



# FDA Regulation of Follow-On Biologics

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## Summary

Congress has been considering legislation that would expand regulatory activities of the Food and Drug Administration (FDA) by opening a pathway for the approval of follow-on biologics. A biologic is a preparation, such as a drug or a vaccine, that is made from living organisms. A follow-on biologic 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.

The new regulatory pathway would be 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 speciality drug products, such as biologics, is often prohibitively high. For example, the rheumatoid arthritis and psoriasis treatment Enbrel costs \$16,000 per year. It is thought that 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 occurred with generic chemical drugs under Hatch-Waxman.

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 description of the proposed legislation. Bills introduced during the 110<sup>th</sup> Congress on this topic include H.R. 1038/S. 623, H.R. 1956, H.R. 5629, S. 1505, and S. 1695.

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Congress has been considering legislation that would expand regulatory activities of the Food and Drug Administration (FDA) by opening a pathway for the approval of follow-on biologics.<sup>1</sup> This pathway would be somewhat analogous to that which allowed for the approval of generic chemical drugs via passage of the Drug Price Competition and Patent Term Restoration Act of 1984 (P.L. 98-417), often referred to as the Hatch-Waxman Act.<sup>2</sup> By offering an alternative to brand-name drug products, the Hatch-Waxman Act is credited with lowering the cost of drugs to consumers, as well as allowing for the expansion of the generic drug industry in the United States.

At the time that Hatch-Waxman was being debated by Congress and implemented by the FDA, the biotechnology industry was just beginning to develop its first 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. Biotechnology products are expected to become a larger and larger share of the drugs sold by the pharmaceutical industry to U.S. consumers. However, with no equivalent to the generic alternatives to chemical drugs, the cost of therapeutic biologics is often prohibitively high for individual patients. For example, the rheumatoid arthritis and psoriasis treatment Enbrel costs \$16,000 per year, and biological drugs for multiple sclerosis range in price from \$16,000 to \$25,000 per year.<sup>3</sup> Spending by Medicare in 2006 on just one such drug, Epogen, was \$2.8 billion.<sup>4</sup> The amount spent on Epogen is more than the entire FY2006 budget for FDA, which was \$1.863 billion (\$1.494 billion in direct appropriations and \$369 million in user fees).<sup>5</sup>

#### 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.

In 2006, U.S. spending on such speciality drugs was \$54 billion, or about 20% of total spending on pharmaceuticals.<sup>6</sup> Speciality drugs are expected to comprise 26% of total pharmaceuticals purchased by 2010, almost doubling to \$99 billion per year, a rate of increase that is second highest among all the components of health care spending, exceeded only by diagnostic imaging.<sup>7</sup>

<sup>1</sup> Sometimes referred to as biogenerics, biosimilars, 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.

<sup>2</sup> For further information, see CRS Report RL32377, *The Hatch-Waxman Act: Legislative Changes Affecting Pharmaceutical Patents*, by Wendy H. Schacht and John R. Thomas, and CRS Report RL30756, *Patent Law and Its Application to the Pharmaceutical Industry: An Examination of the Drug Price Competition and Patent Term Restoration Act of 1984 ("The Hatch-Waxman Act")*, by Wendy H. Schacht and John R. Thomas.

<sup>3</sup> Bruce L. Downey, Chairman and CEO Barr Pharmaceuticals, Inc., testimony before the House Energy and Commerce Subcommittee on Health, May 2, 2007, at [http://energycommerce.house.gov/cmte\\_mtgs/110-he-hrg.050207.Downey-testimony.pdf](http://energycommerce.house.gov/cmte_mtgs/110-he-hrg.050207.Downey-testimony.pdf).

<sup>4</sup> Personal communication with Lisa Yen, Centers for Medicare and Medicaid Services Office of Legislation, February 13, 2009.

<sup>5</sup> CRS Report RL34334, *The Food and Drug Administration: Budget and Statutory History, FY1980-FY2007*, coordinated by Judith A. Johnson.

<sup>6</sup> Speciality drugs consist of mostly high-priced biologic agents. Jonah Houts, Senior Analyst, Express Scripts, Inc., testimony before the Committee on Oversight and Government Reform, March 26, 2007, at <http://oversight.house.gov/documents/20070326173059-55945.pdf>.

<sup>7</sup> *Ibid.*, and Express Scripts, *2006 Drug Trend Report*, April 2006, p. 38.

From 2005 to 2006, the cost of non-specialty (i.e., chemical) drugs rose 6%, whereas speciality (mostly biologic) drugs rose 21%.<sup>8</sup> From 2006 to 2007, the cost of non-specialty drugs rose 4.7%, and speciality drugs rose 14%.<sup>9</sup> Spending on all pharmaceuticals currently represents about 11% of health care spending in the United States.

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. For chemical drugs, some experts argue that “generic medications decrease prices 60% to 90% on branded oral-solid medications.”<sup>10</sup> The Congressional Budget Office estimated the savings generated by generic drug use in 1994 was between \$8 billion and \$10 billion.<sup>11</sup> 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.

Even though patents for several speciality 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) has advocated that the FDA establish a regulatory system for the approval of follow-on biologics under its existing statutory authority.<sup>12</sup> However, the Biotechnology Industry Organization (BIO) has filed a citizen petition with the FDA requesting a number of actions that would inhibit the approval of follow-on biologics.<sup>13</sup>

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 on April 24, 2006.<sup>14</sup> Sales of Omnitrope in the United States only occurred following the April 10, 2006, ruling by the US 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.”<sup>15</sup>

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<sup>8</sup> Express Scripts, *2006 Drug Trend Report*, April 2006, p. 5.

<sup>9</sup> Express Scripts, *2007 Drug Trend Report*, April 2007, p. 6.

<sup>10</sup> Jonah Houts, testimony before the House Committee on Oversight and Government Reform, March 26, 2007.

<sup>11</sup> Congressional Budget Office, “How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry,” July 1998.

<sup>12</sup> 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](http://www.fda.gov/cder/ogd/GPHA_jan_21.htm).

<sup>13</sup> 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>.

<sup>14</sup> “Europe approves two follow-on human growth hormones,” *Nature Biotechnology*, vol. 24 (June 2006), p. 601.

<sup>15</sup> *Ibid.*

Proposed legislation (H.R. 1038/S. 623, H.R. 1956, H.R. 5629, S. 1505, and S. 1695) would provide a mechanism for FDA approval of biological products that are similar to the brand-name product, thereby allowing for market competition and reduction in prices, though perhaps not to the same extent as with generic chemical drugs. 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.”<sup>16</sup> 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.”<sup>17</sup> On June 25, 2008, the Congressional Budget Office (CBO) released a cost estimate on S. 1695. 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.<sup>18</sup>

Although most observers agree that lower prices for biologics would be of great benefit both to consumers and payors, 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.<sup>19</sup> 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.

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.

This report provides an overview of the FDA regulatory issues involved in the approval of follow-on biologics.<sup>20</sup>

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<sup>16</sup> “CBO Weighs 2 Studies That Show Little Savings From Biogenerics,” Inside Health Policy, July 19, 2007.

<sup>17</sup> Ibid.

<sup>18</sup> 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>.

<sup>19</sup> 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.

<sup>20</sup> For patent issues, see CRS Report RL33901, *Follow-On Biologics: Intellectual Property and Innovation Issues*, by Wendy H. Schacht and John R. Thomas.

## 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.

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.”<sup>21</sup> The act was groundbreaking, “the very first premarket approval statute in history.”<sup>22</sup> It set new precedents, “shifting from retrospective post-market to prospective pre-market government review.”<sup>23</sup> 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.

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 Cosmetic Act (FDC Act).”<sup>24</sup> 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.<sup>25</sup>

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

<sup>21</sup> 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.

<sup>22</sup> *Ibid.*, p. 147.

<sup>23</sup> *Ibid.*

<sup>24</sup> Gary E. Gamerman, “Regulation of Biologics Manufacturing: Questioning the Premise,” *Food and Drug Law Journal*, vol. 49, 1994, pp. 213-235.

<sup>25</sup> For further information, see CRS Report RL32797, *Drug Safety and Effectiveness: Issues and Action Options After FDA Approval*, by Susan Thaul.

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 FDA Modernization Act of 1997 (FDAMA) amended the PHS Act 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.

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.<sup>26</sup> Insulin is a peptide hormone, a small protein that regulates carbohydrate metabolism.<sup>27</sup> In the 1940s, insulin “was obtained in the same manner as many biologics, namely extraction from animals. Despite this similarity with biologics, insulin was regulated by FDA.”<sup>28</sup> 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).<sup>29</sup>

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.

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<sup>26</sup> 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).

<sup>27</sup> A protein is a large organic molecule composed of a long chain or chains of amino acids linked by chemical bonds. Insulin is a short chain of 51 amino acids. Examples of carbohydrates include sugars and starch.

<sup>28</sup> Dudzinski, *Food and Drug Law Journal*, vol. 60, p. 154.

<sup>29</sup> 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>.

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.<sup>30</sup> 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.<sup>31</sup> 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.<sup>32</sup> In 1972, regulatory authority for 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).<sup>33</sup>

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.<sup>34</sup> In 1991, the FDA published an Intercenter Agreement between CBER and the Center for Drug Evaluation and Research (CDER).<sup>35</sup> 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

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<sup>30</sup> Janet Woodcock, testimony before the House Committee on Oversight and Government Reform, March 26, 2007.

<sup>31</sup> 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>.

<sup>32</sup> *Ibid.*, p. 148, and The NIH Almanac—Historical Data: Chronology of Events, at [http://www.nih.gov/about/almanac/historical/chronology\\_of\\_events.htm](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 Biologics Standards.

<sup>33</sup> 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>).

<sup>34</sup> 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>.

<sup>35</sup> The Intercenter Agreement is available at <http://www.fda.gov/oc/ombudsman/drug-bio.htm>.

concentrate on vaccines, blood safety, gene therapy, and tissue transplantation.<sup>36</sup> On June 30, 2003, responsibility for most therapeutic biologics was transferred from CBER to CDER.<sup>37</sup> 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.<sup>38</sup> 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).

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; 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.<sup>39</sup>

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.<sup>40</sup>

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

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<sup>36</sup> 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>.

<sup>37</sup> *Federal Register*, vol. 68, no. 123, June 26, 2003, pp. 38067-38068.

<sup>38</sup> 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/transprods.htm>, and Therapeutic Biological Products, at <http://www.fda.gov/cder/biologics/default.htm>.

<sup>39</sup> Guidance for Industry, Applications Covered by Section 505(b)(2), October 1999, at <http://www.fda.gov/CDER/GUIDANCE/2853dft.pdf>.

<sup>40</sup> *Federal Register*, v. 39, no. 248, December 24, 1974, p. 44641.

licensed under 42 USC 262 (section 351 of the PHS Act).”<sup>41</sup> 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.

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. 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.<sup>42</sup>

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<sup>41</sup> *Federal Register*, v. 57, no. 82, April 28, 1992, p. 17951.

<sup>42</sup> 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-\(continued...\)](http://energycommerce.house.gov/cmte_mtgs/110-he-(continued...))

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.”<sup>43</sup> *Pharmaceutical equivalents* are products that contain the same active ingredient in the same strength, dosage form, and route of administration.<sup>44</sup> *Bioequivalence* means that the products are absorbed into the body at a similar rate and extent.<sup>45</sup> *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 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.”<sup>46</sup>

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.<sup>47</sup>

*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

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(...continued)

hrg.050207.Woodcock-testimony.pdf.

<sup>43</sup>Ibid.

<sup>44</sup> 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>.

<sup>45</sup> Ibid.

<sup>46</sup> Janet Woodcock, testimony before the Subcommittee on Health, Committee on Energy and Commerce, May 2, 2007.

<sup>47</sup> Ibid.

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 safety and/or effectiveness. Therefore, the ability to make determinations of substitutability for follow-on protein products may be limited."<sup>48</sup>

## 110<sup>th</sup> Congress Legislation

Early in the first session of the 110<sup>th</sup> Congress, two competing legislative approaches were introduced that would have allowed FDA to approve follow-on biologic products: H.R. 1038 (Waxman)<sup>49</sup> vs. H.R. 1956 (Inslee) and S. 1505 (Gregg). In general, H.R. 1038 was favored by the generic drug industry and others interested in encouraging the development follow-on biologics products whereas H.R. 1956 and S. 1505 were favored by the companies that developed the reference products, also referred to as innovator or brand-name products. With the introduction of S. 1695 (Kennedy) in June 2007, the bipartisan Senate authors claimed to have negotiated a compromise between the brand-name manufacturers and the generic drug industry. The introduction of H.R. 5629 (Eshoo) in March 2008 provided an alternative compromise approach. H.R. 5629 is similar in some respects to S. 1695 with a few important differences that are favored by the brand-name industry. The following paragraphs a summary of the provisions in these five bills.

**Interchangeability.** H.R. 1038 and S. 1695 would have allowed FDA to make a determination on the interchangeability of a brand-name product and follow-on biologic product. H.R. 1956 and S. 1505 would not have allowed FDA to designate a follow-on biologic as interchangeable with (or therapeutically equivalent to) the brand-name product. H.R. 5629 would have allowed FDA to make a determination on interchangeability; however, it would also have required (1) the publication of final guidance on interchangeability prior to determinations on interchangeability, (2) the biological product must be biosimilar to the reference product *and* any licensed product that is interchangeable with the reference product, and (3) the biological product must produce the same clinical result for *each* condition of use on the reference product label.

<sup>48</sup> Ibid.

<sup>49</sup> The companion bill to H.R. 1038 is S. 623 (Schumer), which was introduced on February 15, 2007.

**Clinical studies waiver.** H.R. 5629 would have required clinical studies of immunogenicity; these studies may be waived only if final guidance on immunogenicity determinations has been published. In contrast, S. 1695 would have required that clinical studies submitted in support of a biological product application must be designed to avoid needless duplication or unethical clinical testing; the requirement for clinical and other studies may be waived.

**FDA Guidance documents.** H.R. 1956 and S. 1505 would have required the publication of a final product class-specific guidance document (H.R. 1956) or a final product class-specific rule (S. 1505) before an application for a follow-on biologic could be submitted to the FDA. S. 1695 did not require the publication of a guidance document prior to consideration of a follow-on biologic application, but the bill did specify criteria that would be required if product class-specific guidance was issued. H.R. 5629 would require the publication of product-class specific guidance prior to the approval of a biological product. H.R. 1038 did contain any requirement on the publication by FDA of product class-specific guidance documents.

**Nonproprietary name.** H.R. 1956 and S. 1505 would have set in place provisions governing the nonproprietary naming of biotechnology-derived biologics.<sup>50</sup> These bills would have amended the FDC Act to deem such a biologic to be misbranded if its labeling failed to meet the new requirements. H.R. 1038 would have allowed the Secretary to designate the same official name for the comparable biological product as the reference product, but not if it differs from the reference product with respect to comparability, interchangeability, structural features, mechanism of action, route of administration, dosage form, strength, naming provisions. H.R. 5629 would have required the Secretary to ensure that the labeling and packaging of each biological product bears a unique name that distinguishes it from the reference product and any other biological products that are evaluated against the reference product. S. 1695 did not contain a provision on naming.

According to media reports, “the brand industry successfully pushed for different names [for brand-name and follow-on products] in Europe. The brand industry argues having different names helps pinpoint which drugs are hurting people, but the generic drug industry believes it is a ploy to thwart generic substitution.”<sup>51</sup> The brand name drug companies believe that “having different names would make it easier for FDA to tell when a brand or a biosimilar is the cause of side effects. However, FDA urged European regulators to not use this approach when they were

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<sup>50</sup> The nonproprietary name for a drug (also called a generic, common or established name) identifies a drug’s active ingredient. While a drug’s chemical name can be lengthy and difficult to pronounce and the brand or trademark name is protected by intellectual property protections, the nonproprietary name is in the public domain and is used for all legal and regulatory matters and in all official correspondence. For example, the active ingredient ibuprofen is found in the brand name product called Advil in the United States or Dolofprt in Germany. Using the same name for the active ingredient helps physicians and patients recognize similarities and differences among products in different countries. Variance in non-proprietary names among countries has become less likely due to the International Nonproprietary Name (INN) program launched by the World Health Organization (WHO) in 1950. The United States Adopted Names (USAN) Council is a national committee devoted to non-proprietary drug nomenclature in this country. Usually a manufacturer works with the USAN Council to develop a non-proprietary name; the proposed USAN name is then forwarded to WHO for the INN. Within all 193 member states of WHO, a medical preparation cannot be sold without an established non-proprietary name. From: R. John Fidelino, “In pursuit of distinction: The method of the non-proprietary name,” *Journal of Generic Medicines*, v. 5, October 2007, p. 45-52.

<sup>51</sup> John Wilkerson, “Senate Bill does not Require Biogenerics be ‘Same’ as Brands,” *Inside Health Policy*, June 25, 2007.

debating it last winter. FDA says it already has ‘many alternative mechanisms’ to prevent inappropriate substitution.”<sup>52</sup>

**Market exclusivity for reference product.** S. 1695 would have provided 12 years of exclusive marketing for the brand-name product prior to the approval of a follow-on biologic. H.R. 1956 and S. 1505 would have provided at least 14 years of exclusive marketing for the brand-name product; H.R. 5629 would have provided at least 12 years and possibly up to 14½ years of exclusive marketing for the brand-name product. H.R. 1038 did not provide an exclusivity period.

**Market exclusivity for the first interchangeable product.** H.R. 1038, S. 1695, and H.R. 5629 would have allowed 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. H.R. 1956 and S. 1505 did not contain such a provision.

**Patents.** H.R. 1038 would have set forth provisions governing patent infringement claims against an applicant or prospective applicant for a comparable biological product license. S. 1505 would have allowed patent owners to obtain information from a biosimilar applicant that would allow them to ascertain whether the biosimilar would infringe any pertinent patents. S. 1695 and H.R. 5629 would have established a new process for identifying patents that might be disputed between the brand-name company and the company submitting a biosimilar application. These two bills also would have established a multistep patent resolution process.

**Pediatric uses for biologics.** S. 1695 would have required that all applications involving a follow-on biologic product include data on the use of the product in children. Data would not have been required if the product is interchangeable with the reference product.

**Biological products approved under FDCA.** S. 1695 and H.R. 5629 stipulated that all biological product applications must be submitted under section 351 of the PHS Act. For the small number of biological products that were approved under section 505 of the FDCA, the approved application would be deemed to be a license for the biological product under section 351 as of 10 years after enactment.

**User fees.** S. 1695 and H.R. 5629 would have allowed for the collection of user fees for the approval of a follow-on biological product.

**Special reserve fund.** S. 1695 would have required that the Secretary of HHS along with the Treasury Secretary determine for each fiscal year the amount saved to the federal government and transfer that amount to the Biological Product Savings Fund. Amounts in the fund would have been spent by the Secretary of HHS on activities authorized under the PHS Act.

President Barack Obama has indicated his support in general for the eventual FDA approval of follow-on biologics as a way lower health care costs.<sup>53</sup> The Bush Administration supported efforts to create a pathway for the approval by FDA of follow-on biologics, but it was opposed to several

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<sup>52</sup> John Wilkerson, “HHS Opposes Senate Plan for Biogenerics “Interchangeability” with Brands,” Inside Health Policy, June 28, 2007.

<sup>53</sup> Shannon Pettypiece and Catherine Larkin, “Merck to start biologic program; Drugs based on live cells, not chemicals,” *The San Diego Union-Tribune*, December 10, 2008, p. C1; and, Ed Silverman, “Merck wants to develop follow-on biologics,” *Pharmalot*, December 9, 2008, at [<http://www.pharmalot.com/2008/12/merck-wants-to-develop-follow-on-biologics/>].

provisions such as allowing FDA to make determinations on interchangeability, allowing the approval of follow-on biologics without prior issuance of guidance, the creation of the Biological Products Savings Fund, and the possible waiver by FDA of a requirement for clinical trials prior to the approval of a follow-on biologic.<sup>54</sup> The Bush Administration also believed that a follow-on biologic should have a different nonproprietary name than the brand name product. A June 26, 2007, letter from HHS Secretary Michael Leavitt to the Chairman of the Senate HELP Committee outlines the Bush Administration's position.<sup>55</sup>

In an attempt "to better evaluate the merits, benefits and costs" of these various legislative proposals and reach consensus on a single bill, the Committee on Energy and Commerce asked members of the biotechnology community and other stakeholders to answer a series of 46 questions in order that the responses would allow the Committee "to understand more fully the range of perspectives, concerns, and objectives that might be address in such a legislative proposal."<sup>56</sup> Almost 500 pages of comments from 29 stakeholders were received and posted by the Committee.<sup>57</sup> The Committee is considering the responses and possible adjustments to the proposed legislation.

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<sup>54</sup> Ibid.

<sup>55</sup> Letter found at [http://insidehealthpolicy.com/secure/data\\_extra/dir\\_07/he2007\\_2375.pdf](http://insidehealthpolicy.com/secure/data_extra/dir_07/he2007_2375.pdf).

<sup>56</sup> The April 3, 2008, Committee on Energy and Commerce letter can be found at [[http://energycommerce.house.gov/Press\\_110/110-ltr.040308.list.Biologic%20ltr.pdf](http://energycommerce.house.gov/Press_110/110-ltr.040308.list.Biologic%20ltr.pdf)].

<sup>57</sup> Responses to the April 3, 2008 Committee on Energy and Commerce letter are at [[http://energycommerce.house.gov/Press\\_110/040308.FOB.Responses.shtml](http://energycommerce.house.gov/Press_110/040308.FOB.Responses.shtml)].