

Biologics and Biosimilars: Background and Key Issues

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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 highly similar but not structurally identical, to a brand-name biologic (i.e., the reference product). This is in contrast to a generic chemical drug, which is an exact copy of a brand-name chemical drug (i.e., the reference listed drug). Because biologics are more complex than chemical drugs, both in composition and method of manufacture, biosimilars will not be exact replicas of the brand-name product, but may instead be shown to be highly similar. However, for many years, the drug industry and the Food and Drug Administration (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 both brand-name biologics and biosimilars can be assessed and managed effectively.

The FDA regulates both biologics and chemical drugs. Before a biologic or biosimilar may be marketed in the United States, it must be licensed (i.e., approved) by FDA. To obtain licensure of a new biologic, the sponsor (generally the manufacturer of the product) submits to the agency a biologics license application (BLA) with data demonstrating that the biologic, and the facility in which it is manufactured, processed, packed, or held, meet standards to assure that the product is safe, pure, and potent. The Biologics Price Competition and Innovation Act (BPCIA)—enacted as Title VII of the Patient Protection and Affordable Care Act (ACA, P.L. 111-148)—established an abbreviated licensure pathway for biosimilar biological products or biosimilars. To obtain licensure of a biosimilar, the sponsor submits to FDA a BLA that provides information demonstrating, among other things, biosimilarity based on data from analytical studies (structural and functional tests), animal studies (toxicity tests), and/or a clinical study or studies (tests in human patients).

Since enactment of the BPCIA, as of May 29, 2019, 19 biosimilars—for nine reference products—have been licensed in the United States. However, many of these licensed biosimilars are not yet available to patients, primarily due to ongoing litigation, although various factors may impact uptake of biosimilars.

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.

The high costs of pharmaceuticals in general—and biologics in particular—has led to an increased interest in understanding the federal government's role in the development of costly new therapeutics. In the case of many biosimilars approved by FDA, the associated brand-name biologic was originally discovered by scientists at public-sector research institutions. These brand-name biologics—Remicade, Enbrel, Humira, Avastin—are among the top-selling drugs in the United States and worldwide.

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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 highly similar but not structurally identical to a brand-name biologic, also 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 large 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 the Food and Drug Administration (FDA) in April 2016.

Table 1. Relative Size of Chemical and Biologic Drugs

Drug (nonproprietary name)	Molecular formula
chemical drugs	
aspirin	C ₉ H ₈ O ₄
Tylenol (acetaminophen)	C ₈ H ₉ NO ₂
Sovaldi (sofosbuvir)	C ₂₂ H ₂₉ FN ₃ O ₉ P
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, <https://www.accessdata.fda.gov/scripts/cder/daf/>, 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.

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.¹ In the past, biologics were often dispensed by pharmacies with specialized facilities and personnel. The term *specialty drugs* is now often 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 in the United States, such as Soliris (eculizumab) and Vimizim (elosulfase alfa), exceeds \$250,000 per patient.² The use of biologics and spending on these products has been increasing; see for example **Appendix B**. Spending on biologics in the United States totaled \$120.1 billion in 2017, a 12.5% increase over 2016.³ The amount spent on “original” biologics subject to biosimilar competition in 2017 was \$10.6 billion (8.8% of \$120.1 billion), and the amount spent on biosimilars in 2017 was \$0.9 billion (0.7% of 120.1 billion).⁴ Biologics spending has increased by 10% each year since 2011.⁵

Biologic drugs are often more expensive in the United States than in Europe and Canada.⁶ In Europe, the introduction of biosimilars has reduced prices for biologics, which may be attributed to price regulation interventions and commercial decisions of manufacturers.⁷ For example, in October 2018, AbbVie agreed to an 80% price reduction in certain European countries on the monoclonal antibody Humira, the top selling drug in the world, after the introduction of several biosimilars there.⁸

Biologics and biosimilars are larger in size than chemical drugs and their manufacturing and purification processes can be more complicated and more expensive than those used to make chemical drugs. However, information about manufacturing costs for drugs and biologics is generally not publicly available, although a few studies have attempted to estimate the cost of production of certain biologics. For example, one study examined the cost of insulin production, concluding that “it may be possible to profitably manufacture biosimilar insulins at prices of US\$72 per year or less for human insulin and US\$133 per year or less for insulin analogues.”⁹ The study notes several limitations, including that expenses associated with registration, quality assurance and control, and other costs were not individually considered. Additionally, as explained later in this report, for historical reasons, insulin has been regulated by FDA as a drug rather than as a biologic; as such, there are currently no biosimilar insulins available in the United States. Another analysis looked specifically at the manufacturing processes for therapeutic

¹ For further information, see CRS Report R44132, *Specialty Drugs: Background and Policy Concerns*.

² 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.

³ QuintilesIMS Institute, *Medicine use and spending in the U.S.: A review of 2017 and Outlook to 2022*, April 2018, p. 11.

⁴ *Ibid.*

⁵ *Ibid.*

⁶ Jeanne Whalen, “Why the U.S. Pays More than Other Countries for Drugs,” *The Wall Street Journal*, December 1, 2015.

⁷ IMS Health, *The Impact of Biosimilar Competition*, June 2016, p. 4, http://ec.europa.eu/growth/tools-databases/newsroom/cf/itemdetail.cfm?item_id=8854.

⁸ Ed Silverman, “AbbVie offers a ‘huge’ discount on Humira to fend off European rivals,” *STAT+ Pharmspot*, November 1, 2018. Zachary Brennan, “AbbVie Sees 80% Discounts in Nordic Market With New Humira Biosimilars,” *RAPS Regulatory Focus*, November 2, 2018, at <https://www.raps.org/news-and-articles/news-articles/2018/11/abbvie-sees-80-discounts-in-nordic-market-with-ne>.

⁹ D. Gotham, M. Barber, & A. Hill, “Production costs and potential prices for biosimilars of human insulin and insulin analogues,” *BMJ Global Health*, 2018, doi:10.1136/bmjgh-2018-000850.

monoclonal antibodies, a class of biologics that includes many cancer drugs. According to the paper, which was authored by a bioprocess engineering expert at Genentech, monoclonal antibodies “are becoming a unique class of therapeutic products... with unlimited production capacity and low production costs, whose pricing will have no direct link to drug substance product. The pricing will instead reflect the innovator companies’ clinical investment in addition to costs incurred from failed pipeline products.”¹⁰

As discussed later in the report (see “Federal Research and Biologics Development”), many of the top-selling brand-name biologics—for example, Humira, Remicade, Enbrel, Avastin—were originally discovered by scientists performing basic research at public-sector institutions. However, the next phase of research—clinical testing—is often claimed to be the most expensive step in bringing a pharmaceutical product to market, although estimates for clinical trial costs vary depending on the therapeutic area and study’s assumptions.

FDA Regulation of Biologics

Biological products were originally 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.

FDA generally regulates biologics pursuant to its authorities under the Public Health Service Act (PHSA), but regulates some biologics as drugs under authorities in the Federal Food, Drug and Cosmetic Act (FFDCA). Responsibility for regulation of biologics within FDA is shared by both the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER). CBER regulates what are often referred to as traditional biologics, such as vaccines, blood and blood products, allergenic extracts, and certain devices and test kits.¹¹ CBER also regulates gene therapy products, cellular therapy products, human tissue used in transplantation, and the tissue used in xenotransplantation—the transplantation of nonhuman cells, tissues, or organs into a human.¹²

CDER regulates—in addition to prescription brand-name and generic drugs and over-the-counter drugs—most therapeutic biologics. Responsibility for therapeutic biologics was transferred from CBER to CDER in 2003.¹³ See **Appendix A** for further details. Examples of types of therapeutic biologics regulated by CDER are briefly described in the list below.¹⁴

- 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.

¹⁰ Brian Kelley, “Industrialization of mAb production technology: The bioprocessing industry at a crossroads,” *mAbs*, vol. 1, no. 5 (2009), pp. 443–452. <https://doi.org/10.4161/mabs.1.5.9448>.

¹¹ FDA, <http://www.fda.gov/BiologicsBloodVaccines/default.htm>.

¹² 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.

¹³ *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, <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/default.htm>.

¹⁴ Definitions from NCI Dictionary of Cancer Terms <http://www.cancer.gov/publications/dictionaries/cancer-terms>.

- 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 that stimulate or suppress the immune system and may help the body fight cancer, infection, or other diseases.

Most biological products are regulated—*licensed* for marketing by FDA via a biologics license application (BLA)—under authorities in the Public Health Service Act (PHSA).¹⁵ This is in contrast to chemical drugs, which are *approved* for marketing by FDA via a new drug application (NDA) or abbreviated new drug application (ANDA). To obtain licensure, the sponsor (generally the manufacturer) must demonstrate in the BLA that the biological product, and that the facility in which it is manufactured, processed, packed, or held, meet standards to assure that the product is safe, pure, and potent.¹⁶ 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 effectiveness 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.¹⁷

Historically, certain biological products were regulated as drugs, *approved* via an NDA under the FFDCA rather than as biologics by NIH under the PHSA. In 1941, Congress gave FDA authority over the marketing of insulin, a natural source biological product.¹⁸ The hormone insulin is a small protein (a short chain of 51 amino acids) and in the 1940s, it was obtained in the same way as many biologics—extraction from animals—hence the term “natural source.”¹⁹ Despite this

¹⁵ PHSA Section 351(a).

¹⁶ Ibid. While FDA approves drugs that are “safe and effective” the equivalent terminology for biologics is “safe, pure and potent.” In an April 2015 FDA guidance document, *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*, the agency states that “[t]he standard for licensure of a biological product as *potent* under section 351(a) of the PHS Act has long been interpreted to include effectiveness (see 21 CFR 600.3(s) and the guidance for industry on *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*). In this guidance, we use the terms *safety* and *effectiveness* and *safety*, *purity*, and *potency* interchangeably in the discussions pertaining to biosimilar products.”

¹⁷ 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,” <http://fdabiosimilars.e-paga.com/course/framework/>.

¹⁸ 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).

¹⁹ Ibid., p. 154.

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 have been 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).²⁰

In the late 1970s and early 1980s, the biotechnology industry began to develop its first biologics for use as human therapeutic agents (e.g., recombinant proteins and monoclonal antibodies). Some of these products were regulated as drugs under the FFDCA (e.g., insulin and human growth hormone created using recombinant DNA technology), while others were regulated as biologics under the PHSA (e.g., cytokines, proteins involved in the immune response, and blood factors). As such, currently, while most biologics are licensed under the PHSA, some are approved as drugs under the FFDCA. This will no longer be the case on March 23, 2020, when applications for biologics approved under the FFDCA will be deemed to be licenses under the PHSA (see “New Regulatory Pathway for Biosimilars”).²¹

In 2010, the Biologics Price Competition and Innovation Act (BPCIA)—enacted as Title VII of the Patient Protection and Affordable Care Act (ACA, P.L. 111-148), established an abbreviated pathway under the PHSA for licensure of biosimilar biologics (i.e., biosimilars, sometimes referred to as follow-on biologics). A biosimilar is a biological product that is demonstrated to be “highly similar” (i.e., biosimilar), but not identical, to an FDA-licensed biological product (i.e., the reference product). The next sections describe events leading up to the enactment of the BPCIA and provide an overview of the requirements governing the abbreviated licensure process for biosimilars.

Events Leading Up to Biosimilars Legislation

In contrast to biosimilars, generic drugs have been able to be marketed in the United States since 1984 when the Drug Price Competition and Patent Term Restoration Act of 1984 (P.L. 98-417)—often called the Hatch-Waxman Act—established an abbreviated approval pathway for generic chemical drugs. By offering a lower-priced 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.²² For chemical drugs, “generic medications decrease prices 60% to 90% on branded oral-solid medications,” according to some experts.²³ Generally, generic drug manufacturers achieve 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.

To obtain approval of a generic drug, the manufacturer submits to FDA an ANDA demonstrating that the generic drug is the same as the brand-name drug (i.e., the reference listed drug [RLD]). To prove sameness, the generic must have the same active ingredient(s), strength, dosage form, and route of administration as the RLD; be bioequivalent to the RLD; and meet other requirements (e.g., reviews of chemistry, manufacturing, controls, labeling, and testing).²⁴ This

²⁰ 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, <http://www.fda.gov/OHRMS/DOCKETS/DOCKETS/03p0176/03p-0176-cp00001-01-vol11.pdf>.

²¹ BPCIA §7002(e).

²² For additional information, see CRS Report R44643, *The Hatch-Waxman Act: A Primer*.

²³ 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.

²⁴ FFDCA §505(j).

“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 generally considered to be interchangeable with its reference (brand-name) drug and with other generic products that use the same reference drug.

The Hatch-Waxman Act established a second abbreviated pathway, the so-called 505(b)(2) pathway. This pathway has been used to approve some biological products under the FFDCA, specifically follow-on natural source biologics that had received approval under the FFDCA rather than licensure under the PHSA. In contrast to an ANDA, a 505(b)(2) NDA contains full reports of investigations of safety and effectiveness, but at least some of the information relied upon for approval comes from studies that were not conducted by or for the applicant and for which the applicant has not obtained a right of reference. A 505(b)(2) NDA may rely on published literature or on FDA’s finding of safety and effectiveness for the RLD.

The Hatch-Waxman Act provided a mechanism for the approval of generic drugs and certain follow-on biologics under the FFDCA, but not for follow-on biologics or biosimilars under the PHSA. As a result, after Hatch-Waxman, companies could submit so-called follow-on applications (i.e., 505(b)(2) NDAs) for FDA review only for the small number of biologics that had been approved under the FFDCA (e.g., insulin). Companies were effectively blocked from submitting follow-on applications for the much larger group of therapeutic biologics that had been licensed under the PHSA.

Insulin: Case Study of a Small Biologic

Insulin production has changed over the years as researchers have made alterations to the product that have eased its use by patients. The original insulin, also called regular insulin, is a short-acting product with a duration of action of about eight hours. In the late 1930s through the 1950s, regular insulin was altered by adding substances to gain longer action; these are called intermediate-acting insulins. In 1982, recombinant DNA technology allowed for the replacement of animal insulin by human insulin made by microorganisms in a laboratory fermentation process. Over the past few decades, slight modifications of the insulin molecule—called insulin analogs—have been developed. Long-acting insulin analogs, Lantus (insulin glargine) and Levemir (insulin detemir), entered the market in the early 2000s. Rapid-acting insulin analogs Humalog (insulin lispro) and Novolog (insulin aspart) were developed to allow for quicker absorption and shorter duration of action. As a result, there are now five types of insulin products: long-acting, rapid-acting, intermediate-acting, short-acting (regular insulin), and premixed. The price of certain insulin products has risen significantly. For example, from 2001 to 2015, the price of insulin lispro increased 585% (from \$35 to \$234 per vial). One vial may last a patient less than two weeks.

Currently, three firms—Eli Lilly, Novo Nordisk, Sanofi Aventis—account for over 90% of the global market and 100% of the U.S. insulin market. An FDA analysis found that a drug’s price is directly affected by the number of different companies marketing the drug. Because three firms make all the insulin used in this country, the market behaves differently from the usual case in pharmaceutical markets where generic competition results in price reductions. A 1995 analysis of Eli Lilly’s insulin production process found that the total cost involved in making enough insulin to treat one patient per year was \$33.60. A 2018 study calculated that a year’s supply of human insulin could be priced at \$48 to \$71 per person and analog insulins could be priced at between \$78 and \$133; this amount would cover production costs and still deliver a profit to the manufacturer. How much profit is fair is a large piece of the drug pricing puzzle. A 2017 Government Accountability Office (GAO) report found that the average profit margin for the largest 25 drug companies—companies with the highest pharmaceutical and biotechnology sales revenue in 2015—was 20% in 2015, compared with 6.7% for the largest 500 U.S. companies in general. The three insulin manufacturers are among the largest 25 drug companies. For further details, see CRS In Focus IFI 1026, *Insulin Products and the Cost of Diabetes Treatment*.

Even when patent protection for biological 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, now called the Association for Accessible Medicines), advocated that the FDA establish a regulatory system for the approval of

biosimilars under its existing statutory authority,²⁵ 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.²⁶

In April 2006, the European Medicines Agency (EMA) authorized for marketing in Europe the first biosimilar product, Omnitrope, a human growth hormone derived from recombinant DNA processes. This was followed by the authorization of five other biosimilar products in 2007, two more in 2008, and numerous others thereafter.²⁷

In the United States, FDA approval of Omnitrope via the 505(b)(2) pathway 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.²⁸ The court ruled that the FDA must move forward with consideration of the 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."²⁹

Omnitrope was not the first follow-on biologic approved through the abbreviated 505(b)(2) pathway.³⁰ However, scientific and regulatory uncertainty surrounding its approval may have signaled to Congress that legislation was needed to allow for approval/licensure of follow-on biologics under the PHSA. At the time of the Omnitrope approval in 2006, FDA indicated in a document on the agency's website that this action "does not establish a pathway" for approval of other follow-on biologics. "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."³¹

²⁵ Bill Nixon, President and CEO, Generic Pharmaceutical Association, letter to Daniel Troy, Chief Counsel, FDA, January 18, 2002, http://www.fda.gov/cder/ogd/GPHA_jan_21.htm.

²⁶ BIO Citizen Petition, Follow-on Therapeutic Proteins, April 23, 2003, <http://www.fda.gov/OHRMS/DOCKETS/DOCKETS/03p0176/03p-0176-cp00001-01-vol11.pdf>.

²⁷ European Medicines Agency (EMA), European public assessment reports, available at <https://www.ema.europa.eu/en/human-regulatory/overview/biosimilar-medicines-overview>.

²⁸ 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.

²⁹ "Europe approves two follow-on human growth hormones," *Nature Biotechnology*, vol. 24 (June 2006), p. 601.

³⁰ FDA had approved via the 505(b)(2) pathways several other follow-on biologics: Fortical (calcitonin-salmon) nasal spray, for treatment of postmenopausal osteoporosis, approved in August 2005; Hylanex (hyaluronidase-human), for increasing absorption of an injected drug, approved in December 2005; and GlucaGen (glucagon recombinant for injection), for recovery from insulin induced hypoglycemia, approved in June 1998. More recently, in December 2015, FDA approved Basaglar under a 505(b)(2) NDA, relying in part, on FDA's finding of safety and effectiveness for Lantus (insulin glargine injection) to support approval. In its press release, FDA makes clear that Basaglar is not approved as a generic. Basaglar also is not approved as a biosimilar, as there are no insulin glargine products that are currently licensed under the PHSA, so there is no "reference product" for a proposed biosimilar product. See "Follow-on Protein Products," Testimony of Dr. Janet Woodcock before the House Committee on Oversight and Government Reform, March 26, 2007, and "FDA approves Basaglar, the first 'follow-on' insulin glargine product to treat diabetes," December 16, 2015.

³¹ Anna Wilde Mathews and Jeanne Whalen, "FDA Clears Copycat Version Of Human Growth Hormone," *The Wall Street Journal*, June 1, 2006.

New Regulatory Pathway for Biosimilars

In March 2010, the BPCIA—enacted as Title VII of the ACA—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. The ACA also directed FDA to develop and present to Congress recommendations for a user fee program to support review of biosimilar product applications submitted under Section 351(k) of the PHSa.³² The Biosimilar User Fee Act of 2012 (BsUFA), enacted as Title IV of Food and Drug Administration Safety and Innovation Act (FDASIA, P.L. 112-144), authorized FDA to assess and collect fees for biosimilars (for additional information about the user fee legislation, see **Appendix A**).

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, among other things, 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.³³ A biological product may be demonstrated to be “biosimilar” to the reference product 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.³⁴

To be considered interchangeable with the reference product, the applicant must show that the biologic is biosimilar to the reference product *and* that it can be expected to produce the same clinical result as the reference product in any given patient. Additionally, for products administered more than once, the applicant must demonstrate that “the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.”³⁵ Interchangeable products may be substituted for the reference product by a pharmacist without the intervention of the prescribing health care provider.³⁶ To date, FDA has not approved any interchangeable products.

Because biologics are more complex than chemical drugs, both in composition and method of manufacture, biosimilars will not be exact replicas of the brand-name product, but may instead be shown to be highly similar. However, 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 both brand-name biologics and biosimilars can be assessed and managed effectively.

Under the BPCIA, biologics that were approved as drugs under the FFDCA will transition to biological licenses under the PHSa in March 2020—the so-called “deemed to be a license” provision.³⁷ This BPCIA provision affects the relatively small set of biological products that were

³² ACA §7002(f).

³³ PHSa §351(k)(2)(A).

³⁴ PHSa §351(i)(2).

³⁵ PHSa §351(k)(4).

³⁶ FDA, Implementation of the Biologics Price Competition and Innovation Act of 2009, <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm215089.htm>.

³⁷ BPCIA §7002(e).

approved under the FFDCA: 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). While the BPCIA requires that an NDA for a biologic is deemed to be a BLA on the date that is 10 years after enactment (i.e., March 23, 2020), the statute is silent on implementation. FDA released draft guidance regarding the agency's interpretation of this BPCIA provision in March 2016 and final guidance in December 2018.³⁸

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 under Section 351(a) (a full BLA) or 351(k) (a BLA for a biosimilar or interchangeable biological product).

To balance competition and innovation, the BPCIA established two periods of exclusivity applicable to a brand-name biologic (i.e., the reference product)—one with a duration of 4 years and the other with a duration of 12 years.³⁹ Periods of regulatory exclusivity attach upon approval or licensure of a drug or biologic, respectively, if certain statutory requirements are met, limiting the ability of competitors to reference the data generated by brand-name drug manufacturers. During the four-year exclusivity period, a BLA for a biosimilar or interchangeable product referencing the brand-name biologic may not be submitted to FDA. During the 12-year exclusivity period, approval of a BLA for a biosimilar or interchangeable product referencing the brand-name biologic may not be made effective. This means that FDA may not approve a BLA for a biosimilar or interchangeable product until 12 years after the date on which the reference product was first licensed, and a BLA for a biosimilar or interchangeable product cannot be submitted to FDA until four years after the date on which the reference product was licensed. Certain biologics are not eligible for the reference product exclusivity, for example, if an application is for a minor change to a previously licensed biologic.⁴⁰ A new biologic may be eligible for an additional 6-month period of exclusivity that would attach to the 12- and 4-year periods if the applicant conducts pediatric studies pursuant to a written request from FDA.⁴¹ Additionally, a biologic approved to treat a rare disease or condition may be granted seven years of orphan drug exclusivity for the protected indication, in which case FDA may not license another biologic for the protected orphan indication until after the expiration of the 7-year or 12-year exclusivity period, whichever is later.⁴² While the first biosimilar for a brand-name is not eligible for exclusivity, the first interchangeable product is. This means that FDA will not make an interchangeability determination for a subsequent biologic relying on the same reference product for any condition of use until such exclusivity expires.⁴³ The periods of exclusivity available for biological products under the PHSA are generally longer than those for chemical

³⁸ FDA, *Interpretation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act of 2009 Guidance for Industry*, December 2018, <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM490264.pdf>.

³⁹ PHSA §351(k)(7).

⁴⁰ PHSA §351(k)(7)(C).

⁴¹ PHSA §351(m).

⁴² FFDCA §527(a). See also FDA, "Guidance for Industry Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act," August 2014, <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm407844.pdf>.

⁴³ PHSA §351(k)(6).

drugs under the FFDCA (i.e., five-year new chemical entity exclusivity, three-year new clinical study exclusivity).

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. In guidance, FDA states, “[n]othing in the BPCI Act suggests that Congress intended for biological products approved under section 505 of the FD&C Act—some of which were approved decades ago—to obtain a 12-year period of reference product exclusivity upon being deemed to be licensed under section 351(a) of the PHS Act.”⁴⁴

Additionally, according to FDA guidance, any unexpired period of exclusivity associated with an approved NDA for a biologic subject to the transition would cease to have any effect.⁴⁵ This would include the five-year new chemical entity exclusivity awarded to a drug whose active ingredient FDA has not previously approved, as well as the three-year new clinical study exclusivity, which may be awarded with respect to an NDA or supplemental NDA for a previously approved active ingredient (e.g., for a change in route of administration or new indication). For example, Sanofi, the manufacturer of the insulin Admelog, would lose almost 9 months of Hatch-Waxman exclusivity in the transition (Admelog’s exclusivity expires on December 11, 2020).⁴⁶ Any unexpired periods of orphan drug exclusivity would continue to apply for the protected indication after March 23, 2020, as orphan drug exclusivity can block the approval of a drug approved under the FFDCA or a biologic licensed under the PHSA. Similarly, any unexpired pediatric exclusivity associated with an approved NDA for a biologic would continue to apply to a deemed BLA after March 23, 2020.⁴⁷

Approval and Marketing of Biosimilars

The biosimilars market is still developing and while less than 2% of Americans use biologics, these products represent 40% of total spending on prescription drugs.⁴⁸ As of May 29, 2019, FDA has approved a total of 19 biosimilars for 9 reference products as shown in **Table 2**.

⁴⁴ FDA, *Interpretation of the “Deemed to be a License” Provision of the Biologics Price Competition and Innovation Act of 2009 Guidance for Industry*, December 2018, pp. 9-10, <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM490264.pdf>.

⁴⁵ Ibid.

⁴⁶ Sue Sutter, “Sanofi’s Admelog, a Humalog Follow-On, Approved in US As ‘Black Hole’ for Insulin Looms,” *Pink Sheet*, December 18, 2017.

⁴⁷ FDA, *Interpretation of the “Deemed to be a License” Provision of the Biologics Price Competition and Innovation Act of 2009 Guidance for Industry*, December 2018, p. 7, <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM490264.pdf>.

⁴⁸ FDA Statement, “Remarks from FDA Commissioner Scott Gottlieb, M.D., as prepared for delivery at the Brookings Institution on the release of the FDA’s Biosimilars Action Plan,” July 18, 2018, <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm613881.htm>.

Table 2. Biosimilars Approved for Marketing in the United States by FDA

Reference Product	Nonproprietary Name	Biosimilar (Marketer, approval date)	Nonproprietary Name
Neupogen	filgrastim	Zarxio (Sandoz, March 2015) Nivestym (Pfizer, July 2018)	filgrastim-sndz filgrastim-aafi
Remicade	infliximab	Inflectra (Celltrion/Pfizer, April 2016) Renflexis (Samsung/Merck, April 2017) Ixifi (Pfizer, December 2017)	infliximab-dyyb infliximab-abda infliximab-qbtx
Enbrel	etanercept	Erelzi (Sandoz, August 2016) Eticovo (Samsung, April 2019)	etanercept-szzs etanercept-ykro
Humira	adalimumab	Amjevita (Amgen, September 2016) Cyltezo (Boehringer Ingelheim, August 2017) Hyrimoz (Sandoz, October 2018)	adalimumab-atto adalimumab-adbm adalimumab-adaz
Avastin	bevacizumab	Mvasi (Amgen, September 2017)	bevacizumab- awwb
Herceptin	trastuzumab	Ogivri (Mylan, December 2017) Herzuma (Celltrion, December 2018) Ontruzant (Samsung, January 2019) Trazimera (Pfizer, March 2019)	trastuzumab-dkst trastuzumab-pkrb trastuzumab-dttb trastuzumab-qyyp
Epogen/ Procrit	epoetin	Retacrit (Hospira/Pfizer, May 2018)	epoetin alfa-epbx
Neulasta	pegfilgrastim	Fulphila (Mylan, June 2018) Udenyca (Coherus Bioscience, November 2018)	pegfilgrastim-jmdb pegfilgrastim-cbqv
Rituxan	rituximab	Truxima (Celltrion, November 2018)	rituximab-abbs

Sources: FDA, Biosimilar Product Information, accessed May 29, 2019 <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm580432.htm>.

Although FDA has licensed 19 biosimilars for marketing in the United States, many of these products are not yet available to patients, primarily due to ongoing litigation and settlement agreements. However, even once a biosimilar is launched, additional factors have been identified as potentially limiting biosimilar competition. These factors, which are described in greater detail below, include biosimilar naming and labeling conventions; interchangeability requirements; and access to samples for biosimilars testing. FDA has attempted to address some of these factors in its Biosimilars Action Plan, which was issued in July 2018.⁴⁹ Other factors, such as exclusive contracts with insurers, rebates to payors, and reimbursement policies also have been identified as impeding biosimilar uptake, but are outside the scope of this report.

Patent Litigation and Settlements

The launch of several biosimilar products has been delayed due to ongoing patent litigation and settlements between brand biologic and biosimilar companies. For example, AbbVie has been the subject of Congressional inquiry for its use of a so-called “patent thicket” to protect its biologic

⁴⁹ FDA, “Biosimilar Action Plan: Balancing Innovation and Competition,” July 2018, <https://www.fda.gov/media/114574/download>.

Humira (adalimumab) from biosimilar competition.⁵⁰ According to one analysis, AbbVie filed 247 patent applications with respect to Humira and was issued 132 patents.⁵¹ Humira was initially licensed in the United States in 2002. Although FDA has approved three biosimilar versions of the product—Amgen’s Amjevita, Boehringer Ingelheim’s Cyltezo, and Sandoz’s Hyrimoz—none of these are currently available to U.S. patients. AbbVie has reportedly settled patent lawsuits with several companies to delay biosimilar versions of Humira from becoming available in the United States until 2023 (see **Table 3**).⁵²

Table 3. Settlement Agreements Between AbbVie and Competitors

Settlement agreements addressing launch of Humira and biosimilar competitors

Competitor	Biosimilar licensed by FDA?	U.S. licensure date per settlement
Amgen	Yes—Amjevita on September 23, 2016	January 31, 2023
Samsung Bioepis	No	June 30, 2023
Boehringer Ingelheim	Yes—Cyltezo on August 25, 2017	July 1, 2023
Mylan	No	July 31, 2023
Sandoz	Yes—Hyrimoz on October 30, 2018	September 30, 2023
Fresenius Kabi	No	September 30, 2023
Momenta	No	November 20, 2023
Pfizer	No	November 20, 2023

Source: AbbVie, News Center, accessed May 16, 2019, <https://news.abbvie.com/news/press-releases/>.

Notes: Table created by CRS based on AbbVie press releases and the FDA Purple Book.

Under Title XI of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA; P.L. 108-173), certain settlement agreements between brand and generic drug companies must be filed with the Federal Trade Commission (FTC) and Department of Justice (DOJ). The Patient Right to Know Drug Prices Act (P.L. 115-263) amended MMA Title XI, expanding these reporting requirements to include agreements between biosimilar product applicants and brand biologic companies, as well as agreements between two biosimilar product applicants. Section 4004 of the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act (P.L. 115-271; the SUPPORT for Patients and Communities

⁵⁰ “This term is used in two slightly different ways, both relating to products with a high number of patents. First, a patent thicket may describe the situation where multiple parties have overlapping patent rights on one product, such that a ‘potential manufacturer must negotiate licenses with each patent owner in order to bring a product to market without infringing.’ Patent thickets, in this sense, raise concerns about inefficient exploitation of a technology because the multiplicity of owners increases transaction costs and creates coordination challenges. Second, the term may be used in a looser sense to describe an incumbent manufacturer’s practice of amassing of a large volume of patents relating to a single product, with the intent to intimidate follow-on competitors from entering the market (or to make it too costly and risky to do so). AbbVie’s Humira patent portfolio has been alleged to be an example of this sort of patent thicket,” see CRS Report R45666, *Drug Pricing and Intellectual Property Law: A Legal Overview for the 116th Congress*.

⁵¹ Initiative for Medicines, Access, and Knowledge (I-MAK), “Overpatented, Overpriced: How Excessive Pharmaceutical Patenting is Extending Monopolies and Driving up Drug Prices,” p. 7, see <https://www.i-mak.org/wp-content/uploads/2018/08/I-MAK-Overpatented-Overpriced-Report.pdf>.

⁵² Ed Silverman, “Behind the patent thicket: tactics AbbVie allegedly used to thwart biosimilar versions of Humira, STAT, November 7, 2018, <https://www.statnews.com/pharmalot/2018/11/07/abbvie-biosimilars-humira-patents/>.

Act) amended MMA Title XI, further expanding reporting requirements between biologic manufacturers and biosimilar product applicants.

Some concern has been raised about a lack of transparency surrounding patents for biologics and “patent thickets that are purely designed to deter the entry of approved biosimilars.”⁵³ For drugs approved under the FFDCA, pursuant to the Hatch-Waxman Act, a drug manufacturer must list as part of its NDA any patents that claim the drug that is the subject of the NDA or the method of using that drug.⁵⁴ FDA then publishes this information in the *Approved Drug Products with Therapeutic Equivalence Evaluations*, more commonly known as the Orange Book.⁵⁵ The Orange Book satisfies the statutory requirement that FDA make publicly available, and revise every 30 days, a list of drugs that have been approved for safety and effectiveness and any patent information submitted with respect to such drugs.⁵⁶ When a generic company submits an ANDA referencing a listed drug (typically the brand-name drug), it must provide a certification with respect to each patent listed in the Orange Book for that drug.⁵⁷ The Orange Book also lists any unexpired periods of exclusivity covering an approved drug, in addition to other information applicants may find helpful.⁵⁸

The PHSA, as amended by the BPCIA, does not require manufacturers of biologics to list patent information as part of a BLA, and the patent resolution scheme is different for biologics and biosimilars than for chemical drugs under Hatch-Waxman. The BPCIA provides for “an elaborate process for disclosure and negotiation, sometimes referred to as the ‘patent dance.’ The ‘dance’ generally involves an applicant and reference product sponsor participating in a series of informational exchanges regarding potential disputes over patent validity and infringement.”⁵⁹ Also in contrast to Hatch-Waxman, approval of a biosimilar under the BPCIA is not contingent upon resolution of patent disputes. As such, FDA may approve a biosimilar despite unresolved patent issues.

While FDA is not required by law to publish information about approved biologics and biosimilars, the agency does so voluntarily with the publication of the Purple Book. Unlike the Orange Book, which is available in paper form and as a searchable, electronic database, the Purple Book consists of two lists—one for biological products (including biosimilar and interchangeable products) licensed by CDER and the other for those licensed by CBER.⁶⁰ For brand-name biologics, the list identifies the date the biologic was licensed (i.e., approved), and if

⁵³ FDA Statement, “Remarks from FDA Commissioner Scott Gottlieb, M.D., as prepared for delivery at the Brookings Institution on the release of the FDA’s Biosimilars Action Plan,” July 18, 2018, <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm613881.htm>.

⁵⁴ FFDCA §505(b)(1).

⁵⁵ FDA, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, <https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm>.

⁵⁶ FFDCA §505(j)(7)(A). See also the Orange Book Preface, available at <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm>.

⁵⁷ FFDCA §505(j)(2)(A)(vii). For additional information about the patent certification procedures, see CRS Report R44643, *The Hatch-Waxman Act: A Primer*.

⁵⁸ FDA, Orange Book Preface, available at <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm>.

⁵⁹ CRS Legal Sidebar WSLG1796, *UPDATE: Battle Over Biosimilars: The Supreme Court Considers Dueling Interpretations of the ACA’s Biologics Price Competition and Innovation Act Provisions*. For additional information about the biologics patent dance, see CRS Report R45666, *Drug Pricing and Intellectual Property Law: A Legal Overview for the 116th Congress*.

⁶⁰ FDA, “Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations,” <https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm411418.htm>.

FDA evaluated the product for reference product exclusivity, the date the exclusivity will expire. FDA has not made a determination of the date of first licensure for all biologics. According to the agency, a determination of the date of first licensure and product exclusivity expiration “will generally be made for reasons of regulatory necessity and/or at the request of the [BLA] license holder.”⁶¹ The CDER and CBER lists also cross-reference the names of brand-name biologics licensed with the names of licensed biosimilar products.

In FDA’s July 2018 “Biosimilars Action Plan,” the agency said it would enhance the Purple Book to include more information about approved biologics.⁶² FDA also requested comments from the public on what steps the agency could take, within its statutory authority, related to biologics, including “additional information or features [that] could be incorporated into the Purple Book to make it more useful to stakeholders, including patients, healthcare providers, pharmacists, and manufacturers[.]”⁶³ Commenters proposed that FDA should include more comprehensive information about biologics;⁶⁴ publish prompt reference product exclusivity decisions at the time of biologic approval;⁶⁵ update the Purple Book to clarify which products have been determined not to have exclusivity and those that are still subject to pending decisions;⁶⁶ and to make the Purple Book into a single searchable electronic database (e.g., more like the Orange Book).⁶⁷ Commenters noted that amending the Purple Book to list patent information would require a change in statute and, potentially, a change to the patent resolution scheme. In the 116th Congress, bipartisan legislation has been introduced that would codify the publication of the Purple Book as a single searchable list and would require additional information to be published, including information about patents that claim the biologic or other patentable inventions relating to the biologic, thus providing more patent transparency and potentially promoting biosimilar competition.⁶⁸

Naming

Even once patent litigation is resolved and a biosimilar is marketed, one factor that has been identified as potentially impacting uptake of launched biosimilars is FDA’s proposed naming

⁶¹ FDA, “Background Information: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations (Purple Book),” <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm411424.htm>.

⁶² FDA, “Biosimilars Action Plan: Balancing Innovation and Competition,” July 2018, <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM613761.pdf>.

⁶³ FDA, “Facilitating Competition and Innovation in the Biological Products Marketplace; Public Hearing; Request for Comments,” FDA-2018-N-2689 <https://www.regulations.gov/docketBrowser?rpp=25&so=DESC&sb=commentDueDate&po=25&dct=PS&D=FDA-2018-N-2689>.

⁶⁴ The Academy of Managed Care Pharmacy, Re: Facilitating Competition and Innovation in the Biological Products Marketplace; Public Hearing; Request for Comments, September 21, 2018.

⁶⁵ The Pharmaceutical Research and Manufacturers of America (PhRMA), Re: Docket No. FDA-2018-N-2689: Facilitating Competition and Innovation in the Biological Products Marketplace; Public Hearing; Request for Comments, September 21, 2018.

⁶⁶ Comments from The Association for Accessible Medicines (AAM) and the Biosimilars Council on behalf of our member companies, regarding Docket FDA-2018-N-2689, Facilitating Competition and Innovation in the Biological Products Marketplace, Public Hearing; Request for Comments, September 21, 2018.

⁶⁷ *Ibid.* The Academy of Managed Care Pharmacy, Re: Facilitating Competition and Innovation in the Biological Products Marketplace; Public Hearing; Request for Comments, September 21, 2018.

⁶⁸ For example, S. 659 in the 116th Congress.

scheme, specifically in regard to the nonproprietary name of the biosimilar compared to the reference product. The nonproprietary name, or proper name, is used in the product's labeling, 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. This is in contrast to the proprietary name of a drug or biologic, which is the trademarked name, or brand name. 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.

FDA released draft guidance on the nonproprietary naming of biological products in August 2015; this guidance was finalized on January 12, 2017.⁶⁹ In March 2019, FDA issued a revised draft guidance.⁷⁰ The agency intends to ultimately issue a revised, final version of the 2017 naming guidance incorporating comments on the 2019 draft guidance.⁷¹ According to the naming convention outlined in the January 2017 guidance, “the nonproprietary name designated for each *originator biological product* [i.e., the reference product], *related biological product*, and *biosimilar product* will be a proper name that is a combination of the core name and a distinguishing suffix that is devoid of meaning and composed of four lowercase letters.”⁷² The core name refers to the component shared among an originator biological product and any related biological, biosimilar, or interchangeable product as part of the proper name.⁷³ An example of a core name is filgrastim. The suffix is attached to the core name with a hyphen as a unique identifier, for example, filgrastim-xzwy. This naming convention was to be applied to previously licensed and prospective biologics and biosimilars.

In the March 2019 revised draft guidance, FDA stated that it no longer intends to modify the proper names of biologics that were previously licensed under the PHSA without an FDA-designated suffix in their proper names. The agency also does not intend to apply the naming convention to transition biologics (e.g., insulin).⁷⁴ Instead, FDA will apply the naming convention to biological products at the time they are licensed. This is in contrast to the approach outlined in the agency's 2017 naming guidance, which would have applied this naming convention to previously licensed biologics, as well. For interchangeable products, in the revised guidance, FDA determined that a unique suffix that distinguishes an interchangeable product from other products sharing the same core name would be appropriate.⁷⁵

In general, the biosimilars industry seems to support the shared use of a nonproprietary name, whereas those advocating for the innovator companies prefer a naming scheme that distinguishes

⁶⁹ FDA, Nonproprietary Naming of Biological Products: Guidance for Industry, January 2017, <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf>.

⁷⁰ FDA, Nonproprietary Naming of Biological Products: Update, Draft Guidance, March 2019, <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM632806.pdf>.

⁷¹ FDA, “Statement from FDA Commissioner Scott Gottlieb, M.D., on FDA's steps on naming of biological medicines to balance competition and safety for patients receiving these products,” March 7, 2019, <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm632870.htm>.

⁷² FDA, Nonproprietary Naming of Biological Products: Guidance for Industry, January 2017, p. 1, at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf>

⁷³ Nonproprietary names are selected by the USAN Council according to principles developed to ensure safety, consistency, and logic in the choice of names. For information on the USAN Council, see <http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council.page>.

⁷⁴ FDA, Nonproprietary Naming of Biological Products: Update, Draft Guidance, March 2019, p. 5, <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM632806.pdf>.

⁷⁵ FDA, Nonproprietary Naming of Biological Products: Update, Draft Guidance, March 2019, <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM632806.pdf>.

between the reference biologic product and the biosimilar.⁷⁶ In its October 2015 public comments to FDA, the Federal Trade Commission (FTC) expressed concern that the FDA’s naming proposal assigning unique differentiating suffixes “could result in physicians incorrectly believing that biosimilars’ drug substances differ in clinically meaningful ways from their reference biologics’ drug substances.”⁷⁷ This “misperception” could “deter physicians from prescribing biosimilars” thereby “impeding the development of biosimilar markets and competition.”⁷⁸ FTC reiterated these concerns in its May 2019 public comments on FDA’s March 2019 draft guidance, stating that “[t]his unusual naming convention—applied exclusively to a subset of new entrants—likely would create consumer confusion and discourage use of newly introduced biosimilar and interchangeable products.”⁷⁹

Biosimilars Labeling

Another factor that has been identified as potentially impacting uptake of launched biosimilars is FDA’s policy on biosimilar labeling, specifically the recommendation for inclusion of a biosimilarity statement. 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.⁸⁰ 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, overdose, 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 and final guidance in July 2018.⁸¹ FDA recommends that the highlights section of the labeling contain a “Biosimilarity Statement” describing the biosimilar product’s relationship to its reference product. For example, “NIVESTYM (filgrastim-aafi) is biosimilar* to NEUPOGEN (filgrastim),” followed by the statement:

⁷⁶ Erin Durkin, “WHO Unveils Final Biological Naming Plan That Differs From FDA’s,” *InsideHealthPolicy’s FDA Week*, January 29, 2016.

⁷⁷ 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, https://www.ftc.gov/system/files/documents/advocacy_documents/ftc-staff-comment-submitted-food-drug-administration-response-fdas-request-comments-its-guidance/151028fdabiosimilar.pdf.

⁷⁸ *Ibid.*

⁷⁹ Comment of the Staff of the Federal Trade Commission, In Response to a Request for Comments on FDA’s Guidance for Industry on the “Nonproprietary Naming of Biological Products; Draft Guidance for Industry; Update” [Docket No. FDA-2013-D-1543] 84 Fed Reg. 8534 (Mar. 8, 2019) Submitted on May 6, 2019, https://www.ftc.gov/system/files/documents/advocacy_documents/ftc-staff-comment-fda-department-health-human-services-its-updated-guidance-industry-nonproprietary/ftc_comment_to_fda_2019_biologics_naming_guidance_5-6-19.pdf.

⁸⁰ 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>.

⁸¹ FDA, *Labeling for Biosimilar Products: Guidance for Industry*, Guidance, July 2018, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM493439.pdf>.

* Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product. Biosimilarity of [BIOSIMILAR PRODUCT'S PROPRIETARY NAME] has been demonstrated for the condition(s) of use (e.g., indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information.

Some stakeholders have expressed opposition to the biosimilarity statement, noting that it “could create needless confusion for patients,” and that this statement “does not serve a practical function.”⁸²

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.”⁸³ However, such comparative data are available to prescribers and the public on the FDA website.⁸⁴ 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.⁸⁵ In contrast, the Biotechnology Innovation Organization (BIO), which represents makers of brand-name biologics, 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.”⁸⁶

Interchangeability and Substitution

Another factor that may affect uptake of biosimilars is that a biosimilar generally cannot be automatically substituted for the reference product (i.e., brand-name biologic) at the pharmacy-level unless it is determined to be interchangeable with the reference product. 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.”⁸⁷ In January 2017, FDA released draft guidance on interchangeability, and final guidance on May 10, 2019.⁸⁸ FDA has not yet approved an interchangeable product.

⁸² American Pharmacists Association (APhA), Re: Labeling for Biosimilar Products; Draft Guidance for Industry [Docket No. FDA2016-D-0643-0001], August 2, 2016.

⁸³ FDA, Drugs, *From our perspective: Biosimilar product labeling*, <http://www.fda.gov/Drugs/NewsEvents/ucm493240.htm>.

⁸⁴ Ibid.

⁸⁵ Bronwyn Mixter, “Brand, Generic Groups Differ on Biosimilar Labeling,” *Bloomberg BNA Health Care Daily Report*, June 7, 2016.

⁸⁶ Ibid.

⁸⁷ FDA, *Implementation of the Biologics Price Competition and Innovation Act of 2009*, <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm215089.htm>.

⁸⁸ FDA, *Considerations in Demonstrating Interchangeability With a Reference Product*, Guidance, May 2019,

As mentioned previously, a generic drug generally is considered to be interchangeable with its reference (brand-name) drug and with other generic products that use the same reference drug. All states have enacted laws that allow or require a pharmacist to substitute a generic for the 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.

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 October 22, 2018 “at least 49 states have considered legislation establishing state standards for substitution of a biosimilar prescription product to replace an original biologic product.”⁸⁹ NCSL indicates that a total of 45 states and Puerto Rico have enacted legislation; the provisions of state legislation vary.⁹⁰

Sample Sharing and Biosimilars Development

Another factor that may affect biosimilar competition is access to samples of the reference product for purposes of biosimilar testing and development. As aforementioned, before a company may market a biosimilar, it must demonstrate that its product is highly similar to a reference product. Such comparative testing generally necessitates access to samples of a reference product.⁹¹ FDA has reported receiving numerous inquiries from biosimilar product developers indicating that they would like to develop a biosimilar version of a marketed drug, but are unable to obtain the necessary samples of a reference product. Some brand-name companies have implicated FDA-mandated safety programs—risk evaluation and mitigation strategies or REMS—for why they are not willing to sell samples to the biosimilar product developer, including that generic product developers may not ensure the safe use of these drugs, and that the brand company could be held liable.⁹² A REMS-restricted distribution program controls or limits the chain of supply to ensure drug safety. For biologics not subject to a REMS, companies have implemented self-imposed restricted distribution systems. By withholding access to samples, a brand-name company is generally able to prevent or delay a biosimilar product developer from conducting the required testing and submitting an application to FDA for review.

In December 2018, FDA announced that it would start focusing on “these same potentially anticompetitive practices” as it already has with chemical drugs.⁹³ For example, for chemical drugs, in December 2014, FDA issued draft guidance outlining the steps that a generic developer

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf>.

⁸⁹ Richard Cauchi, “State Laws and Legislation Related to Biologic Medications and Substitution of Biosimilars,” NCSL, October 22, 2018, <http://www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx>.

⁹⁰ Ibid. Alabama, Arkansas, Maine, Mississippi, Oklahoma, and the District of Columbia have not enacted such legislation.

⁹¹ CRS Report R44810, *FDA Risk Evaluation and Mitigation Strategies (REMS): Description and Effect on Generic Drug Development*.

⁹² D. Tucker, G. Wells, & M. Sheer, “REMS: The Next Pharmaceutical Enforcement Priority?” *Antitrust*, Vol. 28, No. 2, Spring 2014. © 2014 by the American Bar Association, https://www.morganlewis.com/news/2014/03/~/_media/files/docs/2014/rem-the-next-pharmaceutical-enforcement-priority.ashx.

⁹³ FDA, “Statement from FDA Commissioner Scott Gottlieb, M.D., on new actions advancing the agency’s biosimilars policy framework,” December 11, 2018, see <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm628121.htm>.

should take to obtain a letter from FDA to the brand company, indicating that its proposed testing protocol is comparably as safe as the brand company's REMS, and that it would not be a violation of the REMS to provide the product samples for such testing.⁹⁴ FDA announced that it would set up a similar system for biosimilar product developers, although FDA cannot compel a company to sell samples to another sponsor. Additionally, for chemical drugs, FDA has published on its website a list of products for which it has received sample access inquiries related to limited distribution of the brand drug.⁹⁵ It is not clear whether FDA will publish a similar list for biosimilar product inquiries. Out of the 76 approved REMS, 15 cover BLAs.⁹⁶ However, the agency said it was evaluating how it could make it easier for biosimilar product developers to use reference products from outside the United States where they may be cheaper and more accessible.⁹⁷ Additionally, legislation has been introduced that would aim to keep brand companies from using REMS and non-REMS restricted distribution systems to prevent or delay biosimilars (and generic drugs) from entering the market.⁹⁸

Federal Research and Biologics Development

The high costs of pharmaceuticals in general—and biologics in particular—has led to an increased interest in understanding the federal government's role in the development of costly new therapeutics. In the case of many biosimilars approved by FDA, the associated brand-name biologic (i.e., the reference product) was originally discovered by scientists at public-sector research institutions. These brand-name biologics—for example, Remicade, Enbrel, Humira, Avastin—are among the top-selling drugs in the United States and worldwide.

In general, the federal government—through the work conducted or supported by NIH—tends to focus more on basic or preclinical research and the pharmaceutical industry concentrates more of its research funding on clinical trials rather than on discovery activity.⁹⁹ 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.

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

⁹⁴ FDA “How to Obtain a Letter from FDA Stating that Bioequivalence Study Protocols Contain Safety Protections Comparable to Applicable REMS for RLD Guidance for Industry,” Draft Guidance, December 2014, <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm425662.pdf>.

⁹⁵ FDA, “Reference Listed Drug (RLD) Access Inquiries,” <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm607738.htm>.

⁹⁶ FDA, “Approved Risk Evaluation and Mitigation Strategies (REMS),” accessed March 15, 2019, <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm>.

⁹⁷ FDA, “Statement from FDA Commissioner Scott Gottlieb, M.D., on new actions advancing the agency's biosimilars policy framework,” December 11, 2018, see <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm628121.htm>. See also, FDA, “Biosimilars Action Plan: Balancing Innovation and Competition,” July 2018, <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM613761.pdf>.

⁹⁸ See, for example, the Creating and Restoring Equal Access to Equivalent Samples (CREATES) Act of 2019 (S. 340, H.R. 965). For additional information about the CREATES Act, see CRS Legal Sidebar LSB10272, *The CREATES Act of 2019 and Lowering Drug Prices: Legal Background & Overview*.

⁹⁹ Hamilton Moses, David H.M. Matheson, 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.

FDA from 1990 through 1999, 6.7% originated from sources other than private industry.¹⁰⁰ A 1993 study found that 7.6% of new drugs approved from 1981 through 1990 originated from nonindustry sources.¹⁰¹ However, rather than focusing on all drug approvals—including many “me too”¹⁰² drugs—another approach 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.¹⁰³ 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.¹⁰⁴

A study by Stevens et al., published in 2011 claims to be more comprehensive than these earlier investigations.¹⁰⁵ The Stevens study identified 153 FDA-approved pharmaceutical products—102 NMEs, 36 biologics, and 15 vaccines—that were discovered at least in part by public-sector research institutions (PSRIs) from 1970 through 2009. About half of these drugs fell into two therapeutic categories: oncology and infectious disease. The study also examined more broadly new drug applications (NDAs), not including biologics, approved from 1990 through 2007. The study identified 1,541 approved NDAs, which includes, but is not limited to, drugs that are NMEs; new esters, salts, or derivatives; and new formulations, combinations, and indications of previously approved drugs. Of the 1,541 NDAs approved by FDA from 1990 through 2007, 143, or 9.3%, resulted from work conducted in publicly funded labs.

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.” 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:

¹⁰⁰ Joseph A. DiMasi, Ronald W. Hansen, and Henry G. Grabowski, “The Price of Innovation: New Estimates of Drug Development Costs,” *Journal of Health Economics*, vol. 22 (2003), pp. 151-185.

¹⁰¹ 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.

¹⁰² “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 <https://www.propublica.org/article/vying-for-market-share-companies-heavily-promote-me-too-drugs>.

¹⁰³ According to FDA, “[c]ertain drugs are classified as new molecular entities (“NMEs”) for purposes of FDA review. Many of these products contain active moieties that have not been approved by FDA previously, either as a single ingredient drug or as part of a combination product; these products frequently provide important new therapies for patients. Some drugs are characterized as NMEs for administrative purposes, but nonetheless contain active moieties 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, <https://www.fda.gov/drugs/development-approval-process-drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products>.

¹⁰⁴ 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.

¹⁰⁵ 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.

- recombinant DNA technology (Cohen-Boyer patents);
- bacterial production methods for recombinant DNA (Riggs-Itakura patents);
- production and chimerization¹⁰⁶ 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.”¹⁰⁷ 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.

¹⁰⁶ 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.

¹⁰⁷ 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. 537.

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.”¹⁰⁸ The act was groundbreaking, “the very first premarket approval statute in history.”¹⁰⁹ It set new precedents, “shifting from retrospective post-market to prospective pre-market government review.”¹¹⁰ 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).”¹¹¹ 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.

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

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.

¹⁰⁸ 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, pp. 143-260.

¹⁰⁹ *Ibid.*, p. 147.

¹¹⁰ *Ibid.*

¹¹¹ Gary E. Gamerman, “Regulation of Biologics Manufacturing: Questioning the Premise,” *Food and Drug Law Journal*, vol. 49, 1994, pp. 213-235.

Section 351(j) of the PHS Act states that the FDCA “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 PHS Act also meet the definition of a drug under Section 201(g) of the FDCA:

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 PHS Act 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 PHS Act provides authority to suspend a license immediately if there is a danger to public health.

The PHS Act 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.

History of 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.¹¹² In 1972, regulatory authority for biologics was transferred from the NIH Division of Biological Standards to the Bureau of Biologics at the FDA.¹¹³

In 1982, the FDA’s Bureau of Drugs and Bureau of Biologics merged to form the National Center for Drugs and Biologics.¹¹⁴ 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).¹¹⁵ CBER continued to use NIH facilities and buildings until it moved in October 2014 to the new FDA headquarters in White Oak, MD.¹¹⁶

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

¹¹² 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.

¹¹³ About FDA, “Significant Dates in U.S. Food and Drug Law History” <http://www.fda.gov/AboutFDA/WhatWeDo/History/Milestones/ucm128305.htm>.

¹¹⁴ FDA, *Science and the Regulation of Biological Products*, “From the Laboratory of Hygiene to CBER” p. 7, <http://www.fda.gov/downloads/AboutFDA/WhatWeDo/History/ProductRegulation/100YearsofBiologicsRegulation/UCM070313.pdf>.

¹¹⁵ *Ibid.*

¹¹⁶ See <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm385240.htm>.

and scientific definitions.¹¹⁷ In 1991, FDA published an Intercenter Agreement between CBER and CDER.¹¹⁸ 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 letting CBER to concentrate on vaccines, blood safety, gene therapy, and tissue transplantation.¹¹⁹ On June 30, 2003, responsibility for most therapeutic biologics was transferred from CBER to CDER.¹²⁰ 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.¹²¹ Remaining at CBER are traditional biologics such as vaccines, allergenic products, antitoxins, antivenoms, venoms, and blood and blood products, including recombinant versions of plasma derivatives (clotting factors produced via biotechnology).

User Fee Legislation

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).¹²² 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.¹²³ User fees made up almost 50% of the FY2019 FDA budget.

The BPCIA, enacted as Title VII of the ACA, directed FDA to develop and present to Congress recommendations for a user fee program to support review of biosimilar product applications submitted under Section 351(k) of the PHSA.¹²⁴ The Biosimilar User Fee Act of 2012 (BsUFA or BsUFA I), enacted as Title IV of Food and Drug Administration Safety and Innovation Act (FDASIA, P.L. 112-144), authorized FDA to assess and collect fees for agency activities

¹¹⁷ 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.

¹¹⁸ The Intercenter Agreement, <http://www.fda.gov/oc/ombudsman/drug-bio.htm>.

¹¹⁹ FDA Press Release, “FDA to Consolidate Review Responsibilities for New Pharmaceutical Products,” September 6, 2002.

¹²⁰ *Federal Register*, vol. 68, no. 123, June 26, 2003, pp. 38067-38068.

¹²¹ Transfer of Therapeutic Products to the Center for Drug Evaluation and Research, <http://www.fda.gov/cber/transfer/transfer.htm>. Also of interest is Approved Products Transferring to CDER, <http://www.fda.gov/cber/transfer/transfprods.htm>, and Therapeutic Biological Products, <http://www.fda.gov/cder/biologics/default.htm>.

¹²² See CRS Report R44864, *Prescription Drug User Fee Act (PDUFA): 2017 Reauthorization as PDUFA VI*.

¹²³ See CRS Report R44517, *The FDA Medical Device User Fee Program: MDUFA IV Reauthorization*, and CRS Report RL34459, *Animal Drug User Fee Programs*.

¹²⁴ ACA §7002(f).

associated with the review of biosimilars from October 2012 through September 2017.¹²⁵ Under BsUFA I, FDA collected six different types of fees from industry;¹²⁶ fee amounts were based on inflation-adjusted PDUFA human drug application fee amounts for each fiscal year. Because no marketed biosimilar biological products existed when the BsUFA I program started, it included fees for products in the development phase—what FDA calls the Biosimilar Product Development (BPD) program—to generate fee revenue for the new program and to enable companies to meet with FDA in the early development of biosimilar biological products.¹²⁷ The BPD program provides assistance to industry sponsors in the early stages of developing a new biosimilar product. As of May 1, 2018, “67 programs were enrolled in the BPD Program to discuss development of proposed biosimilar products or proposed interchangeable products. CDER has received meeting requests to discuss the development of biosimilar or interchangeable products for 31 different reference products.”¹²⁸

The biosimilar user fee program was reauthorized through FY2022 via the Food and Drug Administration Reauthorization Act of 2017 (FDARA, P.L. 115-52), which was signed into law by President Donald J. Trump on August 18, 2017.¹²⁹ Under BsUFA II, the supplement fee and the establishment fee have been dropped and the initial, annual, and reactivation BPD fees have been retained. The product fee is renamed the BsUFA Program fee, “with a new provision that sponsors shall not be assessed more than five BsUFA Program fees for a fiscal year per application.”¹³⁰ The application fee will no longer be reduced by the cumulative amount of BPD fees paid by the sponsor for that product.

¹²⁵ Title IV of the Food and Drug Administration Safety and Innovation Act (FDASIA, P.L. 112-144).

¹²⁶ The following fee types were required under BsUFA I: an initial Biosimilar Product Development (BPD) fee; an annual BPD fee; reactivation BPD; an application fee (with a fee differential depending on whether the application contains clinical data or is a supplemental application); an establishment fee; and a product fee.

¹²⁷ 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.

¹²⁸ Joe Franklin, “Biosimilar and Interchangeable Products: Brief Update from FDA,” FDLI Annual Conference, May 3, 2018, slide 3, at <https://www.fdpi.org/wp-content/uploads/2018/05/Biosimilars-New-Developments-and-Updates-3.pdf>.

¹²⁹ For further information, see CRS Report R44961, *FDA Reauthorization Act of 2017 (FDARA, P.L. 115-52)*.

¹³⁰ FDA, Biosimilar User Fee Act (BsUFA II) Reauthorization Public Meeting, October 20, 2016, slide 31, <https://www.fda.gov/downloads/ForIndustry/UserFees/BiosimilarUserFeeActBsUFA/UCM526071.pdf>.

Appendix B. Top-Selling Drugs

Table B-1. Top 15 Best-Selling Drugs of 2018

Biologics in bold; dollars in billions

Brand Name	Nonproprietary Name	Sponsor Companies	2018 Sales
Humira	adalimumab	AbbVie	\$19.936
Eliquis	apixaban	Bristol-Myers Squibb and Pfizer	\$9.872
Revlimid	lenalidomide	Celgene	\$9.685
Opdivo	nivolumab	Bristol-Myers Squibb and Ono Pharmaceutical	\$7.570
Keytruda	pembrolizumab	Merck	\$7.171
Enbrel	etanercept	Amgen and Pfizer	\$7.126
Herceptin	trastuzumab	Roche (Genentech)	\$6.981
Avastin	bevacizumab	Roche (Genentech)	\$6.847
Rituxan	rituximab	Roche (Genentech) and Biogen	\$6.750
Xarelto	rivaroxaban	Bayer and Johnson & Johnson	\$6.589
Eylea	aflibercept	Bayer and Regeneron Pharmaceuticals	\$6.551
Remicade	infliximab	Johnson & Johnson and Merck & Co.	\$5.908
Pprevnar 13	pneumococcal vaccine	Pfizer	\$5.802
Stelara	ustekinumab	Janssen Biotech (Johnson & Johnson)	\$5.156
Lyrica	pregabalin	Pfizer	\$4.970

Source: Genetic Engineering & Biotechnology News, March 11, 2019.

Notes: Genetic Engineering & Biotechnology News indicate in the Notes for this article that the above amounts include U.S. sales and, where applicable, sales elsewhere in the world. According to the text of the article, the “drugs are ranked based on sales or revenue reported for 2018 by biopharma companies in press announcements, annual reports, investor materials, and/or conference calls.”

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