factors, such as filgrastim.
- Growth factors—substances, such as hormones, made by the body that regulate cell division and cell survival, such as the human growth hormone somatropin.
- Enzymes—proteins that speed up chemical reactions in the body. Enzymes take part in many cell functions, including cell signaling, growth, and division. In cancer treatment, enzyme inhibitors may be used to block certain enzymes that cancer cells need to grow.
- Immunomodulators—substances, such as a vaccine, that stimulate or suppress the immune system and may help the body fight cancer, infection, or other diseases.

Biologics and biosimilars frequently require special handling (such as refrigeration) and processing to avoid contamination by microbes or other unwanted substances. Also, they are usually administered to patients via injection or infused directly into the bloodstream. For these reasons, biologics often are referred to as specialty drugs.[5] In the past, biologics were often dispensed by pharmacies with specialized facilities and personnel. The term *specialty drugs* is now used to describe drugs that are expensive for any of several reasons, including the requirement for special handling.

The cost of specialty drugs, including biologics, may be extremely high. For example, the annual cost of some biologic medications, such as Soliris (eculizumab) and Vimizim (elosulfase alfa), exceeds $250,000 per patient.[6] Spending on biologics in the United States totaled $92 billion in

[1] FDA, http://www.fda.gov/BiologicsBloodVaccines/default.htm.

[2] CBER does not regulate the transplantation of vascularized human organ transplants such as kidney, liver, heart, lung, or pancreas. The Health Resources Services Administration (HRSA) oversees the transplantation of vascularized human organs.

[3] *Federal Register*, vol. 68, no. 123, June 26, 2003, pp. 38067-38068. CDER's work covers more than just medicines. For example, fluoride toothpaste, antiperspirants, dandruff shampoos, and sunscreens are all considered "drugs." FDA, About the Center for Drug Evaluation and Research, at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/default.htm.

[4] Definitions from NCI Dictionary of Cancer Terms at http://www.cancer.gov/publications/dictionaries/cancer-terms.

[5] For further information, see CRS Report R44132, *Specialty Drugs: Background and Policy Concerns*, by (name redacted) .

[6] Aaron S. Kesselheim and Jerry Avorn, "The High Cost of Prescription Drugs in the United States: Origins and Prospects for Reform," *JAMA*, vol. 316, no. 8 (August 23/30, 2016), pp. 858-871.

2013, or 28% of all U.S. drug spending.[7] This was a 9.6% increase over 2012 biologics spending; in contrast, 2013 spending on small molecule chemical drugs increased by 0.1% over 2012.[8] Biologic drugs are often more expensive in the United States than in Europe and Canada; see **Appendix B**. In Europe, the introduction of biosimilars has reduced prices for biologics, in some cases by 33% compared with the original price of the reference product; for one drug in Portugal, the price reduction was 61%.[9]

The next section of this report describes the effort by Congress in recent years to lower the price of commonly used chemical drugs via the Hatch-Waxman Act. The use of biologics and spending on these products has been increasing; see for example **Appendix C**. Congress has been looking for a way, similar to the Hatch-Waxman Act, to provide lower-cost alternatives for biologics.

The Need for Biosimilars Legislation

Congress passed the Drug Price Competition and Patent Term Restoration Act of 1984 (P.L. 98-417)—often called the Hatch-Waxman Act—to allow for the FDA approval of generic chemical drugs.[10] By offering an alternative to brand-name drug products, the Hatch-Waxman Act has been credited with lowering the cost of drugs to consumers, as well as allowing the U.S. generic drug industry to expand.

For chemical drugs, "generic medications decrease prices 60% to 90% on branded oral-solid medications," according to some experts.[11] The generic drug industry achieves cost savings by avoiding the expense of clinical trials, as well as the initial drug research and development costs incurred by the brand-name manufacturer. Before a generic drug is approved for marketing, the generic drug company must demonstrate to the FDA that the drug product is identical to the original product. This "sameness" allows the generic company to rely on, or "reference," the FDA's previous finding of safety and effectiveness for the already approved drug. A generic drug is considered to be interchangeable with its reference (brand-name) drug and with other generic products that use the same reference drug.

During the time that Hatch-Waxman was debated by Congress and later implemented by the FDA, the biotechnology industry was developing its first biologics for use as human therapeutic agents. In 1982, FDA allowed on the market the first biotechnology drug for human use, human insulin (Humulin-R). This was followed by human growth hormone (Protropin) in 1985, alpha interferon (Intron-A) in 1986, tissue plasminogen activator (Activase) in 1987, and erythropoietin (Epogen) in 1989.

Most biological products are regulated—*licensed* for marketing via a biologics license application (BLA)—under the Public Health Service Act (PHSA). Biological products were originally

[7] IMS Institute for Healthcare Informatics, *Medicine use and shifting costs of healthcare: A review of the use of medicines in the United States in 2013*, April 2014, p. 40.

[8] Ibid.

[9] IMS Health, *The Impact of Biosimilar Competition*, June 2016, p. 4, at http://ec.europa.eu/growth/tools-databases/newsroom/cf/itemdetail.cfm?item_id=8854.

[10] To balance the establishment of the generic drug industry, the Hatch-Waxman Act provided the sponsor of a brand-name drug a period of market exclusivity (apart from its patent protection) to allow the sponsor of an innovator drug the opportunity to recoup its research investment, or earn more profit, before the market entry of the lower-priced generic product. For further information, see CRS Report R41114, *The Hatch-Waxman Act: Over a Quarter Century Later*, by (name redacted) and (name redacted) .

[11] Jonah Houts, Express Scripts, Inc., testimony before the House Committee on Oversight and Government Reform, Hearing on "Safe and Affordable Biotech Drugs: The Need for a Generic Pathway," March 26, 2007.

regulated by the National Institutes of Health (NIH) and its precursors. In 1972, this regulatory responsibility was transferred to FDA; see **Appendix A** of this report for further details. All chemical prescription drugs are regulated—*approved* for marketing via a new drug application (NDA) or abbreviated new drug application (ANDA)—under the Federal, Food, Drug and Cosmetic Act (FFDCA).

The Hatch-Waxman Act of 1984

Hatch-Waxman added two pathways to the FFDCA: Section 505(j) and Section 505(b)(2). Section 505(j) established an Abbreviated New Drug Application (ANDA) process for a generic drug that contains the same active ingredient as the brand-name drug. In the ANDA, the generic company establishes that its drug product is chemically the same as the already approved drug, and thereby relies on the FDA's previous finding of safety and effectiveness for the approved drug. The 505(j) pathway is used for the approval of most generic chemical drugs. The 505(b)(2) pathway may be used for a drug that has a significant difference from a brand-name drug but is still sufficiently similar to that drug. The company filing the 505(b)(2) application must submit additional non-clinical and clinical data to show that the proposed product is safe and effective. The application may rely on published literature or on the FDA's finding of safety and effectiveness for the already approved product to support the approval of the proposed product.

The Hatch-Waxman Act provided a mechanism for the approval of generic drugs under the FFDCA, but it did not provide a mechanism for follow-on biologics/biosimilars under the PHSA. As a result, after Hatch-Waxman, companies could submit follow-on biologics applications for FDA review only for the very small number of so-called "natural source" biologics that had been approved under the FFDCA. Companies were effectively blocked from submitting follow-on applications for the much larger group of therapeutic biologics that had been licensed under the PHSA.

Historically, certain biological products were regulated as drugs under the FFDCA rather than as biologics under the PHSA. In 1941, Congress gave the FDA authority over the marketing of insulin.[12] The hormone insulin is a small protein—a short chain of 51 amino acids—that regulates carbohydrate (sugar) metabolism. In the 1940s, insulin was obtained in the same way as many biologics—extraction from animals—hence the term "natural source."[13] Despite this similarity with other biologics, insulin was regulated as a drug by FDA rather than as a biologic by NIH. Besides insulin, a small set of other natural source biological products were regulated as drugs under the FFDCA rather than as biologics under the PHSA: the hormone glucagon, human growth hormone, hormones to treat infertility, hormones used to manage menopause and osteoporosis, and certain medical enzymes (hyaluronidase and urokinase).[14]

Even though patent protection for specialty biologic drug products was approaching expiration, the market competition that occurred with chemical drugs via generics could not happen with therapeutic biologics because FDA lacked clear regulatory authority to approve biosimilars. Although some entities, such as the Generic Pharmaceutical Association (GPhA), advocated that the FDA establish a regulatory system for the approval of biosimilars under its existing statutory

[12] David M. Dudzinski, "Reflections on Historical, Scientific, and Legal Issues Relevant to Designing Approval Pathways for Generic Versions of Recombinant Protein-Based Therapeutics and Monoclonal Antibodies," *Food and Drug Law Journal*, (2005) vol. 60, p. 153. The Insulin Amendments, P.L. 77-366, codified at 21 U.S.C. 356, were repealed by P.L. 105-115, the Food and Drug Administration Modernization Act (FDAMA).

[13] Ibid., p. 154.

[14] Janet Woodcock, Deputy Commissioner, Chief Medical Officer, FDA, testimony before the House Committee on Oversight and Government Reform, March 26, 2007, at http://www.fda.gov/newsevents/testimony/ucm154070.htm; and, BIO Citizen Petition, Follow-on Therapeutic Proteins, April 23, 2003, at http://www.fda.gov/OHRMS/DOCKETS/DOCKETS/03p0176/03p-0176-cp00001-01-vol11.pdf.

authority,[15] the Biotechnology Industry Organization (BIO) filed a citizen petition with the FDA requesting a number of actions that would have inhibited the approval of biosimilars.[16]

In contrast, the pathway to marketing biosimilars in Europe seemingly had fewer barriers. In April 2006, the European Medicines Agency (EMA) authorized for marketing in Europe the first biosimilar product, Omnitrope, a human growth hormone. This was followed by the authorization of five other biosimilar products in 2007, three more in 2008, and many more thereafter (as shown in **Table 2**).

Table 2. Biosimilars Authorized for Marketing in Europe by the EMA

Name	Active Substance	Therapeutic Area	Authorization Date
Omnitrope	somatropin	pituitary dwarfism, Prader-Willi Syndrome, Turner Syndrome	4/12/2006
Binocrit	epoetin alfa	anemia, chronic kidney failure	8/28/2007
Epoetin Alfa Hexal	epoetin alfa	anemia, cancer, chronic kidney failure	8/28/2007
Abseamed	epoetin alfa	same as above	8/28/2007
Retacrit	epoetin zeta	anemia, autologous blood transfusion, cancer, chronic kidney failure	12/18/2007
Silapo	epoetin zeta	same as above	12/18/2007
Ratiograstim	filgrastim	cancer, hematopoietic stem cell transplantation, neutropenia	9/15/2008
Tevagrastim	filgrastim	same as above	9/15/2008
Biograstim	filgrastim	same as above	9/15/2008
Zarzio	filgrastim	same as above	2/6/2009
Filgrastim Hexal	filgrastim	same as above	2/6/2009
Nivestim	filgrastim	same as above	6/8/2010
Inflectra	infliximab	psoriatic arthritis, rheumatoid arthritis, ulcerative colitis, Crohn's disease, psoriasis, ankylosing spondylitis	9/10/2013
Remsima	infliximab	same as above	9/10/2013
Ovaleap	follitropin alfa	anovulation	9/27/2013
Grastofil	filgrastim	neutropenia	10/18/2013
Bemfola	follitropin alfa	anovulation	3/27/2014
Abasaglar (Abasria)	insulin glargine	diabetes mellitus	9/9/2014
Accofil	filgrastim	neutropenia	9/18/2014
Benepali	etanercept	psoriatic arthritis, rheumatoid arthritis, psoriasis,	1/14/2016
Flixabi	infliximab	psoriatic arthritis, rheumatoid arthritis, ulcerative colitis, Crohn's disease, psoriasis, ankylosing spondylitis	5/26/2016

[15] Bill Nixon, President and CEO, Generic Pharmaceutical Association, letter to Daniel Troy, Chief Counsel, FDA, January 18, 2002, at http://www.fda.gov/cder/ogd/GPHA_jan_21.htm.

[16] BIO Citizen Petition, Follow-on Therapeutic Proteins, April 23, 2003, at http://www.fda.gov/OHRMS/DOCKETS/DOCKETS/03p0176/03p-0176-cp00001-01-vol11.pdf.

Source: European Medicines Agency (EMA), European public assessment reports, July 26, 2016, available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124.

Notes: In addition to the products listed above, the EMA authorized two biosimilars that were later voluntarily withdrawn: Valtropin (somatropin) and Filgrastim ratiopharm (filgrastim). Two other products were refused authorization by the EMA: Alpheon (recombinant human interferon alfa-2a) and Solumarv (human insulin).

The FDA approval of Omnitrope was announced in June 2006 following an April 10, 2006, ruling by the U.S. District Court for the District of Columbia in favor of Omnitrope's sponsor, Sandoz.[17] The court ruled that the FDA must move forward with consideration of the abbreviated application, submitted by Sandoz in 2003, which presented Omnitrope as "indistinguishable" from the FDA-approved Genotropin, marketed by Pfizer. Sandoz "alleged that the FDA had violated its statutory obligation to act on the Omnitrope application within 180 days, a time frame that the FDA characterized as merely a congressional aspiration."[18] The 505(b)(2) pathway, created by the Hatch-Waxman Act, was used to approve Omnitrope.[19]

At the time of the Omnitrope approval in 2006, the FDA indicated in a document on the agency's website that this action "does not establish a pathway" for approval of other follow-on biologic drugs. "The agency has said that Congress must change the law before it can approve copies of nearly all other biotech products, and lawmakers haven't moved on the issue."[20]

New Pathway for Biosimilars

Four years later, in March 2010, Congress established a new regulatory authority for FDA by creating an abbreviated licensure pathway in Section 351(k) of the PHSA for biological products that are demonstrated to be "highly similar" (biosimilar) to or "interchangeable" with an FDA-licensed biological product. This authority was accomplished via the Biologics Price Competition and Innovation Act (BPCIA) of 2009, enacted as Title VII of the Affordable Care Act (ACA, P.L. 111-148).[21] In addition, Congress authorized FDA to collect the associated user fees from industry. FDA describes the terms biosimilar and interchangeable in the following paragraphs.

> Under the BPCI Act, a sponsor may seek approval of a "biosimilar" product under new section 351(k) of the PHS Act. A biological product may be demonstrated to be "biosimilar" if data show that the product is "highly similar" to the reference product notwithstanding minor differences in clinically inactive components and there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity and potency.

[17] Anna Wilde Mathews and Jeanne Whalen, "FDA Clears Copycat Version Of Human Growth Hormone," *The Wall Street Journal*, June 1, 2006, and Anna Wilde Mathews, "FDA Is Ordered to Rule on Generic Biotech Drug," *The Wall Street Journal*, April 15, 2006.

[18] "Europe approves two follow-on human growth hormones," *Nature Biotechnology*, vol. 24 (June 2006), p. 601.

[19] Other follow-on products have used the 505(b)(2) pathway: Fortical (calcitonin-salmon) nasal spray, for treatment of postmenopausal osteoporosis, approved in August 2005; Hylenex (hyaluronidase-human), for increasing absorption of an injected drug, approved in December 2005; and Basaglar (insulin glargine injection), for treatment of diabetes, approved in December 2015. All are follow-ons of biologics that were regulated as drugs under the FFDCA.

[20] Anna Wilde Mathews and Jeanne Whalen, "FDA Clears Copycat Version Of Human Growth Hormone," *The Wall Street Journal*, June 1, 2006.

[21] The BPCIA also created FDA-administered periods of regulatory exclusivity for certain brand-name biologics and biosimilar products, as well as procedures for brand-name and biosimilar manufacturers to resolve patent disputes. For further information, see CRS Report R44173, *Follow-On Biologics: Intellectual Property Issues*, by (name redacted).

> In order to meet the higher standard of interchangeability, a sponsor must demonstrate that the biosimilar product can be expected to produce the same clinical result as the reference product in any given patient and, for a biological product that is administered more than once, that the risk of alternating or switching between use of the biosimilar product and the reference product is not greater than the risk of maintaining the patient on the reference product. Interchangeable products may be substituted for the reference product by a pharmacist without the intervention of the prescribing health care provider.[22]

FDA held a two-day public meeting on November 2 and 3, 2010, to obtain perspectives from industry and the general public prior to developing and releasing agency guidance on the new biosimilars pathway. Based on public input at this first meeting, FDA released three draft guidance documents in February 2012 and held another public meeting on May 11, 2012, to obtain feedback on the draft guidance.[23] The FDA released final guidance on the first three draft guidance documents on April 28, 2015. The agency has also released additional guidance on a variety of other topics related to biosimilars. A list of FDA guidance documents on biosimilars is available on the agency's website.[24]

Under Section 351(k) of the PHSA, a company interested in marketing a biosimilar product in the United States must first submit to FDA an application that provides information demonstrating biosimilarity based on data from analytical studies (structural and functional tests), animal studies (toxicity tests), and a clinical study or studies (tests in human patients). The agency may decide, at its discretion, that a certain study or studies are unnecessary in a biosimilar application.

As is the case with other FDA-approved products, any subsequent change to the approved manufacturing process—such as a change in the supplier of a raw material or the replacement of a piece of equipment—requires a demonstration to FDA of the comparability of the product's quality attributes before and after the change to ensure that the safety and efficacy of the product is maintained. For example, the brand-name biologic Remicade (infliximab) underwent 37 manufacturing changes between 1998 and October 2014; each change required a demonstration of comparability, most likely through chemical, physical, and biological assays.[25]

For many years, the drug industry and FDA have coped with the inherent variability in biological products from natural sources. FDA maintains that the batch-to-batch and lot-to-lot variability that occurs for brand-name biologics and biosimilars can be assessed and managed effectively.

In March 2015, FDA announced the approval of Zarxio (filgrastim-sndz), the first biosimilar product approved for marketing in the United States (see **Table 3**). Zarxio, marketed by Sandoz Inc., is biosimilar to Neupogen (filgrastim), marketed by Amgen Inc.[26] Neupogen was originally

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[22] FDA, Implementation of the Biologics Price Competition and Innovation Act of 2009, at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm215089.htm.

[23] The three draft guidances were published in the *Federal Register* on February 15, 2012: (1) Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, (2) Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, and (3) Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product.

[24] FDA, Guidances (Drugs), Biosimilars, at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm.

[25] Comments by Brian Lehman, Manager of Pharmacy Benefits and Policy, Ohio Public Employees Retirement System (OPERS), at the June 20, 2016, Alliance for Health Reform briefing, "The Emerging Biosimilars Market," webcast at https://www.youtube.com/watch?v=XZvhLYZ_TZg; and, FDA, CDERLearn website, *FDA Overview of Biosimilar Products*, slide 13 in Module 4 "Complexity of Biological Product Manufacturing," at http://fdabiosimilars.e-paga.com/course/framework/.

[26] FDA News Release, "FDA approves first biosimilar product Zarxio," March 6, 2015, at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm436648.htm.

licensed by FDA in 1991 as shown in **Appendix D**. Zarxio is approved for the same indications as Neupogen.

Table 3. Biosimilars Approved for Marketing in the United States by FDA

Name	Active Substance	Indications (Therapeutic Area)	Approval Date
Zarxio	filgrastim-sndz	cancer, hematopoietic stem cell transplantation, neutropenia	3/6/2015
Inflectra	infliximab-dyyb	psoriatic arthritis, rheumatoid arthritis, ulcerative colitis, Crohn's disease, psoriasis, ankylosing spondylitis	4/5/2016
Erelzi	etanercept-szzs	rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis	8/30/2016
Amjevita	adalimumab-atto	rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, plaque psoriasis, polyarticular juvenile idiopathic arthritis (4 years of age and older)	9/23/2016

Sources: FDA News Releases.

In April 2016, FDA approved a second biosimilar, Inflectra (infliximab-dyyb). Inflectra is biosimilar to Remicade (infliximab), made by Janssen Biotech, Inc.[27] Remicade was originally licensed in 1998 as shown in **Appendix D**. Inflectra is made by Celltrion, Inc., in the Republic of Korea, for Hospira, of Lake Forest, IL. Hospira was acquired by Pfizer in 2015. According to an FDA representative, as of June 20, 2016, only Zarxio was being marketed in the United States; marketing for Inflectra had not yet begun.[28]

In August 2016, FDA approved a third biosimilar, Erelzi (etanercept-szzs), manufactured by Sandoz.[29] Erelzi is biosimilar to Enbrel (etanercept) which is manufactured by Amgen. Enbrel was originally licensed in 1998, as shown in **Appendix D**. Erelzi is approved for all indications included on the label for Enbrel. According to a Sandoz press release, "the approval is based on a comprehensive package of analytical, nonclinical, and clinical data confirming that Erelzi is highly similar to the US-licensed reference product. Clinical studies included four comparative pharmacokinetic (PK) studies in 216 healthy volunteers and a confirmatory efficacy and safety similarity study in 531 patients with chronic plaque psoriasis. Extrapolation to all indications approved for use on the reference product label is on the basis that the Sandoz biosimilar etanercept and the reference product are essentially the same."[30] A release date for marketing of Erelzi has not yet been set due to a lawsuit filed by Amgen against Sandoz and its parent company Novartis; a trial is scheduled for April 2018.[31]

[27] FDA News Release, "FDA approves Inflectra, a biosimilar to Remicade," April 5, 2016, at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm494227.htm.

[28] Comments by CDER Associate Director for Therapeutic Biologics, Leah Christl, at the June 20, 2016, Alliance for Health Reform briefing, "The Emerging Biosimilars Market," webcast at https://www.youtube.com/watch?v=XZvhLYZ_TZg.

[29] FDA News Release, "FDA approves Erelzi, a biosimilar to Enbrel," August 30, 2016, at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm518639.htm.

[30] Sandoz, "FDA approves Sandoz Erelzi™ to treat multiple inflammatory diseases," press release, August 30, 2016, http://www.sandoz.com/media_center/press_releases_news/global_news/2016-08-30-fda-approves-sandoz-erelzi.shtml.

[31] "FDA approves third biosimilar for sale in US," *American Health Line*, September 6, 2016.

In September 2016, FDA approved a fourth biosimilar, Amjevita (adalimumab-atto), manufactured by Amgen.[32] Amjevita is biosimilar to Humira (adalimumab), which was licensed by FDA in 2002 (as shown in **Appendix D**) and is currently manufactured by AbbVie (formerly a part of Abbott Laboratories). Amjevita was approved for 7 indications (see **Table 3**); in contrast, Humira is approved for 10 indications.[33] Due to patent infringement litigation between Amgen and AbbVie, it is unclear when Amjevita will be commercially available.[34]

An FDA Biosimilar Product Development (BPD) program provides assistance to industry sponsors in the early stages of developing a new biosimilar product.[35] As of May 31, 2016, there were 60 BPD programs (each developing a separate biosimilar product) to 19 different reference products.[36] In addition, six companies had publicly announced nine pending applications for new biosimilar products via Section 351(k) of the PHSA.[37]

FDA Issues Related to Biosimilars

Naming

The proprietary name of a drug product is the trademarked name, or brand name, for the product. It is the name a company uses to market its drug product, and it is usually capitalized, followed by a superscript R in a circle (®). For example, Neupogen® is the proprietary name for filgrastim, the nonproprietary name for the active substance. The *Purple Book* lists biological products, including any biosimilar and interchangeable biological products, licensed by FDA under the PHS Act, as well as the date the product was licensed. **Appendix D** provides CDER and CBER licensed biological products, listed by year of licensure, and has further examples of proprietary names and nonproprietary names.

The nonproprietary name of a drug product is used in drug labeling, drug regulation, and scientific literature to identify a pharmaceutical substance or active pharmaceutical ingredient. For chemical drugs, the nonproprietary name is also known as the generic name.

FDA released draft guidance on the nonproprietary naming of biological products in August 2015.[38] The draft guidance provides the FDA's rationale regarding its proposed naming

[32] FDA News Release, "FDA approves Amjevita, a biosimilar to Humira," September 23, 2016, at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm522243.htm.

[33] The current Humira label can be found via Drugs@FDA. The Humira label as of June 30, 2016, is available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125057s397lbl.pdf. In addition to the indications listed for Amjevita, Humira is also approved to treat hidradenitis suppurativa, uveitis, and pediatric Crohn's disease, as well as polyarticular juvenile idiopathic arthritis in patients as young as two years of age.

[34] Kurt R. Karst, "FDA Licenses First Humira Biosimilar; Denies AbbVie Petition on Fifth Amendment Takings, FDA Law Blog, Spetember 26, 2016, at http://www.fdalawblog.net/fda_law_blog_hyman_phelps/.

[35] Assistance is in the form of meetings between industry and FDA. "The meeting types and goal dates for BPD meetings were developed by the FDA in consultation with public and industry stakeholders as directed by the Biologics Price Competition and Innovation Act of 2009 (BPCI Act)." For further information, see "Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants: Guidance for Industry" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM345649.pdf.

[36] Comments by CDER Associate Director for Therapeutic Biologics, Leah Christl, at the June 20, 2016, Alliance for Health Reform briefing, "The Emerging Biosimilars Market," webcast at https://www.youtube.com/watch?v=XZvhLYZ_TZg.

[37] Ibid.

[38] FDA, Nonproprietary Naming of Biological Products: Guidance for Industry, August 2015, at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf.

convention for biosimilars. Throughout the draft guidance, FDA uses the term "proper name" instead of "nonproprietary name" due to the nomenclature used in the PHSA.[39]

FDA proposes that the proper name for all biological products consist of a core name and a suffix. The core name would be "shared among all related biological products as part of the proper name." An example of a core name is filgrastim. The proper name for all biological products would include a suffix—composed of four lowercase letters attached to the core name with a hyphen—as a unique identifier (filgrastim-xzwy). The suffix would be "devoid of meaning."

For originator biological products[40]—the reference product—FDA intends to use a core name that is the name adopted by the United States Adopted Name (USAN) Council. Nonproprietary names are selected by the USAN Council according to principles developed to ensure safety, consistency, and logic in the choice of names.[41] FDA is interested in receiving comments on "whether the nonproprietary name for an interchangeable product should include a unique suffix, or should share the same suffix as its reference product."

In Europe, reference drugs and biosimilars use the identical International Nonproprietary Name (INN), a World Health Organization (WHO) drug-naming system that has been in place since 1953. The WHO selects INNs based on the advice of experts on a WHO advisory panel.[42] In January 2016, the WHO released its voluntary Biological Qualifier (BQ) proposal for biosimilar naming.[43] "The BQ is an additional and independent element used in conjunction with the INN to uniquely identify a biological substance to aid in the prescription and dispensing of medicines, pharmacovigilance, and the global transfer of prescriptions. The BQ is a code formed of four random consonants in two 2-letter blocks separated by a 2-digit checksum."[44]

In general, biosimilar industry groups support the shared use of a nonproprietary name, whereas those advocating for the innovator companies prefer a naming scheme that distinguishes between the reference biologic product and the biosimilar.[45]

In its October 2015 public comments to FDA, the Federal Trade Commission expressed concern that the FDA's naming proposal "could result in physicians incorrectly believing that biosimilars' drug substances differ in clinically meaningful ways from their reference biologics' drug

[39] Section 351(a)(1)(B)(i) of the PHSA (42 U.S.C. 262(a)(1)(B)(i) and §600.3(k) of the Code of Federal Regulations (21 C.F.R. 600.3(k)).

[40] FDA defines as follows: "Originator biological product" means a biological product submitted in a BLA under Section 351(a) of the PHS Act (i.e., a stand-alone BLA) for which there is no previously licensed biological product submitted under Section 351(a) that is a related biological product. BLA is a biologics license application.

[41] For information on the USAN Council, see http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council.page.

[42] WHO, Essential medicines and health products, Guidance on INN, at http://www.who.int/medicines/services/inn/innguidance/en/.

[43] WHO, *Biological Qualifier: An INN Proposal*, Programme on International Nonproprietary Names (INN), at http://www.who.int/medicines/services/inn/WHO_INN_BQ_proposal_2015.pdf.

[44] Ibid. As explained in the WHO document, the BQ code "will consist of four random consonants and an optional two digits as a checksum. The WHO INN will issue the BQ letters with a checksum, but it is at the discretion of the individual regulatory authority whether the checksum is used as part of the BQ. The form of the BQ may take: (1) four letters; (2) four letters followed by the checksum; or (3) two letters, two digits and two letters, thus mimicking car registration plates to be more memorable. For instance, TRADENAME INN BQ: GROKINO anonutropin alfa bxsh; or GROKINO anonutropin alfa bxsh08; or GROKINO anonutropin alfa bx08sh."

[45] Erin Durkin, "WHO Unveils Final Biological Naming Plan That Differs From FDA's," *InsideHealthPolicy's FDA Week*, January 29, 2016.

substances."[46] This "misperception" could "deter physicians from prescribing biosimilars" thereby "impeding the development of biosimilar markets and competition."[47] The FTC comment provides further explanation:

> Historically, all originator biologics that met the same identification tests and other aspects of identity ... received the same nonproprietary name." [For example, there] are eight different manufacturers of human growth hormone (recombinant) and all of their products carry the same nonproprietary name—*somatropin*. ... [A]ny differences in nonproprietary names generally signal pharmacological and chemical relationship differences between the products. Although the FDA's proposal will use the same USAN as the core name for each biosimilar and its reference biologic, based on historical practice, the addition of unique differentiating suffixes may lead physicians to believe mistakenly that the products necessarily have clinically meaningful differences. ... Differences in the nonproprietary names of biosimilars could contribute to misperceptions that the drug substance of a biosimilar should be identical, not "highly similar" to that of its reference biologic. [Participants at an FTC workshop on biosimilars contend that] the term identical is abused to instill fear and foster misunderstanding. Because biosimilars are new in the U.S., many physicians do not yet fully understand that a lack of identicality is inherent in biologics. Every biologic displays a certain degree of variability, *even between different batches of the same product*.[48]

Labeling

The labeling for a prescription drug product conveys information about the product's safety and effectiveness to a health care provider, allowing the provider to decide if the product is appropriate for a particular patient. In 2006, FDA issued a final rule on the content and format of labeling for prescription drug products, including biological products, and provided the following description:[49]

> A prescription drug product's FDA approved labeling (also known as "professional labeling," "package insert," "direction circular," or "package circular") is a compilation of information about the product, approved by FDA, based on the agency's thorough analysis of the new drug application (NDA) or biologics license application (BLA) submitted by the applicant. This labeling contains information necessary for safe and effective use. It is written for the health care practitioner audience, because prescription drugs require "professional supervision of a practitioner licensed by law to administer such drug" (section 503(b) of the act (21 U.S.C. 353(b))).

FDA requires that labeling begin with a highlights section that includes any warnings about the drug. Other FDA-required elements of labeling include indications and usage, dosage and administration, dosage forms and strengths, contraindications, warnings and precautions, adverse reactions, drug interactions, use in specific populations, drug abuse and dependence, overdosage,

[46] Comment of the Staff of the Federal Trade Commission, Submitted to the Food and Drug Administration, In Response to a Request for Comments on Its Guidance for Industry on the "Nonproprietary Naming of Biological Products; Draft Guidance for Industry; Availability" [Docket No. FDA-2013-D-1543] Submitted on October 27, 2015, p. 2, at https://www.ftc.gov/system/files/documents/advocacy_documents/ftc-staff-comment-submitted-food-drug-administration-response-fdas-request-comments-its-guidance/151028fdabiosimilar.pdf.

[47] Ibid.

[48] Ibid., p. 9.

[49] FDA, "[Docket No. 2000N–1269] (formerly Docket No. 00N–1269) RIN 0910–AA94, Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products," *Federal Register*, vol. 71, no. 15, January 24, 2006, pp. 3922-3997, http://www.gpo.gov/fdsys/pkg/FR-2006-01-24/pdf/06-545.pdf.

clinical pharmacology, nonclinical toxicology, clinical studies, references, how supplied/storage and handling, and patient counseling information.

FDA released draft guidance on biosimilar labeling in March 2016.[50] FDA recommends that the highlights section of the labeling contain a "Biosimilarity Statement" describing the biosimilar product's relationship to its reference product. The biosimilar product is not required by FDA to have the same labeling as the reference product; for example, the number of approved indications for use may differ. FDA recommends that comparative data demonstrating biosimilarity *not* be included in biosimilar product labeling "to avoid potential confusion or misinterpretation of the comparative data."[51] However, such comparative data are available to prescribers and the public on the FDA website.[52]

Comments on the FDA labeling guidance reflected differing views: while the generic industry wants less information in biosimilar labeling, the brand-name industry would like FDA to require more information.[53] For example, the Generic Pharmaceutical Association said that the Biosimilarity Statement "not only is unnecessary but also may be confusing to patients and healthcare providers."[54] In contrast, BIO, which represents makers of brand-name pharmaceuticals among other companies, stated that more information is preferable to less with regard to labeling. "The prescribing physician needs to have access to all relevant information, including the relevant nonclinical and clinical data supporting the finding of biosimilarity, and the resulting labeling should be transparent to allow the prescriber to identify whether the described studies were conducted with the biosimilar or reference product."[55]

Transition

Under the BPCIA, biologics that were approved as drugs under the FFDCA will transition to biological licenses under the PHSA in March 2020. This BPCIA provision affects the small set of biological products mentioned above: hormone insulin, hormone glucagon, human growth hormone, hormones to treat infertility, hormones used to manage menopause and osteoporosis, and certain medical enzymes (hyaluronidase and urokinase).

FDA released draft guidance regarding the agency's interpretation of this BPCIA provision in March 2016.[56] The FDA describes the BPCIA provision as follows:

> Section 7002(e) of the BPCI Act provides that a marketing application for a "biological product" must be submitted under section 351 of the PHS Act, subject to the following exception during a transition period ending on March 23, 2020:
>
> • An application for a biological product may be submitted under section 505 of the FD&C Act not later than March 23, 2020, if the biological product is in a product class

[50] FDA, *Labeling for Biosimilar Products: Guidance for Industry*, Draft Guidance, March 2016, at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM493439.pdf.

[51] FDA, Drugs, *From our perspective: Biosimilar product labeling*, at http://www.fda.gov/Drugs/NewsEvents/ucm493240.htm.

[52] Ibid.

[53] Bronwyn Mixter, "Brand, Generic Groups Differ on Biosimilar Labeling," *Bloomberg BNA Health Care Daily Report*, June 7, 2016.

[54] Ibid.

[55] Ibid.

[56] FDA, *Implementation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act of 2009*, Draft Guidance, March 2016, at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM490264.pdf.

> for which a biological product in such product class was approved under section 505 of the FD&C Act not later than March 23, 2010.
>
> —However, an application for a biological product may not be submitted under section 505 of the FD&C Act if there is another biological product approved under section 351(a) of the PHS Act that could be a "reference product" if such application were submitted under section 351(k) of the PHS Act.
>
> An approved application for a biological product under section 505 of the FD&C Act shall be deemed to be a license for a biological product under section 351 of the PHS Act on March 23, 2020.[57]

In FDA's interpretation, as of March 23, 2020, applications for biological products that were approved under the FFDCA will no longer exist (as NDAs or ANDAs) and will be replaced by approved BLAs under the PHSA. In addition, FDA will not approve any application under the FFDCA for a biological product subject to the transition provisions that is still pending as of March 23, 2020. The FDA suggests that such applications be withdrawn and resubmitted under the PHSA, either Section 351(a) or 351(k). Some industry representatives, such as the Generic Pharmaceutical Association's Biosimilars Council, have commented that the FDA's proposed policy will significantly delay "the review, approval and availability of biological products that compete with expensive brand name biologics."[58]

Perhaps most importantly, under the FDA's interpretation

> any unexpired period of exclusivity associated with an approved NDA for a biological product subject to section 7002(e) of the BPCI Act (e.g., 5-year exclusivity, 3-year exclusivity, or pediatric exclusivity) would cease to have any effect.... However, any unexpired period of orphan drug exclusivity would continue to apply to the drug for the protected use after March 23, 2020, because orphan drug exclusivity can be granted to and can block the approval of a drug approved under section 505 of the FD&C Act or a biological product licensed under section 351 of the PHS Act.[59]

Industry groups, such as the Pharmaceutical Research and Manufacturers of America, have commented that the FDA policy on exclusivity raises significant legal and trade issues.[60]

Lastly, the transitional biological products will not be eligible for the 12-year biologics exclusivity period because they were not first licensed under the PHSA, as specified by the BPCIA. FDA states, "[n]othing in the BPCI Act suggests that Congress intended to grant biological products approved under section 505 of the FD&C Act—some of which were approved decades ago—a period of exclusivity upon being deemed to have a license under the PHS Act that would impede biosimilar or interchangeable product competition in several product classes until the year 2032."[61]

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[57] Ibid., p. 4.

[58] Erin Durkin, "Drug Lobbyists: FDA's BPCIA Transition Guide Hurts Access, Competition," *InsideHealthPolicy*, June 1, 2016.

[59] FDA, *Implementation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act of 2009*, Draft Guidance, March 2016, p. 6, at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM490264.pdf.

[60] Erin Durkin, "Industry: Axing Exclusivity As Biologics Shift To Licenses Unconstitutional," *InsideHealthPolicy*, May 27, 2016.

[61] FDA, Implementation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act of 2009, Draft Guidance, March 2016, p. 7, at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM490264.pdf.

Interchangeability and Substitution

An interchangeable product "can be expected to produce the same clinical result as the reference product in any given patient and, for a biological product that is administered more than once, that the risk of alternating or switching between use of the biosimilar product and the reference product is not greater than the risk of maintaining the patient on the reference product. Interchangeable products may be substituted for the reference product by a pharmacist without the intervention of the prescribing health care provider."[62]

As mentioned previously, a generic drug is considered to be interchangeable with its reference (brand-name) drug and with other generic products that use the same reference drug. Following passage of the Hatch-Waxman Act, one major source of cost saving was the ability of a pharmacist to substitute a generic drug for a brand-name drug without the intervention of a health care provider. However, because a biosimilar is not structurally identical to its brand-name biologic, assessing interchangeability is a separate process. FDA has not yet released guidance on interchangeability, nor has it approved an interchangeable product.[63]

In Europe, the EMA does not make a determination on interchangeability. "The EMA evaluates biosimilar medicines for authorization purposes. The Agency's evaluations do not include recommendations on whether a biosimilar should be used interchangeably with its reference medicine. For questions related to switching from one biological medicine to another, patients should speak to their doctor and pharmacist."[64] Individual member states decide their own policy on interchangeability. Some countries, such as Denmark, "have concluded that all originators [reference products] and biosimilars are interchangeable unless proven not to be"; in contrast, Ireland allows a single switch but multiple switches are not allowed.[65]

In the United States, FDA regulates the drug product but the states regulate pharmacies and the practice of pharmacy. According to the National Conference of State Legislatures (NCSL), as of August 1, 2016, "at least 36 states have considered legislation establishing state standards for substitution of a biosimilar prescription product to replace an original biologic product."[66] NCSL indicates that a total of 23 states and Puerto Rico have enacted legislation; the provisions of state legislation vary.[67]

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[62] FDA, Implementation of the Biologics Price Competition and Innovation Act of 2009, at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm215089.htm.

[63] FDA expects to issue guidance on interchangeability in 2016. Comments by CDER Associate Director for Therapeutic Biologics, Leah Christl, at the June 20, 2016, Alliance for Health Reform briefing, "The Emerging Biosimilars Market," webcast at https://www.youtube.com/watch?v=XZvhLYZ_TZg.

[64] EMA, "Questions and answers on biosimilar medicines (similar biological medicinal products)," September 27, 2012, at http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/12/WC500020062.pdf.

[65] IMS Institute for Healthcare Informatics, *Delivering on the Potential of Biosimilar Medicines: The role of functioning competitive markets*, March 2016, p. 26.

[66] Richard Carluchi, "State Laws and Legislation Related to Biologic Medications and Substitution of Biosimilars," NCSL, June 1, 2016, at http://www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx.

[67] Ibid. The 23 states (and the year a law was enacted) are Arizona (2016), California (2015), Colorado (2015), Delaware (2014), Florida (2013), Georgia (2015), Hawaii (2016), Idaho (2016), Illinois (2015), Indiana (2014), Kentucky (2016), Louisiana (2015), Massachusetts (2014), Missouri (2016), New Jersey (2015), North Carolina (2015), North Dakota (2013), Oregon (2013 and 2016), Tennessee (2015), Texas (2015), Utah (2013 and 2015), Virginia (2013), and Washington (2015). Puerto Rico enacted a law in 2015.

Reauthorization of the Biosimilar User Fee Act (BsUFA)

FDA first gained the authority to collect user fees from the manufacturers of brand-name prescription drugs and biological products in 1992, when Congress passed the Prescription Drug User Fee Act (PDUFA).[68] With PDUFA, FDA, industry, and Congress reached an agreement on two concepts: (1) *performance goals*—FDA would negotiate with industry on target completion times for various review processes, and (2) *use of fees*—the revenue from prescription drug user fees would be used only for activities to support the review of new product applications and would supplement—rather than supplant—congressional appropriations to FDA. The added resources from user fees allowed FDA to increase staff available to review applications and to reduce the median review time for standard applications. Over the years, Congress has added similar authority regarding medical devices, animal drugs, and generic human drugs.[69] User fees make up 43% of the FY2016 FDA budget.

The FFDCA was amended by the Biosimilar User Fee Act of 2012 (BsUFA), authorizing FDA to collect fees for agency activities associated with the review of biosimilars from October 2012 through September 2017.[70] The biosimilars user fee program allows FDA to collect six types of fees from industry. Fee amounts are based on inflation-adjusted PDUFA fee amounts for each fiscal year. Because no marketed biosimilar biological products existed when the BsUFA program started, it included fees for products in the development phase to generate fee revenue for the new program and to enable companies to meet with FDA in the early development of biosimilar biological products.[71] A company may choose to discontinue participation in the biosimilar biological product development program but must pay a reactivation fee to resume further product development with FDA. The BsUFA fees are as follows:

- initial biosimilar biological product development fee, 10% of the PDUFA human drug application fee;
- annual biosimilar biological product development fee, 10% of the human drug application fee;
- reactivation fee, 20% of the human drug application fee;
- biosimilar biological product application fee, 100% of the human drug application fee minus the cumulative amount paid for product development program fees;
- biosimilar biological product establishment fee, 100% of the PDUFA prescription drug establishment fee; and
- biosimilar biological product fee, 100% of the PDUFA prescription drug product fee.

The biosimilar biological product application fee may be waived for the first such application from a small business. A "small business" is defined as an entity, including affiliates, with fewer

[68] See CRS Report R42366, *Prescription Drug User Fee Act (PDUFA): 2012 Reauthorization as PDUFA V*, and CRS Report RL33914, *The Prescription Drug User Fee Act: History Through the 2007 PDUFA IV Reauthorization*, both by (name redacted)

[69] See CRS Report R44517, *The FDA Medical Device User Fee Program: MDUFA IV Reauthorization*, by (name redacted) , and CRS Report RL34459, *Animal Drug User Fee Programs*, by (name redacted)

[70] Title IV of the Food and Drug Administration Safety and Innovation Act (FDASIA, P.L. 112-144).

[71] U.S. Congress, House Committee on Energy and Commerce, Subcommittee on Health, Review of the Proposed Generic Drug and Biosimilars User Fees and Further Examination of Drug Shortages, Statement of Janet Woodcock, CDER Director, FDA, 112th Cong., 2nd sess., February 9, 2012.

than 500 employees that does not have a drug product that has been approved under a human drug or biosimilar biological application and introduced or delivered for introduction into commerce. FY2017 fee rates under BsUFA are shown in **Table 4**. The FDA provides information on the amount of BsUFA fees collected each fiscal year and how the fees are spent in an annual financial report.[72]

As is the case with several other FDA user fee authorities, the five-year biosimilars user fee authority is scheduled to sunset on October 1, 2017. FDA has held a series of meetings with industry to renegotiate the user fee agreement. On December 18, 2015, FDA held a public meeting on the reauthorization of the BsUFA program.[73] During March through May 2016, the agency held negotiation sessions with industry on the reauthorization agreement.[74] In September 2016, the agency posted on its website the draft BsUFA agreement on FDA performance goals and procedures for FY2018 through FY2022.[75] A BsUFA public meeting is scheduled to be held on October 20, 2016.[76] Following a 30-day comment period on the draft, a final BsUFA recommendation will be submitted to Congress.

Table 4. FY2017 Fee Rates Under BsUFA

Fee Category	Fee Rate for FY2017
Initial Biosimilar Product Development (BPD)	$203,810
Annual BPD	$203,810
Reactivation	$407,620
Applications requiring clinical data	$2,038,100
Applications not requiring clinical data	$1,019,050
Supplement requiring clinical data	$1,019,050
Establishment	$512,200
Product	$97,750

Source: *Federal Register*, July 28, 2016.

Note: Under Section 744H(a)(2)(A) of the FFDCA, if a sponsor that submits a biosimilar biological product application has previously paid an initial BPD fee, annual BPD fees, and/or reactivation fees for the product that is the subject of the application, the fee for the application is reduced by the cumulative amount of these previously paid fees.

Federal Research and New Drug Development

In general, the federal government—such as the work conducted or supported by NIH—tends to focus more on basic or preclinical research and the pharmaceutical industry concentrates more of

[72] FY2013 through FY2015 BsUFA Financial Reports are at http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/FinancialReports/BsUFA/default.htm.

[73] FDA, BsUFA Meetings, at http://www.fda.gov/ForIndustry/UserFees/BiosimilarUserFeeActBsUFA/ucm461774.htm.

[74] Ibid.

[75] FDA, Biosimilar Biological Product Reauthorization Performance Goals and Procedures Fiscal Years 2018 Through 2022, at http://www.fda.gov/downloads/ForIndustry/UserFees/BiosimilarUserFeeActBsUFA/UCM521121.pdf.

[76] FDA, BsUFA Meetings at http://www.fda.gov/ForIndustry/UserFees/BiosimilarUserFeeActBsUFA/ucm461774.htm.

its research funding on clinical trials rather than on discovery activity.[77] When trying to assign credit for specific therapeutic advancements, drawing a line between basic and applied research can be challenging. For example, without a major underlying advance, like recombinant DNA, the development of whole new classes of drugs would not have occurred. Concern over the high costs of pharmaceuticals in general and biologics in particular has led some to look more carefully at the federal role in the development of costly new therapeutics.

Various studies have attempted to quantify the contribution of publicly funded research to the discovery of new drugs. A study published in 2003 found that of the 284 new drugs approved by FDA from 1990 through 1999, only 6.7% originated from sources other than private industry.[78] A 1993 study found that 7.6% of new drugs approved from 1981 through 1990 originated from non-industry sources.[79] However, rather than focusing on all drug approvals—including many "me too"[80] drugs—another way to answer this question is to look at the origin of truly innovative new drugs, what FDA calls new molecular entities (NMEs). NMEs are drugs that have not been approved by FDA previously and frequently provide important new therapies for patients.[81] A 2010 study found that of the NMEs and new biologics that received FDA approval between 1998 and 2007, 24.1% originated from work that was publicly funded.[82]

A study by Stevens et al. published in 2011 claims to be more comprehensive than these earlier investigations.[83] The Stevens study found that of the 1,541 drugs approved by FDA from 1990 through 2007, 143, or 9.3%, resulted from work conducted in publicly funded labs. Of the total 1,541 drug applications, FDA granted priority review to 348 applications, and 66 of these (19%) resulted from publicly funded research. The authors state that "viewed from another perspective, 46.2% of the new-drug applications from PSRIs [public-sector research institutions] received priority reviews, as compared with 20.0% of applications that were based purely on private-sector research, an increase by a factor of 2.3."[84] An FDA designation of priority review is for "the evaluation of applications for drugs that, if approved, would be significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when

[77] Hamilton Moses, David H.M. Matheson, and Sarah Cairns-Smith, et al., "The Anatomy of Medical Research: U.S. and International Comparisons," *JAMA*, vol. 313, no. 2 (January 13, 2015), pp. 174-189.

[78] Joseph A. DiMasi, Ronald W. Hansen, Henry G. Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics*, vol. 22 (2003), pp. 151-185.

[79] Kenneth I. Kaitin, Natalie R. Bryant, Louis Lasagna, "The Role of the Research-Based Pharmaceutical Industry in Medical Progress in the United States," *Journal of Clinical Pharmacology*, vol. 33, no. 5 (May 1993), pp. 412-417.

[80] "Me too" drugs are structurally similar to drugs already available on the market. Critics fault industry for developing these duplicative products rather than investing in research on innovative drugs. Me too drugs are often heavily promoted by the pharmaceutical industry in order to gain a foothold on the market. See the January 7, 2015, ProPublica study by Charles Ornstein and Ryann Grochowski Jones at https://www.propublica.org/article/vying-for-market-share-companies-heavily-promote-me-too-drugs.

[81] According to FDA, "[s]ome drugs are characterized as NMEs for administrative purposes, but nonetheless contain active moieties [i.e., parts] that are closely related to active moieties in products that have previously been approved by FDA. For example, CDER classifies biological products submitted in an application under section 351(a) of the Public Health Service Act as NMEs for purposes of FDA review, regardless of whether the Agency previously has approved a related active moiety in a different product." FDA, New Drugs at FDA: CDER's New Molecular Entities and New Therapeutic Biological Products, at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm20025676.htm.

[82] Robert Kneller, "The Importance of New Companies for Drug Discovery: Origins of a Decade of New Drugs," *Nature Review Drug Discovery*, vol. 9, 2010, pp. 867-882.

[83] Ashley J. Stevens, Jonathan J. Jensen, Katrine Wyller, et al., "The Role of Public-Sector Research in the Discovery of Drugs and Vaccines," *The New England Journal of Medicine*, vol. 364, no. 6 (February 10, 2011), pp. 535-541.

[84] Ibid., p. 539.

compared to standard applications."[85] According to the authors, their data "suggest that PSRIs tend to discover drugs that are expected to have a disproportionately important clinical effect."[86]

The 2011 Stevens study considered a PSRI "to have participated in the applied phase of research that led to discovery of a drug if it, solely or jointly, created intellectual property specific to the drug that was subsequently transferred to a company through a commercial license." It is important to understand that the methodology used by the Stevens study "excluded the role of PSRIs in the development of platform technologies that have contributed to the development of whole new classes of drugs." For example, the following platform technologies were all developed with public funds and were excluded from the study:

- recombinant DNA technology (Cohen-Boyer patents);
- bacterial production methods for recombinant DNA (Riggs-Itakura patents);
- production and chimerization[87] methods for antibodies (Cabilly patents);
- methods to produce glycosylated recombinant proteins in mammalian cells (Axel patents); and
- methods of gene silencing with the use of small interfering RNAs (Mello-Fire patents).

Although these platform technologies enabled the development of many of the products approved by FDA during the period evaluated in the study, they were excluded "because the PSRI scientists who developed the platforms generally did not use them to develop specific drug candidates."[88] However, without these platform technologies, many new drugs would not have been developed, resulting perhaps in a vastly different economic outlook for the pharmaceutical industry.

According to Stevens et al., the 36 biologic drugs listed in **Table 5** were "discovered at least in part by PSRIs during the past 40 years."[89]

Table 5. Biologic Drugs Discovered by Public-Sector Research Institutions

Over past 40 years

Nonproprietary Name	Brand Name	Originating Institution(s)	Marketer (in February 2011)
abatacept	Orencia	U. of Michigan & Department of the Navy	Bristol-Myers Squibb
abciximab	ReoPro	State University of New York	Eli Lilly
adalimumab	Humira	Rockefeller University & Scripps	Abbott

[85] FDA, Priority Review, at http://www.fda.gov/ForPatients/Approvals/Fast/ucm405405.htm. A Priority Review designation means FDA's goal is to take action on an application within 6 months (compared to 10 months under standard review).

[86] Ashley J. Stevens, Jonathan J. Jensen, Katrine Wyller, et al., "The Role of Public-Sector Research in the Discovery of Drugs and Vaccines," *The New England Journal of Medicine*, vol. 364, no. 6 (February 10, 2011), p. 541.

[87] A chimeric antibody may have portions of the antibody molecule that were developed in an animal combined with human portions to avoid an immune reaction when administered to a patient.

[88] Ibid., p. 537.

[89] Ibid., p. 538.

Nonproprietary Name	Brand Name	Originating Institution(s)	Marketer (in February 2011)
agalsidase beta	Fabrazyme	Mt. Sinai School of Medicine	Genzyme
aldesleukin	Proleukin	Sloan-Kettering	Novartis
alefacept	*Amevive*	*U. of Michigan & Dana-Farber Cancer Institute*	*Astellas Pharma Inc.*
alglucosidase alfa	Myozyme	Duke University	Genzyme
anakinra	Kineret	U. of Colorado	BioVitrium
antihemophilic factor (human)	Monoclate-P	Scripps CSL	Behring
bivalirudin	*AngioMax*	*Health Research, Inc. (Wadsworth Center)*	*The Medicines Company*
botulinum toxin type A	Botox (Hyperhydrosis)	Mt. Sinai School of Medicine	Allergan
cetrorelix	*Cetrotide*	*Tulane University*	*Merck Serono*
cetuximab	Erbitux	U. of California	Bristol-Myers Squibb
coagulation factor IX	BeneFIX	U. of Washington	Wyeth
daclizumab	Zenapax	National Institutes of Health	Roche
denileukin diftitox	ONTAK	Harvard, Boston Medical Center, & Boston Univ.	Eisai
drotrecogin alfa	*Xigris*	*Oklahoma Medical Research Foundation*	*Eli Lilly*
eculizumab	Soliris	Oklahoma Medical Research Foundation & Yale University	Alexion
enfuvirtide	*Fuzeon*	*Duke University*	*Roche*
etanercept	Enbrel	Massachusetts General Hospital	Amgen
filgrastim	Neupogen	Sloan Kettering	Amgen
ibritumomab (Intravenous route)	Zevalin	National Institutes of Health	BiogenIdec
infliximab	Remicade	New York University	J&J
interferon beta-1A	Avonex	Stanford University	BiogenIdec
laronidase	Aldurazyme	Los Angeles Biomedical Research Institute	Genzyme
natalizumab	Tysabri	Fred Hutchinson Cancer Center	BiogenIdec
orelvekin	*Neumega*	*Children's Hospital, Boston*	*Wyeth*
palivisumab	Synagis	National Institutes of Health	AstraZeneca
pegfilgrastim	Neulasta	Sloan Kettering	Amgen
pegvisomant	*Somavert*	*Ohio University*	*Pfizer*

Nonproprietary Name	Brand Name	Originating Institution(s)	Marketer (in February 2011)
protein C concentrate (Human)	Ceprotin	Oklahoma Medical Research Foundation	Baxter Healthcare
respiratory syncytial virus immune globulin	*Respigam*	*U. of Massachusetts*	*AstraZeneca*
sermorelin acetate	*Geref (Discontinued)*	*Salk Institute*	*Merck Serono*
somatropin	*Nutropin & Protropin (Discontinued)*	*U. of California*	*Genentech*
somatropin recombinant	*Humatrope*	*U. of California*	*Eli Lilly*
tositumomab	*Bexxar*	*U. of Michigan & Dana-Farber Cancer Institute*	*GlaxoSmithKline*

Source: Supplementary Appendix to Stevens, Jensen, Wyller, et al., "The Role of Public-Sector Research in the Discovery of Drugs and Vaccines," *The New England Journal of Medicine*, February 10, 2011.

Notes: Marketer may have changed since original publication date; current marketer may be identified via Drugs@FDA. Drugs in italics were not found in the CDER or CBER Purple Book but were found in Drugs@FDA, except Respigam which was not found in either Purple Book or in Drugs@FDA. Geref and Protropin have been discontinued.

Appendix A. Major Laws on Biologics Regulation

In general, biological products are regulated (*licensed* for marketing) under the Public Health Service Act—originally by the National Institutes of Health (NIH) and its precursors and later, starting in 1972, by the FDA—and chemical drugs are regulated (*approved* for marketing) under the Federal Food, Drug, and Cosmetic Act—by the FDA. This section provides a brief history of these two acts and other relevant laws as they relate to biologics, as well as some of the important amendments that have occurred during the past 100 years.

Relevant Laws

Biologics Control Act of 1902

The regulation of biologics by the federal government began with the Biologics Control Act of 1902, "the first enduring scheme of national regulation for any pharmaceutical product."[90] The act was groundbreaking, "the very first premarket approval statute in history."[91] It set new precedents, "shifting from retrospective post-market to prospective pre-market government review."[92] The Biologics Control Act was passed in response to deaths (many of children) from tetanus contamination of smallpox vaccine and diphtheria antitoxin. The act focused on the manufacturing process of such biological products; it required that facilities manufacturing such biological products be inspected before a federal license was issued to market them.

Pure Food and Drugs Act and the Federal Food, Drug, and Cosmetic Act

The Biologics Control Act predates the regulation of drugs under the Pure Food and Drugs Act, which was enacted in 1906. The 1906 act "did not include any form of premarket control over new drugs to ensure their safety ... [and] did not include any controls over manufacturing establishments, unlike the pre-existing Biologics Act and the later-enacted Federal Food, Drug, and Cosmetic Act (FFDCA)."[93] The Pure Food and Drugs Act was replaced by the FFDCA in 1938. The FFDCA required that drug manufacturers submit, prior to marketing, a new drug application (NDA) demonstrating, among other things, that the product was safe.[94]

The Public Health Service Act

The Biologics Control Act was revised and recodified (42 U.S.C. 262) when the Public Health Service Act (PHSA) was passed in 1944. The 1944 act specified that a biological product that has been licensed for marketing under the PHSA is also subject to regulation (though not approval) under the FFDCA. A biological product is defined under Section 351(i) of the PHSA, as

[90] David M. Dudzinski, "Reflections on Historical, Scientific, and Legal Issues Relevant to Designing Approval Pathways for Generic Versions of Recombinant Protein-Based Therapeutics and Monoclonal Antibodies," *Food and Drug Law Journal*, vol. 60, pp. 143-260.

[91] Ibid, p. 147.

[92] Ibid.

[93] Gary E. Gamerman, "Regulation of Biologics Manufacturing: Questioning the Premise," *Food and Drug Law Journal*, vol. 49, 1994, pp. 213-235.

[94] For further information, see CRS Report RL32797, *Drug Safety and Effectiveness: Issues and Action Options After FDA Approval*, by (name redacted)

> a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product ... applicable to the prevention, treatment or cure of a disease or condition of human beings.

Section 351(j) of the PHSA states that the FFDCA "applies to a biological product subject to regulation under this section, except that a product for which a license has been approved under subsection (a) shall not be required to have an approved application under section 505 of such Act." Most biological products regulated under the PHSA also meet the definition of a drug under Section 201(g) of the FFDCA:

> articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or animals; and articles (other than food) intended to affect the structure or any function of the body of man or other animals.

The PHSA was amended by the FDA Modernization Act of 1997 (FDAMA, P.L. 105-115) to require a single biological license application (BLA) for a biological product, rather than the two licenses—Establishment License Application (ELA) and Product License Application (PLA)—that had been required between 1944 and 1997. The PHSA provides authority to suspend a license immediately if there is a danger to public health.

The PHSA was amended by the Biologics Price Competition and Innovation Act (BPCIA) of 2009, enacted as Title VII of the Affordable Care Act (ACA, P.L. 111-148). The BPCIA created a licensure pathway for biological products demonstrated to be "highly similar" (biosimilar) to or "interchangeable" with an FDA-approved biological product, and it authorized the agency to collect associated fees. The BPCIA also created FDA-administered periods of regulatory exclusivity for certain brand-name biologics and biosimilar products, as well as procedures for brand-name and biosimilar manufacturers to resolve patent disputes.

Regulation of Biologics by Federal Agencies

Following enactment of the 1902 Biologics Act, regulatory responsibility for biologics was first delegated to the Hygienic Laboratory, a precursor of NIH.[95] In 1972, regulatory authority for biologics was transferred from the NIH Division of Biological Standards to the Bureau of Biologics at the FDA.[96]

In 1982, the FDA's Bureau of Drugs and Bureau of Biologics merged to form the National Center for Drugs and Biologics.[97] In 1988, the Center for Drugs and Biologics was split into the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER).[98] CBER continued to use NIH facilities and buildings until it moved in October 2014 to the FDA headquarters in White Oak, MD.[99]

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[95] The NIH Almanac—Historical Data: Chronology of Events, at http://www.nih.gov/about/almanac/historical/chronology_of_events.htm. In 1937, the biologics control program, previously the responsibility of the Division of Pathology and Bacteriology, NIH, was assigned to the newly established NIH Division of Biologics Control (redesignated Biologics Control Laboratory, 1944). In 1955, the biologics control function was placed in the newly formed NIH Division of Biologics Standards.

[96] About FDA, "Significant Dates in U.S. Food and Drug Law History" at http://www.fda.gov/AboutFDA/WhatWeDo/History/Milestones/ucm128305.htm.

[97] FDA, *Science and the Regulation of Biological Products*, "From the Laboratory of Hygiene to CBER" p. 7, at http://www.fda.gov/downloads/AboutFDA/WhatWeDo/History/ProductRegulation/100YearsofBiologicsRegulation/UCM070313.pdf.

[98] Ibid.

[99] See http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm385240.htm.

Because biotechnology products frequently cross the conventional boundaries between biologics, drugs, and devices, determining the jurisdictional status of these products has been difficult for both the FDA and industry. Some products have had characteristics that met multiple statutory and scientific definitions.[100] In 1991, the FDA published an Intercenter Agreement between CBER and CDER.[101] In general, the agreement stated that traditional biologics (vaccines, blood, blood products, antitoxins, allergenic products), as well as most biotechnology products, would be regulated by CBER. The small set of biologics regulated as drugs under the FFDCA (mentioned above) would continue to be regulated by CDER, regardless of the method of manufacture.

In 2002, however, the FDA announced its intention to reorganize review responsibilities, consolidating review of new pharmaceutical products under CDER, thereby allowing CBER to concentrate on vaccines, blood safety, gene therapy, and tissue transplantation.[102] On June 30, 2003, responsibility for most therapeutic biologics was transferred from CBER to CDER.[103] Under this structure, biological products transferred to CDER are regulated as licensed biologics under Section 351 of the PHSA. Examples of products transferred to CDER include monoclonal antibodies, immunomodulators (other than vaccines and allergenic products), growth factors, and cytokines.[104] Remaining at CBER are traditional biologics such as vaccines, allergenic products, antitoxins, antivenins, venoms, and blood and blood products, including recombinant versions of plasma derivatives (clotting factors produced via biotechnology).

[100] See, for example, "Assignment of Agency Component for Review of Premarket Applications," Final Rule, *Federal Register*, vol. 56, no. 225, November 21, 1991, pp. 58754-58758.

[101] The Intercenter Agreement is available at http://www.fda.gov/oc/ombudsman/drug-bio.htm.

[102] FDA Press Release, "FDA to Consolidate Review Responsibilities for New Pharmaceutical Products," September 6, 2002.

[103] *Federal Register*, vol. 68, no. 123, June 26, 2003, pp. 38067-38068.

[104] Transfer of Therapeutic Products to the Center for Drug Evaluation and Research, at http://www.fda.gov/cber/transfer/transfer.htm. Also of interest is Approved Products Transferring to CDER, at http://www.fda.gov/cber/transfer/transfprods.htm, and Therapeutic Biological Products, at http://www.fda.gov/cder/biologics/default.htm.

Appendix B. Comparison of Biologic Drug Prices

Table B-1. Comparison of Biologic Drug Prices

Drug	Package Size	Medicare	Norway	England	Ontario	Indication
Lucentis	0.5 mg syringe/vial	$1,936	$894	$1,159	$1,254	Macular degeneration
Eylea	2 mg/0.05 ml vial	$1,930	$919	$1,274	$1,129	Macular degeneration
Rituxan	500 mg vial	$3,678	$1,527	$1,364	$1,820	Rheumatoid arthritis
Avastin	100 mg vial	$685	$399	$379	$398	Cancer
Prolia	60 mg syringe	$893	$260	$286	$285	Osteoporosis
Herceptin	Per 100 mg	$858	$483	$424	$493	Breast cancer
Orencia	250 mg vial	$881	$437	$472	$390	Rheumatoid arthritis
Aranesp	500 mcg syringe	$1,995	$663	$1,146	$1,227	Anemia
Botox	100 unit vial	$563	$178	$216	$284	Overactive bladder, chronic migraine
Erbitux	100 mg	$527	$270	$278	$302	Colorectal cancer
Tysabri	300 mg vial	$4,842	$1,870	N/A	$2,573	Multiple sclerosis
Actemra	80 mg vial	$305	$168	$160	$144	Rheumatoid arthritis
Yervoy	50 mg vial	$6,738	$4,362	$5,856	$4,618	Skin cancer
Xolair	150 mg syringe/vial	$852	$463	$400	$487	Asthma
Nplate	250 mcg vial	$1,399	$836	$753	$754	Autoimmune disease
Cimzia	Two 200 mg syringes	$2,357	$803	$1,117	$1,058	Crohn's Disease
Soliris	300 mg/30 ml vial	$6,315	$5,730	$4,919	$5,368	Rare diseases
Benefix	1000 unit vial	$1,451	$936	$948	N/A	Hemophilia
Neupogen	Ten 300 mcg vials	$2,943	N/A	N/A	$1,532	White blood cell deficiency
Vectibix	100 mg vial	$987	$472	$592	$498	Colorectal cancer
Benlysta	120 mg vial	$479	$189	N/A	N/A	Lupus
Xiaflex	0.9 mg vial	$3,370	$1,094	$1,015	N/A	Peyronie's disease
Pulmozyme	30 2.5 mg ampules	$2,845	$886	$775	N/A	Cystic fibrosis
Adcetris	50 mg vial	$5,894	$3,887	$3,904	$3,854	Hodgkin lymphoma
Arzerra	1,000 mg vial	$4,819	N/A	$2,842	N/A	Chronic lymphocytic leukemia
Xyntha	250 unit vial kit	$293	$226	$196	N/A	Hemophilia

Source: Jeanne Whalen, "Why the U.S. Pays More than Other Countries for Drugs," *The Wall Street Journal*, December 1, 2015.

Notes: Medicare beneficiaries are responsible for paying 20% of prices listed here. Medicare itself covers 80%. Prices listed reflect a temporary 2% discount imposed by federal spending cuts known as budget sequestration. Foreign prices were converted to U.S. dollars at July 1, 2015, exchange rates. Rankings were determined by Medicare Part B payments to doctors' offices and medical practices in 2013, the latest year for which data were available. Norwegian prices include 25% Value Added Tax levied on pharmaceuticals. England's National Health Service says prices listed here are "indicative" and may vary in some circumstances. Source: WSJ analysis of data from CMS; the Norwegian Medicines Agency and the Norwegian Drug Procurement Cooperation; the National Health Service Business Services Authority; and Ontario's Ministry of Health and Long-Term Care.

Table B-2. Examples of Average Biologic Drug Prices for Top-Selling Drugs in 2015

Monthly price, U.S. dollars

Drug	U.S. nondiscounted	U.S. estimated discounted	Canada	France	Germany
Humira (adalimumab), 40 mg biweekly	$3,430.82	$2,504.50	$1,164.32	$981.79	$1,749.26
Lantus (insulin glargine), 50 insulin units daily	372.75	186.38	67.00	46.60	60.90
Herceptin (trastuzumab), 450 mg every 3 weeks	5,593.47	4,754.45		2,527.97	3,185.87

Source: Aaron S. Kesselheim and Jerry Avorn, "The High Cost of Prescription Drugs in the United States: Origins and Prospects for Reform," *JAMA*, vol. 316, no. 8 (August 23/30, 2016), p. 859.

Note: The "nondiscounted" price is the list price. The "estimated discounted" price accounts for undisclosed discounts ("rebates") that manufacturers offer to U.S. payers.

Appendix C. Top Selling Drugs

Table C-1. The Top Three Selling Drugs, Global Sales, 1996-2015

Biologics in bold; dollars in billions

Year	Number 1 selling drug	Number 2 selling drug	Number 3 selling drug
1996	Norvasc $1.8	Zoloft $1.3	**Epogen $1.1**
1997	Prozac $2.6	Norvasc $2.2	Zoloft $1.5
1998	Prilosec $4.8	Prozac $2.8	Norvasc $2.5
1999	Prilosec $5.9	Norvasc $3.0	Claritin $2.67
2000	Prilosec $6.26	Lipitor $5.0	Norvasc $3.36
2001	Lipitor $6.45	Prilosec $5.7	**Epogen $5.5**
2002	Lipitor $7.97	**Epogen $6.5**	Zocor $5.4
2003	Lipitor $9.9	**Epogen $6.4**	Zocor $5.0
2004	Lipitor $11.7	**Epogen $6.2**	Plavix $5.4
2005	Lipitor $13.1	Plavix $6.3	**Epogen $5.8**
2006	Lipitor $13.8	Advair Diskus $6.18	Plavix $6.1
2007	Lipitor $13.6	Plavix $8.1	Advair Diskus $7.1
2008	Lipitor $13.5	Plavix $9.5	Advair Diskus $7.7
2009	Lipitor $12.65	Plavix $9.8	Advair Diskus $7.88
2010	Lipitor $11.9	Plavix $9.4	Advair Diskus $8.0
2011	Lipitor $10.87	Plavix $9.9	**Remicade $8.9**
2012	**Humira $9.6**	**Remicade $9.1**	**Enbrel $8.5**
2013	**Humira $11.0**	**Remicade $9.8**	**Enbrel $8.78**
2014	**Humira $12.9**	Solvaldi $10.3	**Remicade $9.9**
2015*	Harvoni $10.5	**Humira $10.3**	**Enbrel $6.57**

Source: *Nature Biotechnology*, v. 34 (3), March 2016, pp. 276-283, Supplementary Table 4.

Note: *Data from the first three quarters of 2015.

Table C-2. Top 10 Selling Drugs, U.S. Sales, 2015

Biologics in bold; dollars in millions

Brand name	Nonproprietary name	Company	2015 sales
Harvoni	sofosbuvir	Valeant Pharmaceuticals International	10,090
Humira	**adalimumab**	**AbbVie**	**8,405**
Enbrel	**etanercept**	**Amgen**	**5,099**
Remicade	**infliximab**	**Johnson & Johnson**	**4,453**
Prevnar 13	pneumococcal vaccine	Pfizer	4,026
Neulasta	**pegfilgrastim**	**Amgen**	**3,891**
Revlimid	lenalidomide	Celgene	3,535
Avastin	**bevacizumab**	**Roche**	**3,178**
Tecfidera	dimethyl fumarate	Biogen	2,908
Eylea	**aflibercept**	**Regeneron Pharmaceuticals**	**2,676**

Source: EvaluatePharma, *World Preview2016, Outlook to 2022*, 9th Edition, September 2016, at http://www.evaluate.com/PharmaWorldPreview2016.

Notes: Sales represent company reported sales where available, otherwise based on an average of equity analyst estimates.

Appendix D. The Purple Book

Table D-1. CDER Purple Book: Licensed Biological Products

Listed by year of licensure, including biosimilars

Year	Brand name (nonproprietary name)
1965	Santyl (collagenase)
1978	Elspar (asparaginase)
1986	Intron A (interferon alfa-2b)
1987	Activase (alteplase, cathflo activase)
1989	Epogen/Procrit (epoetin alfa), Alferon N Injection (interferon alfa-n3), Botox (onabotulinumtoxinA)
1991	Neupogen (filgrastim), Leukine (sargramostim)
1992	Proleukin (aldesleukin)
1993	Betaseron (interferon beta-1b), Pulmozyme (dornase alfa)
1994	Oncaspar (pegaspargase), ReoPro (abciximab)
1996	Avonex (interferon beta-1a), ProstaScint (capromab pendetide), Retavase (reteplase)
1997	Neumega (oprelvekin), Rituxan (rituximab), Zenapax (daclizumab), Regranex (becaplermin)
1998	Simulect (basiliximab), Synagis (palivizumab), Remicade (infliximab), Herceptin (trastuzumab), Enbrel (etanercept)
1999	Ontak (denileukin diftitox), Actimmune (interferon gamma-1b)
2000	TNKase (tenecteplase), Myobloc (rimabotulinumtoxinB)
2001	Campath, Lemtrada (alemtuzumab), Aranesp (darbepoetin alfa), Kineret (anakinra)
2002	Zevalin (ibritumomab tiuxetan), Rebif (interferon beta-1a), Elitek (rasburicase), Pegasys (peginterferon alfa-2a), Humira (adalimumab)
2003	Fabrazyme (agalsidase beta), Aldurazyme (laronidase), Xolair (omalizumab)
2004	Erbitux (cetuximab), Avastin (bevacizumab), Tysabri (natalizumab), Kepivance (palifermin), Pegasys Copegus Combination Pack (peginterferon alfa-2a co-packaged with ribavirin)
2005	Naglazyme (galsulfase), Orencia (abatacept)
2006	Myozyme (alglucosidase alfa), Lucentis (ranibizumab), Elaprase (idursulfase), Vectibix (panitumumab)
2007	Soliris (eculizumab), Mircera (methoxy polyethylene glycol-epoetin beta)
2008	Arcalyst (rilonacept), Cimzia (certolizumab pegol), Nplate (romiplostim)
2009	Simponi (golimumab), Dysport (abobotulinumtoxinA), Ilaris (canakinumab), Extavia (interferon beta-1b), Stelara (ustekinumab), Arzerra (ofatumumab), Kalbitor (ecallantide)
2010	Actemra (tocilizumab), Xiaflex (collagenase clostridium histolyticum), Lumizyme (alglucosidase alfa), Prolia, Xgeva (denosumab), Xeomin (incobotulinumtoxinA), Krystexxa (pegloticase)
2011	Benlysta (belimumab), Yervoy (ipilimumab), Nulojix (belatacept), Adcetris (brentuximab vedotin), Eylea (aflibercept), Erwinaze (asparaginase erwinia chrysanthemi)
2012	Voraxaze (glucarpidase), Perjeta (pertuzumab), Zaltrap (ziv-aflibercept), Granix (tbo-filgrastim), Jetrea (ocriplasmin), raxibacumab (raxibacumab)
2013	Kadcyla (ado-trastuzumab emtansine), Simponi Aria (golimumab injection, for IV use), Actemra (tocilizumab), Gazyva (obinutuzumab)

Year	Brand name (nonproprietary name)
2014	Vimizim (elosulfase alfa), Myalept (metreleptin), Tanzeum (albiglutide), Cyramza (ramucirumab), Sylvant (siltuximab), Entyvio (vedolizumab), Plegridy (peginterferon beta-1a), Keytruda (pembrolizumab), Trulicity (dulaglutide), Blincyto (blinatumomab), Opdivo (nivolumab)
2015	Cosentyx (secukinumab), Natpara (parathyroid hormone), Zarxio (filgrastim-sndz), Unituxin (dinutuximab), Praluent (alirocumab), Repatha (evolocumab), Praxbind (idarucizumab), Strensiq (asfotase alfa), Nucala (mepolizumab), Darzalex (daratumumab), Portrazza (necitumumab), Empliciti (elotuzumab), Kanuma (sebelipase alfa)
2016	Anthim (obiltoxaximab), Taltz (ixekizumab), Cinqair (reslizumab), Inflectra (infliximab-dyyb), Tecentriq (atezolizumab), Zinbryta (daclizumab), Erelzi (etanercept-szzs), Amjevita (adalimumab-atto)

Source: FDA, CDER Purple Book, accessed on September 27, 2016 at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM439049.pdf.

Notes: Table includes BLAs only; does not include biological products that were regulated as drugs via an NDA under the FFDCA.

Table D-2. CBER Purple Book: Licensed Biological Products

Recombinant products, listed by year of licensure

Year	Brand name (nonproprietary name)
1997	Benefix (coagulation factor IX)
1999	NovoSeven (coagulation factor VIIa)
2000	Refacto (antihemophilic factor)
2003	Advate (antihemophilic factor, plasma/albumin free)
2008	Recothrom (thrombin topical), Xyntha (antihemophilic factor, plasma/albumin free)
2009	Atryn (antithrombin)
2010	Provenge (sipuleucel-T)
2011	LaViv (azficel-T)
2013	Rixubis (coagulation factor IX), NovoEight (antihemophilic factor), Tretten (coagulation factor XIII A subunit)
2014	Alprolix (coagulation factor IX, Fc fusion protein), Eloctate (antihemophilic factor, Fc fusion protein), Ruconest (C1 esterase inhibitor), Obizur (antihemophilic factor, porcine sequence)
2015	Ixinity (coagulation factor IX), Nuwiq (antihemophilic factor), Imlygic (talimogene laherparepvec), Adynovate (antihemophilic factor, PEGylated), Vonvendi (von Willebrand factor)
2016	Kovaltry (antihemophilic factor, full length), Idelvion (coagulation factor IX, albumin fusion protein), Solchayn (antihemophilic factor, single chain)

Source: FDA, CBER Purple Book, accessed on September 27, 2016, at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM412398.pdf; and, *Nature Biotechnology*, v. 34 (3), March 2016, pp. 276-283, Supplementary Table 3.

Notes: Table includes recombinant products only; does not include most biological products listed in the CBER Purple Book.

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