Proposed FDA User Fee Acts: Generic Drug User Fee Amendments of 2012 (GDUFA) and Biosimilar User Fee Act of 2012 (BSUFA)

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May 18, 2012

Congressional Research Service
7-....
www.crs.gov
R42540

Summary

Congress is considering two new user fee authorities to supplement funding appropriated by Congress to FDA: the Generic Drug User Fee Amendments of 2012 (GDUFA), for activities related to human generic drug review, and the Biosimilar User Fee Act of 2012 (BSUFA), for biosimilar biological product review. A generic drug is identical to a brand-name (innovator) drug in dosage form and strength, route of administration, safety, effectiveness, and intended use. A biosimilar is a biological product that is highly similar to an innovator biological product. A biological product, or biologic, is a preparation, such as a drug or a vaccine, that is made from living organisms. In contrast to the relatively simple structure and manufacture of chemical drugs, biosimilars, with their more complex nature and method of manufacture, will not be identical to the brand-name product, but may instead be shown to be highly similar.

S. 3187 and H.R. 5651 include GDUFA and BSUFA titles in legislative packages that also include the reauthorization of prescription drug (PDUFA) and medical device (MDUFA) user fee authorities, as well as other medical-product provisions. Because current PDUFA and MDUFA authorities sunset on October 1, 2012, leadership of both the Senate Committee on Health, Education, Labor, and Pensions and the House Committee on Energy and Commerce have aimed for passage of the legislation enough before then to avoid disruption of FDA drug and device application review and postmarket safety activities. The proposed five-year authorities for GDUFA and BSUFA build on the model that has evolved since 1992 with the original PDUFA. User fees make up 36% of the overall FY2012 FDA budget, with percentages varying across the agency's programs.

Each new user fee proposal consists of two parts: legislative language and an FDA-negotiated agreement with relevant industry groups. The GDUFA bill language specifies the types of fees, amount of revenue authorized to be collected, and a broad definition of activities on which FDA may use that revenue. It refers to a required FDA-industry agreement that lays out performance goals and procedures. The legislative language would authorize FDA to collect $299 million in generic drug user fees per year. For the first year of this authority, $50 million of total collections would come from fees for currently pending applications. To ensure that generic drug user fee revenue supplements, rather than replaces, congressionally appropriated funds, the bill would require that (1) each year's appropriations bill include at least the same level of non-user fee appropriations, adjusted for inflation, as in FY2009 for overall FDA salaries and expenses, and (2) the Secretary allocate at least $97 million, excluding fees and adjusted for inflation, each year for specified human generic drug activities. FDA commitments outlined in the agreement include specified timetables for the review of, and action on, the various types of submissions; risk-based inspections of foreign and domestic generic drug facilities; and regulatory science initiatives.

The BSUFA proposal would require the collection of six types of fees from the regulated industry, which is composed primarily of biotechnology and pharmaceutical companies. Fee amounts would be based on inflation-adjusted PDUFA fee amounts for each fiscal year. Because there are no currently marketed biosimilar biological products, the proposal includes fees for products in the development phase to generate fee revenue for the new program and to enable companies to have meetings with FDA in the early development of biosimilar biological products. Both the legislative language and the performance goals document state that the agency goals are contingent on, in addition to user fees, the allocation for each fiscal year of at least $20 million (inflation adjusted value) in non-user fee funds to support the review of biosimilar biological product applications.

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Introduction

Congress is now considering legislation that would add two new Food and Drug Administration (FDA) user fee programs:

- Generic Drug User Fee Amendments of 2012 (GDUFA) and
- Biosimilar User Fee Act of 2012 (BSUFA).

In January 2012, Secretary Kathleen Sebelius of the Department of Health and Human Services (HHS) submitted the GDUFA and BSUFA proposals to the Senate Committee on Health, Education, Labor, and Pensions and the House Committee on Energy and Commerce.[1] With the Prescription Drug User Fee Act (PDUFA) in 1992, Congress authorized FDA to collect user fees from the manufacturers of brand-name prescription drugs and biological products and to use the revenue for specified activities.[2] PDUFA became possible when FDA, industry, and Congress agreed on two concepts: (1) *performance goals*—FDA would commit to performance goals it would negotiate with industry that set target completion times for various review processes; and (2) *use of fees*—the revenue from prescription drug user fees would be used only for activities to support the review of human drug applications and would supplement—rather than replace—funding that Congress appropriated to FDA. The added resources from user fees allowed FDA to increase staff to review what was then a backlog of new drug applications and to reduce median standard application review time from 27 months in FY1993 to 12 months in FY1998. For priority applications, median review time decreased from 21 months in FY1993 to 6 months in FY1998.[3] Over the years, Congress has added similar authority regarding medical devices and animal drugs.[4] User fees make up 35% of the FY2012 FDA budget. Their contribution to FDA's human drug program is larger at 51%.[5]

Following the precedent set by PDUFA and taken up in other FDA user fee programs, the two new programs would include both (1) legislation and (2) performance goals agreements

[1] Food and Drug Administration (FDA), "FDA completes work on three drug user fee programs," FDA News Release, January 13, 2012, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm287723.htm; the proposed "Generic Drug User Fee Amendments of 2012," http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrug%20UserFees/UCM287735.pdf; and "DRAFT Generic Drug User Fee Act Program Performance Goals and Procedures," http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf.

[2] The Prescription Drug User Fee Act (PDUFA) and its reauthorizations are in P.L. 102-571, P.L. 105-115, P.L. 107-188, and P.L. 110-85. For discussions of PDUFA, see CRS Report R42366, *Prescription Drug User Fee Act (PDUFA): Issues for Reauthorization (PDUFA V) in 2012*, and CRS Report RL33914, *The Prescription Drug User Fee Act: History Through the 2007 PDUFA IV Reauthorization*, both by (name redacted).

[3] Data previously available from FDA, "CDER Approval Times for Priority and Standard NDAs and BLAs, Calendar Years 1993-2006, updated through 12/31/2006," http://www.fda.gov/cder/rdmt/NDAapps93-06.htm. FDA presented similar numbers in 2011; see John K. Jenkins, Director, Office of New Drugs, Center for Drug Evaluation and Research (CDER), FDA, "CDER New Drug Review: 2011 Update," presentation at FDA/CMS Summit, December 8, 2011, slide 18, http://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm282984.pdf.

[4] The Medical Device User Fee Act (MDUFA) and its reauthorization are in P.L. 107-250 and P.L. 110-85. The Animal Drugs User Fee Act is in P.L. 108-130, and the Animal Generic Drugs User Fee Act is in P.L. 110-316. For discussions of these user fee programs, see CRS Report R42508, *The FDA Medical Device User Fee Program*, by (name reda cted), and CRS Report RL34459, *Animal Drug User Fee Programs*, by (name redacted).

[5] CRS Report R41964, *Agriculture and Related Agencies: FY2012 Appropriations*, coordinated by (name redacted).

developed with representatives of the regulated industry in consultation with representatives of patients and advocates, academic and science experts, and congressional committees.

For each of the proposed user fee programs, this report will

- present some context for agreement among FDA, Members of Congress, industry groups, and patient groups that a user fee program to supplement appropriations provided by Congress would be beneficial;
- summarize the legislative language that HHS has submitted to the congressional authorizing committees; and
- summarize the FDA-industry agreement on performance goals and procedures, also submitted by the HHS Secretary.

Because authorization for FDA to collect fees and use the fee revenue under PDUFA and the Medical Device User Fee Act (MDUFA) expires on October 1, 2012, the bipartisan leadership of both the Senate Committee on Health, Education, Labor, and Pensions and the House Committee on Energy and Commerce have voiced the need to reauthorize those programs before then to avoid disruption of FDA drug and device application review and postmarket safety activities. The Senate Committee reported S. 2516, the Food and Drug Administration Safety and Innovation Act,[6] and Senator Harkin introduced S. 3187,[7] an amended version of S. 2516, that is scheduled for floor consideration. The House Committee voted favorably to report H.R. 5651, the Food and Drug Administration Reform Act of 2012.[8] Both bills include the GDUFA and BSUFA provisions (as Titles III and IV).

The GDUFA provisions in S. 3187, H.R. 5651, and the HHS-proposed legislative language differ in minimal technical ways and in one reporting requirement.[9] The BSUFA provisions in S. 3187 and H.R. 5651 are essentially identical and differ from the HHS proposal in only minor technical details. GDUFA would add new FFDCA Sections 744A, 744B, and 744C, and BSUFA would add new FFDCA Sections 744G, 744H, and 744I.

Generic Drugs

What Are Generic Drugs?

The FDA website describes a generic drug as "identical—or bioequivalent—to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use."[10] In a new drug application (NDA) to FDA, the sponsor of an innovator (brand-

[6] The Senate Committee on Health, Education, Labor, and Pensions marked up and approved the bill on April 25, 2012; Senator Harkin reported S. 2516 to the Senate on May 7, 2012.

[7] Senator Harkin introduced S. 3187, the Food and Drug Administration Safety and Innovation Act, on May 15, 2012. It is scheduled for Senate floor consideration and debate on May 21, 2012.

[8] The Subcommittee on Health of the House Committee on Energy and Commerce marked up and approved the bill on May 8, 2012, and the full Committee marked up and passed H.R. 5651 on May 10, 2012.

[9] Within the GDUFA provisions, the House bill added regulatory science accountability metrics to the topics that the Secretary would be required to cover in annual performance reports to Congress.

[10] FDA, "What Are Generic Drugs?" http://www.fda.gov/Drugs/ResourcesForYou/Consumers/
(continued...)

name) drug must submit to FDA clinical data to support its claim that the drug is safe and effective for its intended use.[11] The Drug Price Competition and Patent Term Restoration Act of 1984 (P.L. 98-417, known as the Hatch-Waxman Act)[12] allows a generic drug manufacturer to submit an abbreviated NDA (ANDA). The ANDA references the detailed scientific and clinical data the innovator company had developed and which FDA has already reviewed. The generic applicant must "scientifically demonstrate that their product is bioequivalent (i.e., performs in the same manner as the innovator drug)."[13] Without the cost of years of clinical trials, generic sponsors face much lower drug development costs than do innovators. More than 70% of prescriptions filled in the United States are dispensed as generic products.[14] However, the generic drugs account for a much smaller percentage of spending on prescription drugs because generic retail prices are about 25% of their brand-name counterparts.[15]

The GDUFA Proposal

Current law does not authorize FDA to collect user fees from manufacturers of generic drugs. In March 2012, median review time for generic drug applications was approximately 31 months; the backlog included over 2,500 applications.[16] Since its FY2008 budget request to Congress,[17] FDA under various administrations has included a proposed generic drug user fee in its annual request to the congressional appropriations committees. In January 2012, HHS submitted a formal proposal to Congress for generic user fee authority.

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BuyingUsingMedicineSafely/UnderstandingGenericDrugs/default.htm?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=understanding generic drugs&utm_content=1/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/default.htm?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=understanding generic drugs&utm_content=1.

[11] For a description of the new drug application and approval process see CRS Report R41983, *How FDA Approves Drugs and Regulates Their Safety and Effectiveness*, by (name redacted).

[12] Several CRS reports discuss the history and current status of the Hatch-Waxman Act. See, for example, CRS Report R41114, *The Hatch-Waxman Act: A Quarter Century Later*, by (name redacted) and (name redacted).

[13] FDA, "Abbreviated New Drug Application (ANDA): Generics," http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/default.htm.

[14] Remarks as Delivered of Margaret A. Hamburg, M.D., Commissioner of Food and Drugs, Generic Pharmaceutical Association (GPhA) Annual Meeting, Orlando, Florida, February 18, 2011, http://www.fda.gov/NewsEvents/Speeches/ucm244201.htm. The Government Accountability Office (GAO) noted that about 78% of drugs dispensed in "retail settings" were generics (GAO, *Drug Pricing: Research on Savings from Generic Drug Use*, January 31, 2012, http://www.gao.gov/assets/590/588064.pdf).

[15] GAO, *Drug Pricing: Research on Savings from Generic Drug Use*, January 31, 2012, http://www.gao.gov/assets/590/588064.pdf.

[16] Statement of Janet Woodcock, M.D., Director, CDER, FDA, before the Committee on Health, Education, Labor, and Pensions, United States Senate, "FDA User Fee Agreements: Strengthening FDA and the Medical Products Industry for the Benefit of Patients," March 29, 2012, http://www.fda.gov/NewsEvents/Testimony/ucm297390.htm. Dr. Woodcock referred to the resources needed because of the number and logistical complexity of generic and ingredient facility inspections. Each year, FDA receives approximately 100 NDAs and 800-900 ANDAs (Remarks as Delivered of Margaret A. Hamburg, M.D., Commissioner of Food and Drugs, GPhA Annual Meeting, Orlando, Florida, February 18, 2011, http://www.fda.gov/NewsEvents/Speeches/ucm244201.htm).

[17] The FY2008 budget request for FDA included proposed generic drug user fees in a table (http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/BudgetReports/2008FDABudgetSummary/ucm122804.htm) and in narrative ("Improving Generic Drug Review Performance," http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/BudgetReports/2008FDABudgetSummary/ucm122189.pdf.

The HHS GDUFA proposal reflects negotiations with industry groups in consultation with consumer groups. FDA held the first of five GDUFA public meetings in September 2010.[18] It held 17 negotiation sessions with representatives of the Generic Pharmaceutical Association, the Bulk Pharmaceutical Task Force of the Society of Chemical Manufacturers and Affiliates, and the European Fine Chemicals Group between February 28, 2011, and September 9, 2011, when it announced a ratified agreement.[19]

The proposal has many conceptual similarities to PDUFA but also includes provisions that reflect components and activities of the generic drug industry and FDA's regulatory approach to generic drugs. The proposal consists of two parts: (1) the draft legislative language and (2) a goals and procedure agreement between FDA and the industry. This is the framework first established for the prescription drug user fee program. The law specifies types of fees, amount of revenue authorized to be collected, and a broad definition of activities on which FDA may use that revenue. The law also refers to the FDA-industry agreement for performance goals and procedures that the fees will support. Tables in **Appendix A** provide detail of the provisions in the proposed legislative language and the FDA-industry agreement. The next two sections of this report provide an overview of those documents.

Proposed GDUFA Legislative Language

The proposal to Congress would authorize FDA to collect $299 million each year from FY2013 through FY2017 in fees from the generic drug industry and provides formulas for calculating inflation adjustments for the years after FY2013. For the first year of the program, $50 million of the $299 million would come from a *one-time backlog fee* to be paid by sponsors of currently pending applications. The fee types that would begin in the first year and continue in subsequent years and their percentage of total GDUFA collections are the

- drug master file (DMF) fee, 6%;
- abbreviated NDA (ANDA) and prior approval supplement (PAS) fee, 24%;
- generic drug facility fee, 56%; and
- active pharmaceutical ingredient (API) facility fee, 14%.

[18] See FDA, "GDUF Public Meetings and Updates," http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm256661.htm.

[19] Minutes of the FDA and industry meetings are at FDA, "GDUF Negotiation Sessions; FDA-Industry Generic Drug User Fee (GDUF) Negotiations Meeting Minutes," http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm256662.htm.

Key Terms in the 2012 GDUFA Proposal

A ***drug master file (DMF)*** is "a submission of information to the FDA to permit the FDA to review this information in support of a third party's submission without revealing the information to the third party" (Arthur B. Shaw, "Drug Master Files," http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/Small BusinessAssistance/UCM279666.pdf). It "may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs" (FDA, "Drug Master Files: Guidelines," http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122886.htm).

A ***prior approval supplement (PAS)*** is the document a holder of an NDA or an ANDA must submit to FDA when requesting a major change, one "that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product" in an approved product. The sponsor must receive FDA approval of the change before introducing the changed product into commerce (FDA, "Guidance for Industry: Changes to an Approved NDA or ANDA," Center for Drug Evaluation and Research, April 2004, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatory Information/Guidances/UCM077097.pdf).

An ***active pharmaceutical ingredient (API)*** is "[a]ny substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body" (FDA, "Guidance for Industry: Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients," Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research, August 2001, http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm129098.pdf).

Like PDUFA, the GDUFA proposal includes limitations, often referred to as triggers, designed to ensure that fees supplement rather than replace congressional appropriations. These require that budget authority (appropriations minus fees) go no lower than the FY2009 amounts, adjusted for inflation, for (1) FDA salaries and expenses overall and (2) human generic drug activities. Again similar to PDUFA, but different from the narrower MDUFA and BSUFA definitions, the GDUFA proposal defines human generic drug activities to include the review of submissions and drug master files, approval letters and complete response letters, letters regarding deficiencies, inspections, monitoring or research, postmarket safety activities, and regulatory science.

Other provisions include risk-based biennial inspections, parity of domestic and foreign inspection schedules by FY2017, a $15,000–$30,000 higher inspection fee for a foreign facility than for a domestic facility to reflect cost differences, streamlined hiring authority, and required annual performance and fiscal reports. The generic drug user fee authority would cease to be effective October 1, 2017.

Proposed GDUFA FDA-Industry Agreement

The Agreement begins with an overview of the "overall program scope, assumptions, and aspirations." It then summarizes major program goals over the five-year authorization period to include that FDA will review and act on 90% of complete electronic ANDAs within 10 months of submission; review and act on 90% of all pending applications, amendments, and supplements by the end of FY2017; and commit to risk-adjusted inspections, efficiency enhancements, regulatory science initiatives, and metric goals.

Thirteen topics are listed for a FY2013 regulatory science plan and the Agreement refers to a working group that will recommend areas in which FDA could issue draft guidances to clarify agency recommendations regarding complex product development.

Biosimilar Products

What Are Biosimilars?

A biosimilar is a biological product that is highly similar to a brand-name (innovator) biological product made by a pharmaceutical or biotechnology company.[20] A biological product, or biologic, is a preparation, such as a drug or a vaccine, that is made from living organisms. In contrast to the relatively simple structure and manufacture of chemical drugs, biosimilars, with their more complex nature and method of manufacture, will not be identical to the brand-name product, but may instead be shown to be highly similar.

The biotechnology industry began developing its first biologics for use as human therapeutic agents in the late 1970s and early 1980s. The first FDA approval of a biotechnology drug for human use, human insulin, occurred in 1982. Others followed, including 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 share of the drugs sold by the pharmaceutical industry to U.S. consumers. However, with no parallel to the generic alternatives for chemical drugs, the cost of therapeutic biologics is often prohibitively high for individual patients. For example, the costs per year (in 2009) of some commonly used biologic drugs are reported as follows: Enbrel for rheumatoid arthritis, $26,000; Herceptin for breast cancer, $37,000; Rebif for multiple sclerosis, $40,000; Humira for Crohn's disease, $51,000; and Cerezyme for Gaucher's disease, $200,000.[21]

Biological products are, in general, regulated—licensed for marketing—under the Public Health Service (PHS) Act, and chemical drugs are regulated—approved for marketing—under the Federal Food, Drug, and Cosmetic Act (FFDCA). The Drug Price Competition and Patent Term Restoration Act of 1984 (P.L. 98-417), often referred to as the Hatch-Waxman Act, provided a mechanism for the approval of generic drugs under the FFDCA but not under the PHS Act.[22]

On March 23, 2010, President Obama signed into law a comprehensive health care reform bill, the Patient Protection and Affordable Care Act (PPACA; P.L. 111-148). Title VII of PPACA, the Biologics Price Competition and Innovation Act of 2009 (BPCIA), established a new regulatory authority within the FDA by creating a licensure pathway for biosimilars analogous to that which allowed for the approval of generic chemical drugs via the Hatch-Waxman Act. Under the new pathway, a biosimilar may be approved by demonstrating that it is highly similar to a biological product that is already allowed on the market by FDA. The BPCIA also authorized FDA to collect associated user fees.

[20] There are no clinically meaningful differences between a biosimilar and the brand-name (also referred to as innovator) biological product in terms of the safety, purity, and potency of the product. Although a biosimilar or follow-on biologic is sometimes referred to as a biogeneric or generic biologic, the FDA and many others consider use of the word *generic* to be inaccurate because the term generic in the context of chemical drugs means identical and a biosimilar is not identical to the brand-name product. The FDA often uses the term *follow-on protein product*, because many biologics are proteins.

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

[22] For additional information about the Hatch-Waxman Act, see CRS Report R41114, *The Hatch-Waxman Act: A Quarter Century Later*, by (name redacted) and (name redacted).

The BSUFA Proposal

In May 2011, FDA requested public input on the development of a biosimilars user fee program.[23] The agency conducted a series of ten negotiation sessions with industry representatives.[24] It also conducted two meetings with public stakeholders, composed of patient advocacy groups and societies of health professionals. Minutes of these meetings are posted on the agency's website.[25] The recommendations for a new biosimilars user fee program, released on January 13, 2012, were modeled after the prescription drug user fee (PDUFA) program.[26]The recommendations are composed of legislative language and the FDA-industry agreement on performance goals and procedures. Both the legislative language and the performance goals document state that the agency goals are contingent on the allocation for each fiscal year of at least $20 million (inflation adjusted value) in non-user fee funds, plus user fees, to support the review of biosimilar biological product applications. Tables in **Appendix B** provide detail of the provisions in the proposed legislative language and the FDA-industry agreement. The next two sections of this report provide an overview of those documents.

Proposed BSUFA Legislative Language

The proposal to Congress for the biosimilars user fee program would require the collection of six types of fees from industry. Fee amounts would be based on inflation-adjusted PDUFA fee amounts for each fiscal year. There are some unique features of the biosimilars user fee proposal. Because there are currently no marketed biosimilar biological products, the proposal includes fees for products in the development phase to generate fee revenue for the new program and to enable companies to have meetings with FDA in the early development of biosimilar biological products.[27] A company may choose to discontinue participation in the biosimilar biological product development program but must pay a reactivation fee to resume further product development with FDA. The proposed BSUFA fees are

- initial biosimilar biological product development fee, 10% of the PDUFA human drug application fee;
- annual biosimilar biological product development fee, 10% of the human drug application fee;
- reactivation fee, 20% of the human drug application fee;

[23] FDA, "FDA requests input on development of user fee program for biosimilar and interchangeable biological products," press release, May 9, 2011, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm254572.htm.

[24] Those present include representatives from companies such as MedImmune, Teva, Pfizer, Merck, Mylan, Sandoz/Novartis, Amgen, Hospira, Watson, Apotex, Momenta, and Shire HGT. Also present were representatives of the Biotechnology Industry Organization (BIO), the Pharmaceutical Manufacturers Association (PhRMA), and the Generic Pharmaceutical Association (GPhA).

[25] FDA, Biosimilar and Interchangeable Products User Fee Meetings, at http://www.fda.gov/ForIndustry/UserFees/ucm268124.htm.

[26] FDA, "FDA completes work on three drug user fee programs," press release, January 13, 2012, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm287723.htm.

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

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

The proposed legislative language would allow for the waiver of the biosimilar biological product application fee for the first such application from a small business. A "small business" is defined as an entity with fewer than 500 employees, including affiliates, that does not have a drug product that has been approved under a human drug or biosimilar biological application and introduced or delivered for introduction into commerce. The biosimilars user fee authority would cease to be effective October 1, 2017.

Proposed BSUFA FDA-Industry Agreement

The Agreement delineates proposed performance goals for the review of biosimilar applications by the agency. FDA is to review and act on a targeted percentage of original biosimilar biological product applications within 10 months of receipt and resubmitted applications within 6 months; in both cases, performance targets will start at 70% in FY2013 and rise to 90% in FY2017. FDA is to review and act on 90% of original supplements within 10 months, 90% of resubmitted supplements within 6 months, and 90% of manufacturing supplements within 6 months.

Aside from definitions, the Agreement also covers several other topics including clinical holds, major dispute resolution, special protocol assessment, meeting management, and review of proprietary names to reduce medication errors.

Appendix A. Generic Drug User Fee Proposal

Table A-1. HHS-Proposed Legislative Language: The Generic Drug User Fee Amendments of 2012

Main Issue	HHS-Proposed Language[a]
FFDCA Sec. 744G. Regarding the Authority to Assess and Use Human Generic Drug Fees	
(a) Types of fees	GDUFA would establish three ongoing types of fees—drug master file (DMF), application filing (abbreviated new drug application (ANDA) and prior approval supplement (PAS)), and facility (generic drug (GDF) and active pharmaceutical ingredient (API)). It would also establish a one-time backlog fee.
(a)(1) One time backlog fee	Each person that owns a pending ANDA on 10/1/2012 (when GDUFA would become effective) that has not yet received tentative approval would be required to pay a one-time backlog fee. Backlog fees would total $50 million divided by the number of pending ANDAs.
(a)(2) Drug Master File fee	Each person that owns a Type II ("Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation, or Drug Product") active pharmaceutical ingredient (API) master file that is "referenced ... in a generic drug submission by any initial letter of authorization" would be required to pay a drug master file fee. This fee would be paid only the first time the drug master file is referenced. This paragraph also includes requirements for (1) the Secretary to publish fees, (2) when the master file would be available for reference, and (3) fee due dates.
(a)(3) Abbreviated new drug application (ANDA) and Prior Approval Supplement (PAS) filing fee	Each applicant that submits an abbreviated new drug application would be required to pay a fee. Each applicant that submits a prior approval supplement to an ANDA would be required to pay a fee. This paragraph also includes requirements for (1) the Secretary to publish fees, (2) fee due dates, (3) refund conditions, (4) resubmission fees in specified circumstances, and (5) fee for API information not included by reference to Type II API drug master file.
(a)(4) Generic drug facility fee and active pharmaceutical ingredient (API) facility fee	Each person who owns a facility identified or intended to be identified in at least one approved or pending generic drug submission would be required to pay an annual fee. Each person who owns a facility that produces or which is pending review to produce one or more APIs identified or intended to be identified in at least one approved or pending generic drug submission would be required to pay an annual fee. Each person who owns a facility that meets both sets of criteria would be required to pay both fees. This paragraph also includes requirements for (1) the Secretary to publish fees and (2) fee due dates.
(b) Fee revenue amounts	The total estimated revenue for all fees for FY2013 would be $299 million, of which $50 million would be from the one-time backlog fee for pending applications. For FY2014 through FY2017, the total estimated revenue for the continuing fees would be $299 million. Other than the one-time backlog fee, the relative proportion of each fee to the total annual amount would be: 6% from drug master file fees; 24% from ANDA and prior approval supplement fees; 56% from generic drug facility fees; and 14% from API facility fees. The fee for facilities located outside the United States would be $15,000-$30,000 higher than fees for facilities located in the United States, based on the difference in the cost of inspections as determined by the Secretary.

Main Issue	HHS-Proposed Language[a]
(c)(1) Inflation adjustment	Each year, the Secretary would adjust the total revenues for inflation, as follows: The sum of one plus— the average change in the personnel compensation cost per full-time equivalent FDA position for the first three of the preceding four fiscal years multiplied by the proportion of such costs to total costs of human generic drug activities for those years; and the average change in the Consumer Price Index (CPI) for urban consumers in Washington-Baltimore, DC-MD-VA-WV for the first three years of the preceding four years of available data multiplied by the proportion of all costs other than personnel compensation and benefits to total costs of human generic drug activities for the first three years of the preceding four fiscal years. These adjustments would be added on a compounded basis each fiscal year.
(c)(2) Final year adjustment	The Secretary would be authorized to increase total fee revenue if necessary to provide for up to three months of operating reserves for the process of human generic drug activities for the first three months of FY2018 if adequate carryover balances are not available.
(d) Annual fee setting	Based on revenue amounts established by the Act, the Secretary would be required to establish for FY2013: (1) by October 12, 2012, the one-time generic drug backlog fee for pending applications, the drug master file fee, the ANDA fee, and the prior approval supplement fee; and (2) within 45 days of the date to comply with the requirement for identification of facilities, the generic drug facility fee and the API facility fee; and For subsequent years, the Secretary would be required to establish the various fees 60 days before the start of each fiscal year based on revenue amounts and adjustments provided in the Act.
(e) Limit	The total amount of fees charged, as adjusted under subsection (c), for a fiscal year may not exceed the total costs for such fiscal year for the resources allocated for human generic drug activities.
(f) Identification of facilities	The Secretary would be required, by October 1, 2012, to publish in the Federal Register a notice of the requirement to facility owners to identify certain facilities or sites. The owners would be required to comply within 60 calendar days of that notice. Each owner would be required to submit, update, or reconfirm the required information before June 1 of each subsequent fiscal year. The Secretary would specify the format and type of information required, which would include "identification of a facility identified or intended to be identified in an approved or pending generic drug submission." Other required information includes whether the facility manufactures APIs and/or finished dosage forms and questions about its location, positron emission tomography drug manufacture, and whether it manufactures drugs that are not generic drugs. Any owner or operator of a site identified in a generic drug submission in which a bioanalytical study is conducted, or a clinical research organization, a contract analytical testing site, or a contract repackager site, would be required to provide ownership, name, and site address information to the Secretary, whose "inspectional authority shall extend to all such sites."
(g) Effect of failure to pay fees	This paragraph describes the effects of failure to pay fees that would be established by this section. Examples: the Secretary would not receive an ANDA from a person or affiliate of that person until that person pays the outstanding one-time backlog fee were paid; and all drugs or APIs manufactured in a facility with an outstanding fee would be deemed misbranded.
(h) Limitations	If appropriations for FDA salaries and expenses for a fiscal year were not at least the amount for FY2009 excluding fees for that year, adjusted as described in this section, the fees must be refunded. The Secretary would be authorized to assess fees (other than the one-time backlog fees) after the start of a fiscal year rather than at its start.

Main Issue	HHS-Proposed Language[a]
(i) Crediting and availability of fees	This section would authorize fee collection and obligation only in the amount provided in advance in appropriations acts. Fees would remain available until expended and would be available only for human generic drug activities. Paragraph (m)(8) would define such activities as follows: Human generic drug activities means the following activities of the Secretary associated with generic drugs and inspection of facilities associated with generic drugs: (A) The activities necessary for the review of generic drug submissions, including review of drug master files referenced in such submissions. (B) The issuance of approval letters which approve abbreviated new drug applications or supplements to such applications or complete response letters which set forth in detail the specific deficiencies in such applications and, where appropriate, the actions necessary to place such applications in condition for approval. (C) The issuance of letters related to Type II active pharmaceutical drug master files which set forth in detail the specific deficiencies in such submissions and, where appropriate, the actions necessary to resolve those deficiencies or, if appropriate, document that no deficiencies need to be addressed. (D) Inspections related to generic drugs. (E) Monitoring of research conducted in connection with the review of generic drug submissions and drug master files. (Paragraph (m)(8) definition, continued) (F) Postmarket safety activities with respect to drugs approved under abbreviated new drug applications or supplements, including the following activities: (i) Collecting, developing, and reviewing safety information on approved drugs, including adverse event reports. (ii) Developing and using improved adverse-event data-collection systems, including information technology systems. (iii) Developing and using improved analytical tools to assess potential safety problems, including access to external data bases. (iv) Implementing and enforcing Section 505(o) [21 USC §355(o)] (relating to postapproval studies and clinical trials and labeling changes) and Section 505(p) [21 USC §355(p)] (relating to risk evaluation and mitigation strategies) insofar as those activities relate to abbreviated new drug applications. (v) Carrying out Section 505(k)(5) [21 USC §355(k)(5)] (relating to adverse event reports and postmarket safety activities). (G) Regulatory science activities related to generic drugs. The generic drug fees for a fiscal year after FY2012 would only be available if the Secretary allocates no less than $97 million, excluding fees and adjusted for inflation, for specified human generic drug activities. Compliance would include having a total up to 10% below that amount. Until enactment of a FY2013 appropriations act for FDA, FY2013 fees authorized by this section may be collected and credited. The Secretary would be authorized to accept early payment of authorized fees. This section would authorize to be appropriated for each of FY2013 through FY2017 fees according the total revenue amount and adjustments as specified in this section.
(j) Collection of unpaid fees	Any unpaid fee shall be treated as a claim of the United States Government.
(k) Construction	"This section may not be construed to require that" HHS reduce FTE positions of officers, employees, and advisory committee members in other areas to offset those "engaged in human generic drug activities."

Main Issue	HHS-Proposed Language[a]
(l) Positron Emission Tomography Drugs	Fees upon application for a drug or an API and facility fees would not be required for a PET drug or an API for a PET drug. Such facilities would be required to comply with identification requirements.
(m) Definitions	This paragraph would define the terms abbreviated new drug application, active pharmaceutical ingredient, adjustment factor, affiliate, facility, Finished Dosage Form, Generic Drug Submission, human generic drug activities, Prior Approval Supplement, resources allocated for the human generic drug activities, submission, and Type II Pharmaceutical Ingredient Drug Master File.
(n) Disputes concerning fees	A person seeking return of a fee paid in error would be required to submit a written request to the Secretary within 180 calendar days after the fee was paid.
(o) Substantially complete applications	This paragraph would require an ANDA to "be deemed not to have been 'substantially complete'" if it is not received because of failure to pay an applicable fee. If the fee was the only reason, then when the fee is received, the application would be considered substantially complete and received.
FFDCA Sec. 744H. Regarding GDUFA Reauthorization and Reporting Requirements	
(a)(b)(c) Annual performance and fiscal reports	The Secretary would be required to submit to the congressional committees annual performance and fiscal reports, and make them available to the public on the FDA website.
(d) Consultation, public input and review, transmittal of recommendations, minutes of negotiation meetings	The Secretary would be required, in preparation for the reauthorization of GDUFA: –to consult with congressional committees, scientific and academic experts, health-care professionals, representatives of patient and consumer advocacy groups, and the generic drug industry to develop recommendations for GDUFA II, including goals and plans for meeting the goals; –before beginning reauthorization negotiations with the generic drug industry, to seek public input, including a Federal Register notice of a public hearing, a subsequent period for written comments from the public, and publication of those comments on the FDA website; –during negotiations with the generic drug industry, to hold at least monthly discussions with representation of patient and consumer advocacy groups; –after negotiations with the generic drug industry, to present recommendations to Congressional committees, public recommendations in the Federal Register, provide for a public comment period, hold a public meeting, and revise recommendations if necessary after considering such public views and comments; –to transmit the revised recommendations to Congress not later than January 15, 2017, including a summary of the public views and comments and any changes made in response to those views and comments; and –before presenting reauthorization recommendations to Congress, to make publicly available on the FDA website minutes of all negotiations meetings between FDA and the generic drug industry, including summaries of substantive proposals and significant controversies or differences of opinion and their resolution.
Uncodified and Miscellaneous Provisions	
Sunset dates (uncodified)	The authority to assess and use human generic drug fees would cease to be effective October 1, 2017. [Sec. 104] The reporting requirements would cease to be effective January 18, 2018. [Sec. 104]
Effective date (uncodified)	Provisions would take effect on October 1, 2012 or the date of enactment, except that fees would be assessed for all human generic drug submissions and Type II active pharmaceutical drug master files received on or after October 1, 2012 regardless of the date of enactment. [Sec. 105]

Main Issue	HHS-Proposed Language[a]
FFDCA Sec. 502(aa) Misbranding	This section would add a new subsection FFDCA Section 502(aa) to consider misbranded a drug, an API, or a drug containing an API made in a facility for which fees have not been paid or identifying information that has not been submitted as required by this Act. [Sec. 106]
FFDCA Sec. 745A Electronic submissions	This section would add a new FFDCA Section 745A to require generic drug applications submitted under FFDCA 505(j) to be in electronic format beginning 24 months after the Secretary has issued final guidance. [Sec. 107]
FFDCA Sec. 714 Streamlined hiring	This section would add a new FFDCA Section 714 to authorize the Secretary to appoint employees to FDA positions without regard to competitive service provisions in U.S.C. title 5 if they related to human generic drug activities (as in FFDCA 744G) according to related performance goals. [Sec. 108] This streamlined hiring authority would terminate three years after enactment. [Sec. 108]

Source: CRS adaptation of FDA, "Generic Drug User Fee Amendments of 2012," proposal, http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM287735.pdf.

a. The House bill added regulatory science accountability metrics to the topics that the Secretary would be required to cover in annual performance reports to Congress. Otherwise, the GDUFA provisions in S. 3187, H.R. 5651, and the HHS-proposed legislative language differ in minimal technical, but not substantive, ways.

Table A-2. Performance Goals and Procedures in Agreement Between FDA and Generic Drug Industry Representatives for FY2013 through FY2017 Under the Anticipated GDUFA

Topic	Draft GDUFA Commitments
(1) Overview: Overall Program Scope, Assumptions, and Aspirations	User fee funding would be approximately $299 million annually, adjusted for inflation, and will supplement appropriated funding from Congress. The agreement estimates the numbers per year of ANDAs and PASs submitted, DMFs referenced, and facilities involved. It also notes that there will be no significant changes in the facility inventory, including the foreign-domestic split, over the five-year GDUFA authorization. FDA would have streamlined hiring authority for all GDUFA-related positions. FDA expects the program to begin on October 1, 2012, continue for five years, and be continued after that based on terms to be negotiated. Industry and FDA will populate and maintain necessary databases to support GDUFA. Industry will submit information electronically using standards as specified by FDA or in statute. FDA will try to maintain pre-GDUFA levels of productivity while hiring and training staff to meet performance goals, build necessary systems, and implement program changes as specified in this Agreement. FDA will use a complete review standard. The Agreement lists a series of goals that FDA commits to "aspire to," "expects," "utilize," "work towards," "prioritize," "intend to," "strive to." These relate to timing and extent of communication with industry, performance goals, parity of foreign and domestic facility inspections, risk-based prioritization of inspections, whether to rely on a routine surveillance inspection in lieu of an application-specific inspection, and other topics. FDA agrees to try to meet specific timelines in its review and action on ANDAs and its response to appeals regarding pending ANDAs, amendments and supplements. "Because the agreed generic drug user fee program is intended to be additive to budget appropriations, agreed upon legislative language will require that annual program appropriations from Congress must be equal to or exceed the FDA appropriation for FY 2009." In order to meet performance goals in the Agreement, legislative language will require total GDUFA fees to be made of the following proportions: facility fees 70%, application fees 30%. Overall fees will be divided by industry segments as follows: finished dosage form (FDF) 80% and API 20%. For the first year of the program, a one-time backlog fee for pending ANDAs will generate $50 million of the first year's total GDUFA funding. The Overview section of the Agreement ends with this: "Note: If these assumptions differ significantly from actuality, FDA may not be able to achieve the goals and efficiency enhancements outlined in this goals letter, despite the supplemental funding provided by the program."

Topic	Draft GDUFA Commitments
(1) Overview: Summary of Major Program Goals including Five Year Goals	Application metrics—For Abbreviated New Drug Applications (ANDAs) in the year 5 cohort, FDA will review and act on 90% of complete electronic ANDAs within 10 months after the date of submission. Certain amended applications may have differing metrics as discussed below. Backlog metrics—FDA will review and act on 90% of all ANDAs, ANDA amendments and ANDA prior approval supplements regardless of current review status (whether electronic, paper, or hybrid) pending on October 1, 2012 by the end of FY2017. CGMP Inspection metrics—FDA will conduct risk-adjusted biennial CGMP surveillance inspections of generic API and generic finished dosage form (FDF) manufacturers, with the goal of achieving parity of inspection frequency between foreign and domestic firms in FY2017. Efficiency Enhancements—FDA will implement various efficiency enhancements discussed below on October 1, 2012 or upon enactment of the program, whichever is later. Regulatory Science—FDA will continue, and for some topics begin, undertaking various regulatory science initiatives discussed below on October 1, 2012 or upon enactment of the program, whichever is later, focusing first on the initiatives discussed below and with additional initiatives to be identified with input from an industry working group.
(2) Efficiency enhancements to be undertaken on October 1, 2012, or upon enactment of the program, whichever is later	(A) ANDA Review Efficiency Enhancements. FDA agrees to issue complete response letters (as detailed in the Agreement), rather than discipline specific letters, for all ANDAs; make every reasonable effort to communicate easily correctable deficiencies; schedule teleconferences in specified situations; develop refusal-to-receive standards for various types of submissions; expedite certain Paragraph IV applications; meet other specified performance goals. (B) DMF Review Efficiency Enhancements. FDA agrees to certain activities regarding Type II API DMFs, including issuing a letter detailing all identified deficiencies and other specified items; making every reasonable effort to communicate easily correctable deficiencies, including using telephone information requests; scheduling teleconferences in specified situations; and issuing letters to indicate when a DMF does not have any further open matters. (C) Inspection Efficiency Enhancements. FDA agrees to use a risk-adjusted biennial CGMP surveillance inspection model for inspection of API and FDF manufacturers with goal of achieving parity of foreign and domestic facility inspections by FY2017; prioritize inspections that are the only outstanding requirement for an otherwise approvable ANDA and inspections of facilities that have not yet been inspected; make specified information available to the public on a timely basis; study foreign government regulatory inspections and develop a program to use certain information when appropriate. (D) Other Efficiency Enhancements. FDA agrees to develop or enhance facility databases that the industry will populate. The databases will contain, along with other information, addresses and Data Universal Numbering System (DUNS) numbers, will link facilities to DMFs and ANDAs. FDA agrees to develop a current chemistry manufacturing and controls (CMC) records database and to develop and issue electronic data submission standards. Industry agrees to submit necessary information to FDA in electronic format using specified standards.
(3) Regulatory science initiatives	FDA agrees to convene a working group and consider suggestions from industry and other stakeholders to develop an annual list of regulatory science initiatives for review by the CDER Director.

Topic	Draft GDUFA Commitments
(4) Metric goals /measurements	The Agreement includes specific commitments, including timeframes, from FDA regarding: (a) staff to be hired and trained (for example, FDA will hire and train at least 25% of incremental staff in FY2013); (b) review and action on the various types of submissions, including applications, amendments, and supplements (for example, FDA will review and act on 60% of original ANDA submissions within 15 months from the date of submission for the year 3 cohort); (c) controlled correspondence (for example, FDA will respond to 70% of controlled correspondence in 4 months from date of submission in FY2015); (d) inspections (for example, the goal of achieving parity of inspection frequency between foreign and domestic firms in FY2017); and (e) review and action on backlogged applications, amendments, and supplements (FDA will review and act on all submissions pending on October 1, 2012 by the end of FY2017).
Definitions	The Agreement includes a set of definitions "for the purposes of this goals letter": Act on an application Backlog Closing out a request for a first cycle review teleconference Complete response letter Controlled correspondence Pharmaceutical Ingredient Drug Master File Expedited review of application Finished Dosage Form Generic Drug Program Parity Solicited amendment Prior Approval Supplements Active pharmaceutical ingredient Delaying amendments Cohort Complete review DMF or Type II API DMF Electronic Facility First major deficiency application Major and minor amendments Refuse to receive Submission date Unsolicited amendment

Topic	Draft GDUFA Commitments
FY 2013 Regulatory Science Plan	Topic 1: Bioequivalence of local acting orally inhaled drug products
	Topic 2: Bioequivalence of local acting topical dermatological drug products
	Topic 3: Bioequivalence of local acting gastro-intestinal drug products
	Topic 4: Quality by design of generic drug products
	Topic 5: Modeling and simulation
	Topic 6: Pharmacokinetic studies and evaluation of anti-epileptic drugs
	Topic 7: Excipient effects on permeability and absorption of BCS Class 3 Drugs
	Topic 8: Product- and patient-related factors affecting switchability of drug-device combination products (e.g., orally inhaled and nasal drug products and injection drug products)
	Topic 9: Postmarketing surveillance of generic drug usage patterns and adverse events.
	Topic 10: Evaluation of drug product physical attributes on patient acceptability
	Topic 11: Postmarking assessment of generic drugs and their brand-name counterparts
	Topic 12: Physicochemical characterization of complex drug substances
	Topic 13: Develop a risk-based understanding of potential adverse impacts to drug product quality resulting from changes in API manufacturing and controls.
FY 2014 Regulatory Science Preliminary Topics for Consideration	"In addition to those topics to be identified by the Working Group described in section 3.A of this letter, topics will include recommendations for draft guidances to clarify FDA recommendations with regard to complex product development and to help limit deficiencies in applications."

Source: CRS adaptation of FDA, "DRAFT Generic Drug User Fee Act Program Performance Goals and Procedures," http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf.

Appendix B. Biosimilars User Fee Proposal

Table B-1. HHS-Proposed Statutory Language: The Biosimilars User Fee Act of 2012

Main Issue	HHS-Proposed Language[a]
FFDCA Section 744A. Definitions.	
Definitions	Provides definitions for a number of terms: biosimilar biological product application, biosimilar biological product, supplement, final dosage form, biosimilar biological product establishment, process for the review of biosimilar biological product applications, costs of resources allocated for the process for the review of biosimilar biological product applications, adjustment factor, person, affiliate, biosimilar initial advisory meeting, biosimilar biological product development meeting, financial hold.
FFDCA Section 744B. Authority to Assess and Use Biosimilar Biological Product Fees	
(a) Types of fees	Several types of fees would be assessed and there would be certain exceptions to the collection of such fees.
(a)(1) Biosimilar development program fees	An initial biosimilar biological product development program fee would be assessed for submitting: a request for a biosimilar biological product development meeting; or, an IND application to support a biosimilar biological product application. The fee would be due within 5 days after the request is granted or when the IND application is submitted, whichever is earlier. If an IND was submitted prior to enactment of BSUFA, this fee would be paid within 60 days of enactment or within 5 days after the request for a biosimilar biological product development meeting is granted. An annual biosimilar biological product development program fee would be assessed for each following fiscal year unless: a marketing application for the biological product was accepted for filing; or, participation in the biosimilar biological product development program was discontinued. This fee would be due on the first business day of each fiscal year, or the first business day after enactment of an appropriations act providing for the collection and obligation of such fees. Program participation would be discontinued if notification is submitted by August 1. If no IND application was submitted, written notification of discontinuation would be required. If an IND application was submitted, discontinuation would occur by withdrawing the IND application. If program participation was discontinued, a reactivation fee would be required: within 5 days after a request for a biosimilar biological product development meeting is granted; or, when the IND application is submitted, whichever is earlier. The reactivation fee would be 2X the amount of the initial biosimilar biological product development program fee for that fiscal year. The annual biosimilar biological product development program fee would be paid beginning in the next fiscal year. If the initial or the annual or the reactivation fee is not paid, the biosimilar biological product development meeting would not occur and, except under extraordinary circumstances, the IND application would not be received. Except under extraordinary circumstances, the sponsor of a clinical investigation would be prohibited from continuing the investigation (financial hold). Any biosimilar biological product application or supplement would be incomplete until all fees are paid. There would be no refunds, waivers, exemptions or reductions of initial or annual or reactivation fees.

Main Issue	HHS-Proposed Language[a]
(a)(2) Biosimilar Biological Product Application and Supplement Fee	The fee for a biosimilar biological product application would be equal to the fee for a human drug application fee minus the cumulative amount paid for the following fees regarding the product named in the application: initial biosimilar biological product development program fee, annual biosimilar biological product development program fee, and any reactivation fee. If clinical data are not required, then the fee would be equal to 50% of the fee for a human drug application fee minus the cumulative amount paid for the following fees regarding the product named in the application: initial biosimilar biological product development program fee, annual biosimilar biological product development program fee, and any reactivation fee. The fee for a supplement for which clinical data are required would be equal to 50% of the fee for a human drug application. Fees would be due upon submission of the application; exception applies for previously filed application or supplement that was not approved or was withdrawn. If application is refused for filing or is withdrawn, 75% of the fee would be refunded; the full fee would be required if resubmitted (unless the fee is waived for small business).
(a)(3) Biosimilar Biological Product Establishment Fee	An establishment fee would be assessed for each establishment listed in an approved biosimilar biological product application that manufactures the biosimilar biological product named in the application. The fee would be due the first business day of the fiscal year, or the first business day after enactment of an appropriations Act providing for the collection and obligation of such fees.
(a)(4) Biosimilar Biological Product Fee	An annual fee would be paid each fiscal year by the applicant named in the biosimilar biological product application. The fee would be due the first business day of the fiscal year, or the first business day after enactment of an appropriations Act providing for the collection and obligation of such fees.
(b) Fee amounts	Fee amounts would be based on the adjusted fee amount for each fiscal year as follows: initial biosimilar biological product development program fee, 10% of human drug application fee; annual biosimilar biological product development program fee, 10% of human drug application fee; biosimilar biological product application fee, equal to human drug application fee; biosimilar biological product establishment fee, equal to prescription drug establishment fee; biosimilar biological product fee, equal to prescription drug product fee.
(c)(1) Annual fee setting	The Secretary would, 60 days before the start of each fiscal year that begins after September 30, 2012, establish for the next year, the: initial biosimilar biological product development program fee; annual biosimilar biological product development program fee; biosimilar biological product application fee; biosimilar biological product establishment fee; and biosimilar biological product fee.
(c)(2) Limit	For each fiscal year, the total amount of fees, as adjusted, would not be allowed to exceed the total costs for the resources allocated for the process for the review of biosimilar biological product applications.
(d) Application fee waiver for small business	The Secretary would grant to the sponsor named in a biosimilar biological product application a waiver from the application fee for the first such application that a small business or its affiliate submits for review. "Small business" would be defined as an entity with less than 500 employees, including employees of affiliates, and that does not have a drug product that has been approved under a human drug application (defined in FFDCA §735) or a biosimilar biological application (defined in FFDCA §744A) and introduced or delivered for introduction into interstate commerce.

Main Issue	HHS-Proposed Language[a]
(e) Effect of failure to pay fees	A biosimilar biological product application or supplement to which fees apply would not be considered to be complete and would not be accepted for filing until all fees are paid.
(f) Crediting and availability of fees	This section would authorize fee collection and obligation only in the amount provided in advance in appropriations acts. Fees would remain available until expended and would be available solely for the review of biosimilar biological product applications. The biosimilar fees for a fiscal year after FY2012 would only be available if the Secretary allocates no less than $20 million, excluding fees, adjusted. Would allow early payment of authorized fees. Would authorize to be appropriated for FY2013 through FY2017 fees equal to the total revenue amount as specified under subsection(b)(3), as adjusted for inflation and offset.
(g) Collection of unpaid fees	Any unpaid fee would be treated as a claim of the United States Government.
(h) Written requests for waivers and refunds	A sponsor would be required to submit a written request to the Secretary for a waiver or a refund not later than 180 days after the fee is due.
(i) Construction	"This section may not be construed to require that" HHS reduce FTE positions of officers, employees, and advisory committee members in other areas to offset those "engaged in the process of the review of biosimilar biological product applications."
Section 744C. Reauthorization; Reporting Requirements	
(a) Performance report	Beginning with FY2013, a report on the progress of FDA in achieving the performance goals during that fiscal year and future plans in meeting the goals would be required to be submitted each year to the House Energy and Commerce Committee and the Senate HELP Committee.
(b) Fiscal report	Beginning with FY2013, a report on the use by FDA of the fees collected during that fiscal year would be required to be submitted each year to the House Energy and Commerce Committee and the Senate HELP Committee.
(c) Public availability	Performance and fiscal reports would be required to be available on the FDA website.
(d) Study	A consulting firm would be hired to study the workload volume and full costs of the process for the review of biosimilar biological product applications; interim results would be published for public comment by June1, 2015 and final results by the end of FY2016.
(e) Reauthorization	In developing reauthorization recommendations for FY2013 through FY2017, consultation would be required to occur with Congress, scientific and academic experts, health care professionals, patient and consumer advocacy groups, and the regulated industry. After negotiations with industry are completed, FDA would be required to present the recommendations to Congress, publish the recommendations in the Federal Register, provide a 30 day public comment period, hold a public meeting to receive views from the public, and revise the recommendations as necessary. Not later than January 15, 2017, the Secretary would be required to transmit to Congress the revised recommendations.

Main Issue	HHS-Proposed Language[a]
Uncodified and Miscellaneous Provisions	
Sunset dates (uncodified)	The authority to assess and use biosimilar biological product fees would cease to be effective October 1, 2017. [Sec. 104] The reporting requirements would cease to be effective January 31, 2018. [Sec. 104]
Effective date (uncodified)	Provisions would take effect on October 1, 2012 or the date of enactment, except that fees would be assessed for all biosimilar biological product applications received on or after October 1, 2012 regardless of the date of enactment. [Sec. 105]
Savings clause	Notwithstanding the PDUFA sunset date of October 1, 2012, and notwithstanding the amendments made by this Act, fees relating to drugs [part 2 of subchapter C of chapter VII of the FFDCA], as in effect on the day before the date of the enactment of this Act, would continue to be in effect with respect to human drug applications and supplements (as defined in such part as of such day) that on or after October 1, 2007, but before October 1, 2012, were accepted by the FDA for filing with respect to assessing and collecting any fee required by such part for a fiscal year prior to FY2013.
Technical amendment	(a) Paragraph (1) of Section 735 (21 USC §379g) is amended in subparagraph (B) by striking "or (k)."

Source: CRS adaptation of FDA, "Biosimilar Statutory Language," http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM287749.pdf.

a. The BSUFA provision (Title IV) in both S. 3187 and H.R. 5651 are essentially identical and differ from the HHS proposal in only minor technical details. The legislation would add new Sections 744G, 744H and 744I to the FFDCA.

Table B-2. Performance Goals and Procedures in Agreement Between FDA and Industry Representatives for FY2013 Through FY2017 Under the Draft BSUFA

Topic	Draft BSUFA Commitments
I. Review Performance Goals	For FY2013 & FY2014: review and act on 70% of original biosimilar biological product applications within 10 months and 70% of resubmitted original biosimilar biological product applications within 6 months. For FY2015: review and act on 80% of original biosimilar biological product applications within 10 months and 80% of resubmitted original biosimilar biological product applications within 6 months. For FY2016: review and act on 85% of original biosimilar biological product applications within 10 months and 85% of resubmitted original biosimilar biological product applications within 6 months. For FY2017: review and act on 90% of original biosimilar biological product applications within 10 months and 90% of resubmitted original biosimilar biological product applications within 6 months. Review and act on 90% of original supplements within 10 months and 90% of resubmitted supplements within 6 months. Review and act on 90% of manufacturing supplements within 6 months.
II. First Cycle Review Performance	For original biosimilar biological product applications and supplements with clinical data, FDA will report on substantive review issues, and include the planned review timeline, for 90% of applications within 74 days. This is a preliminary review, additional deficiencies may be identified later in the review cycle. If the applicant submits a major amendment, the planned review timeline will no longer apply.
III. Review of Proprietary Names to Reduce Medication Errors	FDA will use fees to implement various measures to reduce medication errors related to look-alike proprietary names, unclear label abbreviations, acronyms, dose designations, and error prone label and packaging design. During the biosimilar biological product development phase, review 90% of proprietary names filed within 180 days of receipt. Review 90% of biosimilar biological product application proprietary names filed within 180 days of receipt.
IV. Major Dispute Resolution	For procedural or scientific matters involving biosimilar biological product applications, 90% of responses to appeals will occur within 30 days. Conditions of appeal process are specified.
V. Clinical Holds	The Center should respond to a sponsor's complete response to a clinical hold within 30 days of FDA's receipt; 90% of such responses are provided within 30 days of FDA's receipt of the sponsor's response.

Topic	Draft BSUFA Commitments
VI. Special Protocol Assessment	Upon request, FDA will evaluate certain protocols and related issues to assess if the design is adequate to meet scientific and regulatory requirements. Within 45 days of receipt, FDA will provide a written response. Qualifying protocols include a clinical study to prove biosimilarity and/or interchangeability. For FY2013 & FY2014, 70% of special protocols assessments and agreement requests completed and returned to sponsor within timeframes. For FY2015, 80% of special protocols assessments and agreement requests completed and returned to sponsor within timeframes. For FY2016, 85% of special protocols assessments and agreement requests completed and returned to sponsor within timeframes. For FY2017, 90% of special protocols assessments and agreement requests completed and returned to sponsor within timeframes.
VII. Meeting Management Goals	Specifies goals for agency response to industry requests for meetings with FDA, timeframes for the scheduling of these meetings, preparation of meeting minutes, and various conditions associated with these meetings, such as statement of purpose, agenda, list of objectives/outcomes, lists of attendees and participants, etc.
VIII. Definitions and explanations of terms	A number of terms are defined or explained including: "review and act on;" goal date extensions for major amendments; resubmitted original application;" Biosimilar Initial Advisory Meeting; and, four types of biological product development (BPD) meetings.

Source: CRS adaptation of FDA, "Biosimilar Biological Product Authorization Performance Goals and Procedures Fiscal Years 2013 through 2017," http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM281991.pdf.

Appendix C. Acronyms

ANDA	abbreviated new drug application
API	active pharmaceutical ingredient
BCS	Biopharmaceutics Classification System
BPCIA	Biologics Price Competition and Innovation Act
BSUFA	Biosimilars User Fee Act
CGMP	current good manufacturing practices
CPI	Consumer Price Index
DMF	drug master file Type II relates generally to drug substances
FDA	Food and Drug Administration
FDF	finished dosage form
FFDCA	Federal Food, Drug, and Cosmetic Act
FTE	full-time equivalent position
GDUFA	Generic Drug User Fee Amendments
HHS	Department of Health and Human Services
IND	investigational new drug
MDUFA	Medical Device User Fee Act
NDA	new drug application
PAS	prior approval supplement
PDUFA	Prescription Drug User Fee Act
PET	positron emission tomography
PHSA	Public Health Service Act
PPACA	Patient Protection and Affordable Care Act
U.S.C.	United States Code

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