



FDA Regulation of Follow-On Biologics

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Summary

On March 23, 2010, President Obama signed into law a comprehensive health care reform bill, the Patient Protection and Affordable Care Act (PPACA; P.L. 111-148). PPACA establishes a new regulatory authority within the Food and Drug Administration (FDA) by creating a licensure pathway for follow-on biologics, also called biosimilars, and authorizing the agency to collect associated fees.

A biologic is a preparation, such as a drug or a vaccine, that is made from living organisms. A follow-on biologic, or biosimilar, is similar to the brand-name (innovator) product made by the pharmaceutical or biotechnology industry. In contrast to a biologic, most commonly used drugs are synthesized via a chemical process. Biologics often require special handling (such as refrigeration) and are usually administered to patients via injection or infused directly into the bloodstream.

The new regulatory pathway is analogous to the FDA's authority for approving generic chemical drugs under the Drug Price Competition and Patent Term Restoration Act of 1984 (P.L. 98-417). Often referred to as the Hatch-Waxman Act, this law allows the generic company to establish that its drug product is chemically the same as the already approved innovator drug, and thereby relies on the FDA's previous finding of safety and effectiveness for the approved drug. The generic drug industry achieves cost savings by avoiding the expense of clinical trials, as well as the initial drug research and development costs that were incurred by the brand-name manufacturer.

The cost of specialty drug products, such as biologics, is often prohibitively high. For example, the costs per year (in 2009) of some commonly used biologic drugs: Enbrel for rheumatoid arthritis, \$26,000; Herceptin for breast cancer, \$37,000; Rebif for multiple sclerosis, \$40,000; Humira for Crohn's disease, \$51,000; and Cerezyme for Gaucher's disease, \$200,000. A pathway enabling the FDA approval of follow-on biologics will allow for market competition and reduction in prices, though perhaps not to the same extent as that which occurred with generic chemical drugs under Hatch-Waxman (P.L. 98-417).

In contrast to chemical drugs, which are small molecules and for which the equivalence of chemical composition between the generic drug and innovator drug is relatively easy to determine, a biologic, such as a protein, is much larger in size and much more complex in structure. Therefore, comparing a follow-on protein with the brand-name product is more scientifically challenging than comparing chemical drugs. In many cases, current technology will not allow complete characterization of biological products. Additional clinical trials may be necessary before the FDA would approve a follow-on biologic.

This report provides a brief introduction to the relevant law, the regulatory framework at the FDA, the scientific challenges for the FDA in considering the approval of follow-on biologics, and a brief description of the biologics provisions in PPACA. Economic studies on potential savings to the federal government over 10 years due to the use of follow-on biologics have ranged between nothing and \$14 billion.

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Background

At the time that Hatch-Waxman was being debated by Congress and subsequently implemented by the FDA, the biotechnology industry was just beginning to develop its first biologics for use as human therapeutic agents. The first FDA approval of a biotechnology drug for human use, human insulin, occurred in 1982, followed by human growth hormone in 1985, alpha interferon in 1986, tissue plasminogen activator in 1987, and erythropoietin in 1989. Most biologics require special handling (such as refrigeration) and are usually administered to patients via injection or infused directly into the bloodstream.

Biologic vs. Follow-on Biologic

A *biologic* is a preparation, such as a drug or a vaccine, that is made from living organisms. In contrast, a chemical drug is synthesized via a chemical process. A *follow-on biologic* is similar but not identical to the brand-name, or innovator, product made by the pharmaceutical or biotechnology industry; *biosimilar* is the term used in the European Union.

Biotechnology products are expected to become a larger share of the drugs sold by the pharmaceutical industry to U.S. consumers. However, with no equivalent to the generic alternatives for chemical drugs, the cost of therapeutic biologics is often prohibitively high for individual patients. For example, the costs per year (in 2009) of some commonly used biologic drugs: Enbrel for rheumatoid arthritis, \$26,000; Herceptin for breast cancer, \$37,000; Rebif for multiple sclerosis, \$40,000; Humira for Crohn's disease, \$51,000; and Cerezyme for Gaucher's disease, \$200,000.⁴ Spending by Medicare in 2006 on Epogen, a treatment for anemia, was \$2.8 billion, more than the entire FY2006 budget for FDA, which was \$1.863 billion.⁵ Medicare

¹ Also referred to as biosimilars, or sometimes as biogenerics or generic biologics. The FDA and many others consider the use of the word *generic* to be inaccurate because the term has been used, in the context of chemical drugs, to mean identical. The FDA often uses the term *follow-on protein product*, because many biologics are proteins; biosimilar is used in the European Union.

² CRS Report R41114, *The Hatch-Waxman Act: A Quarter Century Later*, by Wendy H. Schacht and John R. Thomas.

³ For patent issues, see CRS Report RL33901, *Follow-On Biologics: Intellectual Property and Innovation Issues*, by Wendy H. Schacht and John R. Thomas.

⁴ Alfred B. Engelberg, Aaron S. Kesselheim, and Jerry Avorn, "Balancing Innovation, Access, and Profits--Market Exclusivity for Biologics," *New England Journal of Medicine*, vol. 361, no. 20 (November 12, 2009), pp. 1917-1919.

⁵ Personal communication with Lisa Yen, Centers for Medicare and Medicaid Services Office of Legislation, February 13, 2009. FDA's budget is composed of \$1.494 billion in direct appropriations and \$369 million in user fees; see CRS Report RL34334, *The Food and Drug Administration: Budget and Statutory History, FY1980-FY2007*, coordinated by Judith A. Johnson.

spending on biologics totaled about \$13 billion in 2007.⁶ Spending on all pharmaceuticals currently represents about 11% of health care spending in the United States.

Increasingly insurers are adopting strategies to manage the use of expensive biologics, such as a tiered formulary (resulting in higher patient cost-sharing) and prior authorization (requiring physicians to obtain approval from an insurer for coverage before a prescription is filled or administered).⁷ In situations in which such expensive drugs have no effect on overall survival, insurers may turn to “innovative payment models, such as providing payment only in cases in which a drug actually leads to clinical improvement.”⁸

Market Competition

For chemical drugs, some experts argue that “generic medications decrease prices 60% to 90% on branded oral-solid medications.”⁹ The Congressional Budget Office estimated the savings generated by generic drug use in 1994 was between \$8 billion and \$10 billion.¹⁰ The generic drug industry achieves these cost savings by avoiding the expense of clinical trials, as well as the initial drug research and development costs that were incurred by the brand-name manufacturer. In the case of chemical pharmaceuticals, before a generic drug can be marketed, the generic drug company must demonstrate to the FDA that the drug product is identical to the original product. This “sameness” allows the generic company to rely on or “reference” the FDA’s previous finding of safety and effectiveness for the approved drug.

Even though patents for several specialty biotechnology drug products have expired, very few have had to face the same type of market competition that occurs with chemical drugs. In contrast to the relatively simple structure and manufacture of chemical drugs, follow-on biological products, with their more complex nature and method of manufacture, will not be identical to the brand-name product, but may instead be shown to be similar. The Generic Pharmaceutical Association (GPhA) advocated that the FDA establish a regulatory system for the approval of follow-on biologics under its existing statutory authority.¹¹ However, the Biotechnology Industry Organization (BIO) filed a citizen petition with the FDA requesting a number of actions that would inhibit the approval of follow-on biologics.¹²

On April 12, 2006, the European Commission approved the first biosimilar product Omnitrope, a human growth hormone, in Europe following a positive scientific opinion issued by the European Medicines Agency (EMA); a second biosimilar human growth hormone, Valtropin, was approved

⁶ Medicare Payment Advisory Commission, *Report to the Congress: Improving Incentives in the Medicare Program*, Chapter 5: Medicare payment systems and follow-on biologics, Washington, DC, June 2009, pp. 103-133, http://www.medpac.gov/documents/Jun09_EntireReport.pdf.

⁷ Thomas H. Lee and Ezekiel J. Emanuel, “Tier 4 Drugs and the Fraying of the Social Compact,” *The New England Journal of Medicine*, vol. 359, no. 4 (July 24, 2008), pp. 333-335.

⁸ *Ibid.*

⁹ Jonah Houts, testimony before the House Committee on Oversight and Government Reform, March 26, 2007.

¹⁰ Congressional Budget Office, “How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry,” July 1998.

¹¹ Bill Nixon, President and CEO, Generic Pharmaceutical Association, letter to Daniel Troy, Chief Counsel, FDA, January 18, 2002, at http://www.fda.gov/cder/ogd/GPHA_jan_21.htm.

¹² BIO Citizen Petition, Follow-on Therapeutic Proteins, April 23, 2003, at <http://www.fda.gov/OHRMS/DOCKETS/DOCKETS/03p0176/03p-0176-cp00001-01-vol11.pdf>.

on April 24, 2006.¹³ Sales of Omnitrope in the United States only occurred following the April 10, 2006, ruling by the U.S. District Court in the District of Columbia in favor of Omnitrope's sponsor, Sandoz. The court ruled that the FDA must move forward with consideration of the abbreviated application, submitted by Sandoz in 2003, that presents 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."¹⁴

Federal Trade Commission Report

In June 2009 the Federal Trade Commission (FTC) released a report that examines the potential impact of follow-on biologics on the price of biologic drugs and compares this with the impact of generic drugs on the chemical drug market.¹⁵ The report found that for a number of reasons the competition between follow-on and brand-name biologics is unlikely to be similar to generic and brand-name chemical drug competition.¹⁶ Based on these findings, the FTC report concluded that the 12- to 14-year market exclusivity period is too long to promote innovation, particularly since the brand-name firm will retain substantial market share after the follow-on biologic enters the market. The report also stated that follow-on biologic manufacturers are unlikely to require a 180-day marketing exclusivity period as an incentive to develop interchangeable products. Lastly, the report concluded that special procedures to resolve patent issues are unnecessary and could undermine patent incentives and harm consumers.

The Obama Administration believed that its proposal of a seven-year market exclusivity period was "a generous compromise between what the FTC research has concluded and what the pharmaceutical industry has advocated."¹⁷ In contrast, a group representing the biotechnology industry believed that 12 to 14 years of market exclusivity was necessary to promote innovation and that patent resolution procedures would benefit patients, physicians, insurers, and manufacturers.¹⁸ Others provided commentary and recommendations on the length of the data

¹³ "Europe approves two follow-on human growth hormones," *Nature Biotechnology*, vol. 24 (June 2006), p. 601.

¹⁴ *Ibid.*

¹⁵ Federal Trade Commission, *Emerging Health Issues: Follow-on Biologic Drug Competition*, Washington, DC, June 10, 2009, <http://www.ftc.gov/os/2009/06/P083901biologicsreport.pdf>.

¹⁶ The FTC report lists the following six reasons: (1) The substantial costs to obtain FDA approval, plus the substantial costs to develop manufacturing capacity, will limit the number of FOB competitors; (2) The lack of automatic substitution between an FOB drug and a pioneer biologic drug will slow the rate at which FOBs can acquire market share; (3) An FOB drug also may have difficulty gaining market share due to concerns about safety and efficacy differences with the pioneer biologic drug; (4) Biologic drugs currently are not reimbursed according to strategies that insurers often use to encourage the use of lower-priced drugs; (5) As a result of these factors, FOB entry, although important, will be less-dramatic than generic drug competition. FOB entry is likely in biologic drug markets larger than \$250 million in annual sales. Only two or three FOB manufacturers are likely to attempt entry for a given pioneer drug product. These entrants are unlikely to introduce their drugs at discounts any larger than between 10 and 30% of the pioneer product's price; (6) The effect on pioneer manufacturers also will be different. They are expected to respond and offer competitive discounts to maintain market share and are likely to retain 70 to 90% of their market share and will continue to reap substantial profits, even after FOB entry.

¹⁷ Letter from Nancy-Ann DeParle, Director, Office of Health Reform, and Peter Orszag, Director, Office of Management and Budget, to Henry A. Waxman, Chairman of the House Energy and Commerce Committee, June 24, 2009, http://energycommerce.house.gov/Press_111/20090625/biologicsresponse.pdf

¹⁸ A rebuttal to the FTC report prepared by the Biotechnology Industry Organization (BIO) can be found at http://bio.org/healthcare/followonbkg/FTC_biosimilars_report_rebuttal.pdf

exclusivity period, including John Calfee of the American Enterprise Institute,¹⁹ Alex Brill, a principal at Matrix Global Advisors, LLC and former chief economist to the House Ways and Means Committee (seven years),²⁰ and Duke University economist Henry Grabowski (12.9 to 16.2 years).²¹

Economic Studies on Potential Savings

Economic studies on potential savings to the federal government over 10 years due to the use of follow-on biologics have ranged “between nothing and \$14 billion.”²² A study by Avalere Health estimated “government savings at \$3.6 billion in the first 10 years”; another study by Express Scripts estimated “10-year consumer savings at \$71 billion and federal savings at \$14 billion.”²³ On June 25, 2008, the Congressional Budget Office (CBO) released a cost estimate on a bill introduced in the 110th Congress, S. 1695 (Kennedy). The CBO study found that enactment of S. 1695 would save the federal government \$5.9 billion over 10 years (2009-2018) and would reduce total expenditures on biologics in the United States by about \$25 billion over the same period.²⁴ The Obama Administration FY2010 budget proposal estimated the amount of savings, following the implementation of a pathway for the approval of follow-on biologics, at \$9.2 billion over a 10-year period (2010-2019).²⁵

Patient Safety

Although most observers agree that lower prices for biologics would be of great benefit both to consumers and payers, some have expressed concern that the abbreviated application process allowing for expedited FDA approval of these complex therapeutics might compromise patient safety. A report published in October 2008 investigated the nature, frequency and timing of safety-related regulatory actions for biologics approved in the United States and the European Union.²⁶ It found that 41 of 174 biologics approved since 1995 were the subject of 82 regulatory actions regarding safety. These regulatory actions were primarily letters to healthcare professionals and some “black box” warnings on product labels but no product withdrawals.

¹⁹ John Calfee, *When Patents Are Not Enough: Data Exclusivity for Follow-On Biologics*, American Enterprise Institute, Washington, DC, December 2008, http://www.aei.org/docLib/20081208_23731HPO10Calfee_g.pdf.

²⁰ Alex M. Brill, *Proper Duration of Data Exclusivity for Generic Biologics: A Critique*, November 2008, http://www.tevad.com/Brill_Exclusivity_in_Biogenics.pdf.

²¹ Letter from Henry Grabowski, Professor of Economics and Director of the Program in Pharmaceuticals and Health Economics, to Federal Trade Commission, Office of the Secretary, July 6, 2009, http://econ.duke.edu/~grabow/FDS/FullFTC_response.pdf. See also Henry Grabowski, Iain Cockburn, and Genia Long, et al., “Data Exclusivity Periods and Next Generation Improvements to Innovator Biologics: Key Issues,” Duke University Department of Economics Working Paper, No. 2009-05, April 29, 2009, <http://www.econ.duke.edu/Papers/PDF/DWPaper2009-05.pdf>.

²² “CBO Weighs 2 Studies That Show Little Savings From Biogenics,” *Inside Health Policy*, July 19, 2007.

²³ *Ibid.*

²⁴ Congressional Budget Office, Cost Estimate, S. 1695, Biologics Price Competition and Innovation Act of 2007, June 25, 2008, at <http://www.cbo.gov/ftpdocs/94xx/doc9496/s1695.pdf>.

²⁵ House Budget Committee, Summary of the President’s Fiscal Year 2010 Budget, p. 6 at http://budget.house.gov/pres_budgets/fy2010/02.27.2009_FY2010_Pres_Budget_Summary.pdf.

²⁶ Thijs J. Giezen, Aukje K. Mantel-Teeuwisse, and Sabine M. J. M. Straus, et al., “Safety-related regulatory actions for biologics approved in the United States and the European Union,” *Journal of the American Medical Association*, vol. 300, no. 16 (October 22, 2008), pp. 1887-1896.

The October 2008 study found that the probability of a first safety-related regulatory action was 14% 3 years after approval and 29% 10 years after approval. The authors noted that these may be underestimates—not all drugs are marketed right after approval (and some may never be marketed), but all biologics that obtained market authorization were included in the study. As is the case with chemically produced drugs, many safety problems are identified only after drug approval because some serious adverse drug effects are rare and will only become apparent following use in large numbers of patients. Lastly, and perhaps most importantly for individuals interested in follow-on biologics products, the study found that the first biologics approved in a chemical, pharmacological and therapeutic subgroup (in other words, innovator products) were especially prone to safety-related regulatory action compared with later approved products in that subgroup.

Relevant Laws

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 well as some of the important amendments that have occurred during the past 100 years.

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.”²⁷ The act was groundbreaking, “the very first premarket approval statute in history.”²⁸ It set new precedents, “shifting from retrospective post-market to prospective pre-market government review.”²⁹ The Biologics Act was passed in response to deaths (many in children) from tetanus contamination of smallpox vaccine and diphtheria antitoxin. The act focused on the manufacturing process of such biologic products and required an inspection of the manufacturing facility before a federal license was issued to market the product.

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

The Biologics 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

²⁷ David M. Dudzinski, “Reflections on Historical, Scientific, and Legal Issues Relevant to Designing Approval Pathways for Generic Versions of Recombinant Protein-Based Therapeutics and Monoclonal Antibodies,” *Food and Drug Law Journal*, vol. 60, pp. 143-260.

²⁸ *Ibid.*, p. 147.

²⁹ *Ibid.*

Cosmetic Act (FDC Act).³⁰ The Pure Food and Drugs Act was replaced by the FDC Act in 1938. The FDC Act required that drug manufacturers submit a new drug application (NDA) prior to marketing that demonstrated, among other things, that the product was safe.³¹

The Public Health Service Act

The Biologics Act was revised and re-codified (42 USC 262) when the Public Health Service Act (PHS Act) was passed in 1944. The 1944 Act specified that a biological product that has been licensed for marketing by the FDA under the PHS Act is also subject to regulation (though not approval) under the FDC Act. A biological product is defined under section 351(i) of the PHS Act, 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.

Section 351(j) of the PHS Act states that “the FDC Act 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 FDC Act:

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 FDA Modernization Act of 1997 (FDAMA) 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.

Natural Source Biological Products and the Hatch-Waxman Act

As stated previously, biological products are, in general, regulated—licensed for marketing—under the PHS Act, and chemical drugs are regulated—approved for marketing—under the FDC Act. However, through a historical quirk, the FDA was given regulatory authority over certain natural source biological products; these products have been regulated as drugs under the FDC Act rather than as biologics under the PHS Act. In 1941, three years prior to the re-codification of the Biologics Act, Congress gave the FDA authority over the marketing of insulin.³² Insulin is a peptide hormone, a small protein that regulates carbohydrate metabolism.³³ In the 1940s, insulin

³⁰ Gary E. Gamerman, “Regulation of Biologics Manufacturing: Questioning the Premise,” *Food and Drug Law Journal*, vol. 49, 1994, pp. 213-235.

³¹ For further information, see CRS Report RL32797, *Drug Safety and Effectiveness: Issues and Action Options After FDA Approval*, by Susan Thaul.

³² Dudzinski, *Food and Drug Law Journal*, vol. 60, p. 153. The Insulin Amendments P.L. 77-366, codified at 21 USC 356, were repealed by P.L. 105-115, the Food and Drug Administration Modernization Act (FDAMA).

³³ A protein is a large organic molecule composed of a long chain or chains of amino acids linked by chemical bonds. (continued...)

“was obtained in the same manner as many biologics, namely extraction from animals. Despite this similarity with biologics, insulin was regulated by FDA.”³⁴ In addition to insulin, the distinction of a biological product regulated as a drug under the FDC Act rather than as a biologic under the PHS Act holds true for a small set of products that are mostly hormones: glucagon, human growth hormone, hormones to treat infertility, hormones used to manage menopause and osteoporosis, and certain medical enzymes (hyaluronidase and urokinase).³⁵

This distinction is important because the Hatch-Waxman Act provides a mechanism for the approval of generic drugs under the FDC Act but not under the PHS Act. Generic pharmaceutical companies could seek to gain approval of follow-on biological products for the small number of biologics approved under the FDA Act but not the much larger group of biologics approved under the PHS Act. Hatch-Waxman added two abbreviated pathways to the FDC Act for subsequent versions of already approved products: section 505(j) and section 505(b)(2).

Section 505(j) established an Abbreviated New Drug Application (ANDA) process for a generic drug that contains the *same* active ingredient as the brand-name innovator drug. In the ANDA, the generic company establishes that its drug product is chemically the same as the already approved innovator drug, and thereby relies on the FDA’s previous finding of safety and effectiveness for the approved drug. The 505(j) pathway is used for the approval of most generic chemical drugs.

Under the second pathway, a drug that has a significant difference from an innovator drug, but is still sufficiently *similar* to that drug, may be the subject of a 505(b)(2) application. The company filing the application must submit additional non-clinical and clinical data to show that the proposed product is safe and effective.³⁶ However, the application may rely on published literature or on the FDA’s finding of safety and effectiveness for the already approved product to support the approval of the proposed product. The 505(b)(2) pathway has been used to approve Omnitrope, a follow-on human growth hormone, and a few other follow-on protein products.³⁷ All have been members of the small set of biologic products that were regulated as drugs.

Regulatory Framework

Following enactment of the 1902 Biologics Act, regulatory responsibility for biologics was first delegated to the Hygienic Laboratory, a precursor of NIH.³⁸ In 1972, regulatory authority for

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Insulin is a short chain of 51 amino acids. Examples of carbohydrates include sugars and starch.

³⁴ Dudzinski, *Food and Drug Law Journal*, vol. 60, p. 154.

³⁵ Janet Woodcock, Deputy Commissioner, Chief Medical Officer, FDA, testimony before the House Committee on Oversight and Government Reform, March 26, 2007, at <http://oversight.house.gov/documents/20070326104056-22106.pdf>; BIO Citizen Petition, Follow-on Therapeutic Proteins, April 23, 2003, at <http://www.fda.gov/OHRMS/DOCKETS/DOCKETS/03p0176/03p-0176-cp00001-01-vol11.pdf>.

³⁶ Janet Woodcock, testimony before the House Committee on Oversight and Government Reform, March 26, 2007.

³⁷ These products are GlucaGen (glucagon recombinant for injection), Hylenex (hyaluronidase recombinant human), Hydase and Amphadase (hyaluronidase), and Fortical (calcitonin salmon recombinant) Nasal Spray. Center for Drug Evaluation and Research, U.S. Food and Drug Administration, *Omnitrope (somatropin [rDNA origin]) Questions and Answers*, May 30, 2006, at <http://www.fda.gov/cder/drug/infopage/somatropin/qa.htm>.

³⁸ *Ibid.*, p. 148, and 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 was assigned to the newly established Division of Biologics Control. In 1955, the biologics control function was placed in the newly formed Division of (continued...)

biologics was transferred from the NIH Division of Biological Standards to the FDA Bureau of Biologics, which eventually became the agency's Center for Biologics Evaluation and Research (CBER).³⁹

Because biotechnology products frequently cross the conventional boundaries between biologics, drugs, and devices, determining the jurisdictional status of these new products has been difficult for both the FDA and industry. Some products have had characteristics that met multiple statutory and scientific definitions.⁴⁰ In 1991, the FDA published an Intercenter Agreement between CBER and the Center for Drug Evaluation and Research (CDER).⁴¹ 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 mentioned earlier that are regulated as drugs under the FDC Act would continue to be regulated by CDER, regardless of the method of manufacture.

In 2002, however, the FDA announced its intention to reorganize review responsibilities, consolidating review of new pharmaceutical products under CDER, thereby allowing CBER to concentrate on vaccines, blood safety, gene therapy, and tissue transplantation.⁴² On June 30, 2003, responsibility for most therapeutic biologics was transferred from CBER to CDER.⁴³ Under the new structure, biological products transferred to CDER will continue to be regulated as licensed biologics under section 351 of the PHS Act. Examples of products transferred to CDER include monoclonal antibodies; proteins intended for therapeutic use (interferons, thrombolytic enzymes); immunomodulators (other than vaccines and allergenic products); and, growth factors, cytokines, and monoclonal antibodies intended to alter production of blood cells.⁴⁴ Remaining at CBER are traditional biologics such as vaccines, allergenic products, antitoxins, antivenins, venoms, and blood and blood products, including recombinant versions of plasma derivatives (clotting factors produced via biotechnology).

As stated previously, the Hatch-Waxman Act added two abbreviated pathways under the FDC Act—505(j) and 505(b)(2)—but not under the PHS Act, for the approval of additional products subsequent to the innovator product. Because of the complex nature of most biological products and their methods of manufacture, such products will not be identical to the brand-name product;

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Biologics Standards.

³⁹ The NIH Almanac; Donna Hamilton, "A Brief History of the Center for Drug Evaluation and Research," FDA History Office, November 1997, at <http://www.fda.gov/cder/about/history/Histext.htm>. During the early 1980s, the Bureau of Drugs and the Bureau of Biologics merged to form the National Center for Drugs and Biologics. In 1984, all of the National Centers within FDA were redesignated simply as Centers. In 1987, 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). CBER continues to use NIH facilities and buildings until the expected move in 2012 to the new FDA headquarters in White Oak, Maryland (see <http://www.fda.gov/oc/whiteoak/projectschedule.html>).

⁴⁰ 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, at <http://www.fda.gov/OHRMS/DOCKETS/98fr/91-27869.pdf>.

⁴¹ The Intercenter Agreement is available at <http://www.fda.gov/oc/ombudsman/drug-bio.htm>.

⁴² FDA Press Release, "FDA to Consolidate Review Responsibilities for New Pharmaceutical Products," September 6, 2002, at <http://www.fda.gov/bbs/topics/NEWS/2002/NEW00834.html>.

⁴³ *Federal Register*, vol. 68, no. 123, June 26, 2003, pp. 38067-38068.

⁴⁴ Transfer of Therapeutic Products to the Center for Drug Evaluation and Research, at <http://www.fda.gov/cber/transfer/transfer.htm>. Also of interest is Approved Products Transferring to CDER, at <http://www.fda.gov/cber/transfer/transfprods.htm>, and Therapeutic Biological Products, at <http://www.fda.gov/cder/biologics/default.htm>.

therefore, the 505(j) pathway cannot be used for product approval. However, if a biological product is sufficiently similar to the innovator product, the 505(b)(2) pathway may be used by a company for the approval of its biologic. Following the enactment of Hatch-Waxman, the FDA published in 1999 a draft guidance on applications covered by section 505(b)(2); the guidance has never been finalized.⁴⁵

As things currently stand, and as discussed above, the 505(b)(2) pathway has been used only for those biologics that have been regulated as drugs under the FDC Act. However, the vast majority of biologics have been regulated under the PHS Act. The FDA's position is that additional legislation is required to provide such a pathway under the PHS Act. For traditional biologics regulated under the PHS Act, the agency's longstanding policy has been that a full BLA, including clinical testing, would be required for the licensing of each such product. In a 1974 *Federal Register* notice, the FDA stated that

[u]nlike the regulation of human and animal drugs, all biological products are required to undergo clinical testing in order to demonstrate safety, purity, potency and effectiveness prior to licensing, regardless whether other versions of the same product are already marketed or standards for the product have been adopted by rulemaking. Indeed, many of the existing standards require specific clinical testing before approval will be granted. This is required because all biological products are to some extent different and thus each must be separately proved safe, pure, potent, and effective.... There is no such thing as a "me-too" biologic.⁴⁶

When publishing the final rule on the ANDA procedure that had been outlined in Hatch-Waxman, the FDA stated in 1992 that "these procedures are inapplicable to ... biological drug products licensed under 42 USC 262 (section 351 of the PHS Act)."⁴⁷ Most recently, during hearing testimony on May 2, 2007, before the Subcommittee on Health of the House Energy and Commerce Committee, Janet Woodcock, Deputy Commissioner and Chief Medical Officer of the FDA, stated in response to questioning that there is no pathway under the PHS Act for the approval or licensing of follow-on biologics that is similar to the 505(b)(2) pathway under the FDC Act, and that the FDA would be willing to work with Congress in crafting a legislative approach to creating such a pathway.

Scientific Challenges

Comparing a follow-on protein with the brand-name product is more scientifically challenging than comparing generic and brand-name chemical drugs. For chemically synthesized drugs, which are relatively small molecules, the equivalence of chemical composition between the generic drug and innovator drug is relatively easy to determine. In contrast, therapeutic proteins are much larger in size (100- to 1,000-fold larger than chemically synthesized drugs), have a much more complex three-dimensional structure, and may consist of mixtures rather than one pure entity.

⁴⁵ Guidance for Industry, Applications Covered by Section 505(b)(2), October 1999, at <http://www.fda.gov/CDER/GUIDANCE/2853dft.pdf>.

⁴⁶ *Federal Register*, v. 39, no. 248, December 24, 1974, p. 44641.

⁴⁷ *Federal Register*, v. 57, no. 82, April 28, 1992, p. 17951.

A protein is a large organic molecule composed of a long chain of component parts, called amino acids, which are linked by chemical bonds. This amino acid chain folds into a complex three-dimensional structure. Slight changes in the chain or three-dimensional shape can influence the protein's biological activity. All manufactured biologics (brand or follow-on) can vary slightly from lot to lot, even when the manufacturing process has not been changed. Proteins can also be altered by the addition of other chemicals, such as sugar groups (glycosylation), at various points along the amino acid chain. In many cases, current technology will not allow complete characterization of biological products. In prepared testimony before Congress, FDA Deputy Commissioner Janet Woodcock outlined the scientific challenges involved in determining the safety and effectiveness of follow-on biologics, often referred to by FDA as follow-on protein products:

Current technologies, such as peptide mapping, protein sequencing, and mass spectroscopy enable manufacturers to determine, with certainty, the amino acid sequence of a recombinant protein. However, the amino acid sequence is the most rudimentary characteristic of a protein. Conclusive analysis of other aspects of a protein's structure requires much more sophisticated technologies and is fraught with uncertainties that are proportional to the size and complexity of the protein itself. Such complexities include folding of the protein's amino acid chain into highly organized structures, post-translational modification of the protein with a broad range of biochemical additions (e.g., glycosylation, acetylation, phosphorylation, etc.), and association of multiple protein molecules into aggregates. It is the combination of the protein's amino acid sequence and its structural modifications that give a protein its unique functional characteristics. Therefore, the ability to predict the clinical comparability of two products depends on our understanding of the relationship between the structural characteristics of the protein and its function, as well as on our ability to demonstrate structural similarity between the follow-on protein and the reference product. Although this currently may be possible for some relatively simple protein products, technology is not yet sufficiently advanced to allow this type of comparison for more complex protein products.⁴⁸

Another challenge for the FDA is determining whether the follow-on biologic is sufficiently similar to the brand-name biologic that the two products are interchangeable. Several terms are important to this discussion. Products that are considered to be *therapeutically equivalent* "are approved drug products, usually made by different manufacturers, that are pharmaceutical equivalents and for which bioequivalence has been demonstrated. Therapeutic equivalents can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling."⁴⁹ *Pharmaceutical equivalents* are products that contain the same active ingredient in the same strength, dosage form, and route of administration.⁵⁰ *Bioequivalence* means that the products are absorbed into the body at a similar rate and extent.⁵¹ *Interchangeability* "is not defined by FDA and could have a number of different meanings. It could refer to products that are therapeutic equivalents, and thus could, in some circumstances, be substituted at the pharmacy level without a physician's intervention. Alternatively, the term could

⁴⁸ Janet Woodcock, Deputy Commissioner, Chief Medical Officer, FDA, testimony before the Subcommittee on Health, Committee on Energy and Commerce, May 2, 2007, at http://energycommerce.house.gov/cmte_mtgs/110-he-hrg.050207.Woodcock-testimony.pdf.

⁴⁹ *Ibid.*

⁵⁰ Janet Woodcock et al., "The FDA's Assessment of Follow-on Protein Products: A Historical Perspective," *Nature Reviews Drug Discovery*, published online April 13, 2007, at <http://www.nature.com/reviews/drugdisc>.

⁵¹ *Ibid.*

describe similar products that are not ‘substitutable’ but which, under a physician’s supervision, could be used to treat the same disease or condition in the same patient.”⁵²

Most drugs approved under section 505(j) are therapeutically equivalent to the already approved drug product. In her testimony, Dr. Woodcock explains the importance of a determination of therapeutic equivalence for a generic drug and the reasons why such a determination for a follow-on protein product may not be possible, at least at the present time:

In many jurisdictions, therapeutically equivalent drugs may be substituted at the pharmacy level, without a physician’s intervention.... Because of the variability and complexity of protein molecules, current limitations of analytical methods, and the difficulties in manufacturing a consistent product, it is unlikely that, for most proteins, a manufacturer of a follow-on protein product could demonstrate that its product is identical to an already approved product. Therefore, the section 505(j) generic drug approval pathway, which is predicated on a finding of the same active ingredient, will not ordinarily be available for protein products.⁵³

Immunogenicity, or the ability to elicit an immune response, is another important term in the discussion of follow-on proteins. An immune response to a therapeutic protein can range from detectable, but clinically insignificant, to one that can cause safety problems for the patient or limit the effectiveness of the product. For some biologics, such as vaccines, stimulating an immune response is the intended outcome. However, for other types of therapeutic products, an immune response can lower the clinical effect of a protein. Dr. Woodcock describes the implications at length in the prepared testimony:

Adverse safety events from an immune response could include hypersensitivity reactions such as anaphylaxis, rash, fever and kidney problems, to cross-reaction with an endogenous (naturally occurring in the body) protein (e.g., erythropoietin). Immunogenicity may be influenced by patient-related, disease-related, or product-related factors. Immune responses to administered protein products can be extremely serious or life-threatening; therefore, this issue requires significant attention. The ability to predict immunogenicity of a protein product, particularly the more complex proteins, is extremely limited. Therefore, some degree of clinical assessment of a new product’s immunogenic potential will ordinarily be needed. The extent of independent testing needed will again depend on a variety of scientific factors such as the indication, whether the product is to be administered chronically, the overall assessment of the product’s immunogenic potential, and whether there is the possibility of generating a cross-reaction with an important endogenous molecule.

Even if a follow-on protein product is found to be safe and effective by the FDA, this finding does not mean that the follow-on protein product would be interchangeable with, or substitutable for, the originally approved brand-name product. To establish that the follow-on protein product is substitutable for the brand-name product, the manufacturer of the follow-on product must demonstrate through additional clinical data that repeated switches from the follow-on product to the brand-name product (and vice versa) would have no negative effect on the safety and/or effectiveness of the products. In other words, there must be no problems with immunogenicity. “For many follow-on protein products, and, in particular, the more complex proteins, there is a significant potential for repeated switches between products to have a negative impact on the

⁵² Janet Woodcock, testimony before the Subcommittee on Health, Committee on Energy and Commerce, May 2, 2007.

⁵³ *Ibid.*

safety and/or effectiveness. Therefore, the ability to make determinations of substitutability for follow-on protein products may be limited.”⁵⁴

Legislation

Legislative History

Efforts by Congress to address the need for an pathway for the licensure of follow-on biologics began with the introduction of the Access to Life-Saving Medicine Act (H.R. 6257, Waxman, and S. 4016, Schumer) which was introduced near the end of the 109th Congress and received no further action.

Early in the first session of the 110th Congress, two competing legislative approaches were introduced that would have allowed FDA to approve follow-on biologic products. In general, the approach taken by H.R. 1038 (Waxman) and its companion bill S. 623 (Schumer) were favored by the generic drug industry, while H.R. 1956 (Inslee), and S. 1505 (Gregg) were favored by companies that have developed the innovator or brand-name products. The introduction of S. 1695 (Kennedy) in June 2007 provided a third approach. The bipartisan Senate sponsors (Senators Kennedy, Hatch, Enzi, and Clinton) of S. 1695 claimed to have negotiated a compromise between the brand-name manufacturers and the generic drug industry. The sponsors of S. 1695 intended to add the bill’s language to legislation (H.R. 2900/S. 1082/H.R. 3580) reauthorizing FDA’s user fee programs when this larger FDA bill entered conference negotiations. However, when H.R. 3580 became P.L. 110-85 on September 27, 2007, it did not include S. 1695. The introduction of H.R. 5629 (Eshoo) in March 2008 provided yet another approach. H.R. 5629 was similar in some respects to S. 1695 with a few important differences that were favored by the brand-name industry. S. 1695 was reported on November 19, 2008. No further action was taken on this or the other follow-on biologics bills in the 110th Congress.

In the 111th Congress, H.R. 1427 (Waxman) contained a number of changes when compared with H.R. 1038 (Waxman) from the 110th Congress.⁵⁵ H.R. 1548 (Eshoo) was essentially the same as H.R. 5629 (Eshoo) as introduced in the 110th Congress with a few minor changes. Health care reform legislation also provided a pathway for the approval of follow-on biologics. The biologics provisions were added to PPACA in “Title VII—Improving Access to Innovative Medical Therapies” as “Subtitle A—Biologics Price Competition and Innovation,” sections 7001 through 7003. The following paragraphs briefly describe the biologics provisions in the Patient Protection and Affordable Care Act (PPACA; P.L. 111-148).

Biologics Provisions in PPACA, P.L. 111-148

Interchangeability

A determination on interchangeability is required if the application shows that the biological product (1) is biosimilar to the reference product, (2) can be expected to produce the same clinical

⁵⁴ Ibid.

⁵⁵ A companion bill, S. 726 (Schumer), was introduced on March 26, 2009.

result in any given patient, and (3) can be alternated or switched with use of the reference product without risk to the patient in terms of safety or diminished efficacy compared with use of the reference product alone. There is no requirement on the publication of guidance.

Clinical studies

PPACA requires information in the FDA application demonstrating that the follow-on biologic is similar to the reference product based on data from a clinical study or studies to demonstrate safety, purity, and potency for one or more appropriate conditions of use for which the reference product is licensed. However, the Secretary may determine that elements in the application, such as clinical studies, may be unnecessary.

FDA Guidance documents

FDA may publish proposed guidance for public comment prior to publication of final guidance, and if so, FDA must establish a process to allow public input regarding priorities for issuing guidance. The issuance or non-issuance of guidance would not preclude the review of, or action on, an application.

Data exclusivity for reference product

Data exclusivity is separate from the protection provided by a patent. Data exclusivity is the period of time during which the manufacturer of a follow-on product, in the preparation of its application for FDA approval, is blocked from referring to the data submitted in the original application to FDA for the approval of the brand-name product; this results in a period of exclusive marketing for the brand-name product.

PPACA provides a 12-year exclusivity period from the date on which the reference product was first approved. If a reference product has been designated an orphan drug, an application for a biosimilar or interchangeable product may not be filed until the later of (1) the seven-year period of orphan drug exclusivity described in the FDCA or (2) the 12-year period established by the Senate bill.

Market exclusivity for the first interchangeable product

PPACA allows for a period of exclusive marketing for the follow-on biologic product that is the first to be established as interchangeable with the reference product.

*Patents*⁵⁶

PPACA sets forth provisions governing patent infringement claims against an applicant or prospective applicant for a follow-on biological product license. It establishes new processes for identifying patents that might be disputed between the brand-name company and the company submitting a biosimilar application and also would establish a multistep patent resolution process.

⁵⁶ This section was written by John Thomas.

Biological products approved under FFDCA

PPACA stipulates that all biological product applications must be submitted under section 351 of the PHS Act. For the small number of biological products that have been approved under section 505 of the FFDCA, the approved application is deemed to be a license for the biological product under section 351 as of 10 years after enactment.

User fees

The Secretary of HHS must develop recommendations regarding goals for the review of follow-on biologic product applications for FY2013 through the end of FY2017 and present them to Congress. The recommendations must be published in the *Federal Register* with a 30-day public comment period, and a public meeting must be held. The revised recommendations would be presented to Congress by January 15, 2012. Based on these recommendations, it is the sense of the Senate that Congress should authorize a user fee program effective October 1, 2012. Through October 1, 2010, the Secretary must collect data on the cost of follow-on biologic application review as conducted according to the prescription drug user fee program. Two years after receiving the first user fee for a follow-on biological product application and every two years thereafter until October 1, 2013, the Secretary must perform an audit of the application review costs. An alteration of the user fee would occur depending on results of the audit, as specified in the bill.

Pediatric biologics⁵⁷

PPACA provides for an extra six months of market exclusivity for a new biologic drug if pediatric studies are conducted prior to FDA approval of the drug. An extra six months of market exclusivity is provided for a biologic drug already on the market if pediatric studies are conducted and the request for the extension is made not less than nine months before the expiration of the original exclusivity period.

PPACA requires an IOM study to be conducted that will review and assess the number and importance of biological products for children that are being tested as a result of these biologics provisions, as well as biological products that are not being tested for pediatric use, and offer recommendations for ensuring pediatric testing of biological products.

Savings

PPACA requires the HHS Secretary and the Treasury Secretary to determine for each fiscal year the amount saved to the federal government as a result of enactment of the approval pathway for biosimilar biological products; the savings will be used for deficit reduction.

⁵⁷ This section was written by John Thomas.

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