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FDA Regulation of Follow-On Biologics

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Summary

The 110th Congress is currently considering legislation (S. 1082) to reauthorize the Food and Drug Administration (FDA) user fee programs. Congress may decide to include within the FDA legislation a measure that would expand the agency's regulatory activities by opening a pathway for the approval of follow-on biologics (e.g., H.R. 1038/S. 623, H.R. 1956, or S. 1505). 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 to the brand-name, or innovator, product made by the pharmaceutical or biotechnology industry.

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. 84-417), often referred to as the Hatch-Waxman Act. 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 Embrel 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 relatively small molecules and for which the equivalence of chemical composition between the generic drug and innovator drug is 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. It will be updated as legislative events warrant.

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FDA Regulation of Follow-On Biologics

The 110th Congress is considering legislation (S. 1082) that would reauthorize provisions affecting Food and Drug Administration (FDA) regulation of pharmaceutical and medical device marketing. Lawmakers may include within this legislative package a measure (such as H.R. 1038/S. 623, H.R. 1956, or S. 1505) that would open a pathway for FDA approval of so-called "follow-on" biologics.[1] 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. 84-417), often referred to as the Hatch-Waxman Act.[2] 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.

> 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.

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 Embrel costs $16,000 per

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[1] 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 generic implies identical. The FDA often uses the term *follow-on protein product*, because many biologics are proteins.

[2] For further information, see CRS Report RL32377, *The Hatch-Waxman Act: Legislative Changes Affecting Pharmaceutical Patents*, by Wendy 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 Schacht and John R. Thomas.

year, and biological drugs for multiple sclerosis range in price from $16,000 to $25,000 per year.[3]

In 2006, spending on such speciality drugs was $54 billion, or about 20% of total spending on pharmaceuticals.[4] 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.[5] From 2005 to 2006, the cost of non-speciality (i.e., chemical) drugs rose 6%, whereas speciality (mostly biologic) drugs rose 21%.[6] 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. For chemical drugs, some experts argue that "generic medications decrease prices 60% to 90% on branded oral-solid medications."[7] The Congressional Budget Office estimated the savings generated by generic drug use in 1994 was between $8 billion and $10 billion.[8] 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.[9] However, the Biotechnology Industry Organization (BIO) has filed a citizen petition with the FDA requesting a

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[3] 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].

[4] 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].

[5] Ibid., and Express Scripts, *2006 Drug Trend Report*, April 2006, p. 38.

[6] Express Scripts, *2006 Drug Trend Report*, April 2006, p. 5.

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

[8] Congressional Budget Office, "How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry," July 1998.

[9] 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].

number of actions that would inhibit the approval of follow-on biologics.[10] Proposed legislation (H.R. 1038/S. 623, H.R. 1956, and S. 1505) 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.

This report provides an overview of the FDA regulatory issues involved in the approval of follow-on biologics.[11]

Relevant Laws

In general, biological products are regulated under the Public Health Service Act (first by precursors to the Public Health Service and later by the FDA), and chemical drugs are regulated 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."[12] The Act was groundbreaking, "the very first premarket approval statute in history."[13] It set new precedents, "shifting from retrospective post-market to prospective pre-market government review."[14] 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 inspections 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

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[10] 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].

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

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

[13] Ibid, p. 147.

[14] Ibid.

and the later-enacted Federal Food Drug and Cosmetic Act (FDC Act)."[15] 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.[16]

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 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 under the PHS Act, and chemical drugs are regulated 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. Three years prior to the re-codification of the Biologics Act, Congress gave the FDA authority over the marketing of insulin.[17] Insulin is a peptide hormone, a small protein that regulates carbohydrate

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

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

[17] 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).

metabolism.[18] 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."[19] 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).[20]

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. Specifically, 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.[21] 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.[22] All have been biologics that were regulated as drugs.

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[18] 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.

[19] Dudzinski, *Food and Drug Law Journal*, vol. 60, p. 154.

[20] 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].

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

[22] 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].

Regulatory Framework

Following enactment of the 1902 Biologics Act, regulatory responsibility for biologics was first delegated to the Hygienic Laboratory, a precursor of the National Institutes of Health (NIH).[23] 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).[24]

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.[25] In 1991, the FDA published an Intercenter Agreement between CBER and the Center for Drug Evaluation and Research (CDER).[26] 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.[27] On June 30, 2003, responsibility for most therapeutic

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[23] 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 Biologics Standards.

[24] 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]).

[25] 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].

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

[27] 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].

biologics was transferred from CBER to CDER.[28] 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.[29] 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; 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.[30]

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

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

[29] 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].

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

> proved safe, pure, potent, and effective.... There is no such thing as a "me-too" biologic.[31]

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)."[32] 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

In prepared testimony, Dr. Woodcock outlined the scientific challenges involved in determining the safety and effectiveness of follow-on biologics. The FDA prefers to call these products follow-on protein products. In contrast to chemical drugs, which are relatively small molecules and for which the equivalence of chemical composition between the generic drug and innovator drug is easy to determine, therapeutic proteins are much larger in size and much more complex in structure. 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. 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. Dr. Woodcock describes these technical problems in her prepared testimony:

> 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

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[31] Federal Register, v. 39, no. 248, December 24, 1974, p. 44641.

[32] Federal Register, v. 57, no. 82, April 28, 1992, p. 17951.

> 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.

Several terms are important in the discussion of the follow-on proteins and their approval by the FDA. 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."[33] *Pharmaceutical equivalents* are products that contain the same active ingredient in the same strength, dosage form, and route of administration.[34] *Bioequivalence* means that the products are absorbed into the body at a similar rate and extent.[35] *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."[36]

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

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[33] 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].

[34] 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].

[35] Ibid.

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

> 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.[37]

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 safety and/or effectiveness. Therefore, the ability to make determinations of substitutability for follow-on protein products may be limited."[38]

Legislation

Two different legislative approaches for the approval by the FDA of follow-on biologics have been introduced in the 110th Congress. In general, H.R. 1038/S. 623 is the approach favored by the generic drug industry, whereas H.R. 1956 and S. 1505

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[37] Ibid.

[38] Ibid.

are favored by the companies that have developed the innovator or brand-name products. Highlights of the bills are outlined below.

H.R. 1038 (Waxman), the Access to Life-Saving Medicine Act, was introduced on February 14, 2007. A companion bill, S. 623 (Schumer), was introduced on February 15, 2007. H.R. 1038 would amend section 351 of the PHS Act to establish a process for the approval of an abbreviated biological product application for products that contain the same or similar active ingredients as a previously licensed biological product (the reference product). The bills allow a person to file an abbreviated biological product application with the FDA that includes (1) data demonstrating that the product is comparable to or interchangeable with the reference product; (2) information to show that the conditions or conditions of use prescribed, recommended, or suggested in the labeling proposed for the biological product have been previously approved for the reference product; and (3) information to show that the route of administration, the dosage form, and the strength of the biological product are the same as those of the reference product.

H.R. 1038 sets forth a number of conditions for approval of such an application by the FDA. The bill allows an applicant to request that the FDA make a determination as to the interchangeability of a comparable product and the reference product, based on whether a product can be expected to produce the same clinical result as the reference product in any given patient. H.R. 1038 provides for a period of up to 36 months of market exclusivity for the first approved interchangeable product, during which time the agency is precluded from approving a second interchangeable product. H.R. 1038 requires the FDA to establish requirements for the efficient review, approval, suspension, and revocation of comparable biological product applications. The bill sets forth provisions governing patent infringement claims against an applicant or prospective applicant for a comparable biological product license. H.R. 1038 was referred to the Committee on Energy and Commerce and to the Judiciary Committee.

H.R. 1956 (Inslee), the Patient Protection and Innovative Biologic Medicines Act of 2007, was introduced on April 19, 2007. The bill would amend section 351 of the PHS Act to provide for the approval of similar biological products. The bill would allow any person to submit an application to the FDA for approval of a biologics license for a biological product that is to be similar to an already approved biological product (the reference product). The application would be approved only if (1) the applicant demonstrates that the similar biological product conforms to the applicable final product-class specific guidance and, on the basis of the data submitted in conformance with such guidance, the FDA concludes the product is safe, pure, and potent; (2) the facility in which the similar biological product is manufactured, processed, packed, or held meets standards designed to ensure that the biological product continues to be safe, pure, and potent; and (3) the applicant consents to the inspection of the manufacturing facility.

H.R. 1956 would allow FDA approval of an application submitted for a similar biological product (1) only for indications for which the reference product is approved and (2) only if, with respect to each such indication, the application conforms to the applicable final product-class specific guidance, and on the basis of

non-clinical and clinical data submitted regarding such indication, the FDA concludes the product is safe, pure, and potent.

H.R. 1956 would not allow the FDA to designate a similar biological product as therapeutically equivalent to the reference product. Two years after enactment, and every two years thereafter, the bill would require that a report be submitted to Congress making recommendations on (1) whether it is feasible, in the current state of scientific and technical knowledge, to make therapeutic equivalence determinations for similar biological products, and (2) if so, the statutory criteria that should govern such determinations.

H.R. 1956 would not allow an application for a similar biological product to be submitted to the FDA unless (1) the FDA has published final product-class specific guidance applicable to the reference product and (2) not less than 12 years have elapsed from the date on which the reference product was approved or licensed. Under the bill, approval of an application would not be effective until at least 14 years after the date the reference product was approved or licensed. Approval would not be effective until 15 years after the reference product was approved or licensed if (1) during the 12-year period following the approval or licensing of the reference product, the FDA approves a supplement to the new drug or biologics license application for the reference product that seeks approval to market the reference product for a new indication and (2) the new indication provides a significant clinical benefit in comparison with existing therapies. The bill would allow any person to submit a request to the FDA for the issuance of product-class specific guidance, and the bill provides specific requirements on the issuance of such guidance documents.

S. 1505 (Gregg), the Affordable Biologics for Consumers Act of 2007, was introduced on May 24, 2007. S. 1505 was referred to the Senate Committee on Health, Education, Labor, and Pensions. The bill would amend section 351 of the PHS Act to provide for the approval of biosimilars. S. 1505 would allow any person to submit an application to the FDA for approval of a biologics license for a biosimilar that is to be similar to an already approved biotechnology-derived therapeutic biological product (the reference product). The application would be approved only if (1) the applicant demonstrates that the biosimilar conforms to the applicable final product class-specific rule and, on the basis of the data submitted in conformance with such rule, the FDA concludes the product is safe, pure, and potent; (2) the applicant demonstrates that the biosimilar is as similar to the reference product as may be achieved given the state of scientific knowledge and technology capabilities at the time of submission of the application; (3) the applicant demonstrates that the biosimilar has the same route of administration, dosage form, mechanism of action, and strength as the reference product; (4) the facility in which the biosimilar is manufactured, processed, packed, or held meets standards designed to ensure that the biological product continues to be safe, pure, and potent; and (5) the applicant consents to the inspection of the manufacturing facility.

S. 1505 would allow FDA approval of an application submitted for a biosimilar (1) only for indications for which the reference product is approved; (2) only if, with respect to each such indication, the application conforms to the applicable final product class-specific rule, and on the basis of non-clinical and clinical data submitted regarding such indication, the FDA concludes the product is safe, pure, and

potent; and (3) only if the applicant agrees to provide to the FDA, on an ongoing basis, all written documents it prepares for any purpose (including any patent litigation) that characterizes the difference between the biosimilar and the reference product.

S. 1505 would not allow the FDA to designate a biosimilar as interchangeable with (or therapeutically equivalent to) the applicable reference product. Two years after enactment, and every two years thereafter, the bill would require an assessment of the state of scientific and technical knowledge regarding the ability of the FDA to make a determination that a biosimilar is interchangeable with (or therapeutically equivalent to) a reference product on a product class basis. If the assessment finds that the state of scientific and technical knowledge enables the FDA to make a determination of interchangeability (or therapeutic equivalence) with respect to one or more product classes, a report would be submitted to Congress that describes such findings and recommendations for statutory criteria that should govern such a determination.

S. 1505 would not allow an application for a biosimilar to be submitted to the FDA unless (1) the FDA has published a final product class-specific rule applicable to the reference product and (2) not less than 12 years have elapsed from the date on which the reference product was approved or licensed. Approval would not be effective until at least 14 years after the date on which the reference product was approved or licensed. Approval would not be made effective until at least 16 years after the reference product was approved or licensed if (1) during the 12-year period following the approval or licensing of the reference product, the FDA approves a supplement to the new drug or biologics license application for the reference product that seeks approval to market the reference product for a new indication and (2) the new indication provides a significant clinical benefit. The bill would allow any person to submit a request to the FDA for the issuance of a product class-specific rule, and the bill provides specific requirements on the issuance of such a rule.