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FDA Human Medical Product User Fee Programs: In Brief

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Overview

The Food and Drug Administration (FDA) regulates human medical products to ensure they are safe and effective for their intended use in patients.[1] Medical products include prescription and nonprescription (over-the-counter) drugs, biologics, and medical devices. FDA regulation of these products involves both premarket and postmarket regulatory requirements.[2] Premarket requirements, which use a significant portion of the agency's resources, include the review of products and product applications for FDA approval or clearance prior to marketing. Postmarket requirements are varied, but may include passive surveillance mechanisms used to monitor the performance of medical products once they are marketed and certain postmarket studies and reporting.

FDA Review of Human Medical Products

Center for Biologics Evaluation and Research (CBER) regulates traditional biologics, such as vaccines.

Center for Devices and Radiological Health (CDRH) regulates medical devices.

Center for Drug Evaluation and Research (CDER) regulates prescription brand-name and generic drugs, over-the-counter drugs, and most therapeutic biologics.

To support these premarket and postmarket activities, the agency relies on (1) discretionary appropriations provided through the annual appropriations process, and (2) user fees paid by each regulated industry. The primary purpose of the user fee programs is to reduce the time necessary to review and make decisions on medical product marketing applications. Lengthy review times affect the industry, which waits to market its products, and patients, who wait to use these products. Some critics of the current scope of the user fee programs are concerned that FDA's mission to protect public health may be compromised if reliance on these fees affects the impartiality of FDA's scientists.

User fees are authorized in legislation on a five-year cycle, with authority for their actual collection and expenditure provided each year through the annual appropriations process.[3] The four user fee programs discussed in this report are prescription drugs, medical devices, generic drugs, and biosimilars.[4] The Food and Drug Administration Reauthorization Act of 2017 (FDARA, P.L. 115-52) reauthorizes each of the human medical product user fee programs for five more years, FY2018 through FY2022.[5] The original authorizing legislation for each of the four user fee programs is as follows: (1) the Prescription Drug User Fee Act of 1992 (PDUFA, P.L. 102-571); (2) the Medical Device User Fee and Modernization Act of 2002 (MDUFMA, P.L. 107-250); (3) the Generic Drug User Fee Amendments of 2012 (GDUFA, Title III of the Food and Drug Administration Safety and Innovation Act [FDASIA], P.L. 112-144); and (4) the

FDA also regulates animal drugs and feeds, human foods, dietary supplements, cosmetics, radiological devices, and tobacco products.

[2] For more information, see CRS Report R41983, How FDA Approves Drugs and Regulates Their Safety and Effectiveness, by Susan Thaul.

[3] For a detailed discussion of the funding sources for the review human medical products, see CRS Report R44582, Overview of Funding Mechanisms in the Federal Budget Process, and Selected Examples.

[4] The FDA also has user fee authorities for animal drugs, tobacco products, priority review, food reinspection, food recall, voluntary qualified food importer, and, most recently, outsourcing facilities (related to drug compounding) and some wholesale distributors and third-party logistics providers (related to pharmaceutical supply chain security). These other authorities are not addressed in this report.

[5] For more information, see CRS Report R44961, FDA Reauthorization Act of 2017 (FDARA, P.L. 115-52).

Biosimilar User Fee Act of 2012 (BsUFA, Title IV of FDASIA, P.L. 112-144). **Appendix A** outlines various features of the user fee programs.

A shared element of all four user fee programs is that the user fees are to supplement congressional appropriations, not replace them. The laws include limiting conditions, known as "triggers," to enforce this goal. FDA may collect and use fees only if the direct appropriations for specified activities involved in the review of products remains at a level at least equal (adjusted for inflation) to an amount or benchmark specified in each law.[6] Originally the fees were authorized to be used to support only premarket review activities, allowing FDA to hire additional staff to review premarket applications with the goal of reducing review time. Over time, Congress added preclinical drug development and certain postmarket activities to the allowable activities that may be paid for with user fee revenue.

In exchange for paying user fees, industry receives from FDA a commitment to meet performance goals, such as completing premarket review within a specified timeframe. Prior to each five-year reauthorization cycle, FDA and industry negotiate the performance goals, which are finalized in a written agreement. The reauthorization process allows for input from other relevant stakeholders, including academic experts and representatives of patient and consumer advocacy groups, and provides opportunity for public comment on the agreement. For the next reauthorization cycle, the Federal Food, Drug, and Cosmetic Act (FFDCA) requires the Health and Human Services (HHS) Secretary to submit the four user fee agreements to Congress by January 15, 2022.[7] In each previous reauthorization, Congress has accepted unchanged the terms and conditions as negotiated between FDA and the industry. The four performance goal documents for FY2018 through FY2022 are provided on the FDA website.[8]

Due to the importance of user fees to FDA's budget, reauthorization of the user fee programs has been considered to be "must pass" legislation. Congress generally uses the reauthorization bill to address related FDA regulatory concerns; it therefore serves as an important driver for the ongoing modification of overall agency regulatory policy. However, passage of the 21st Century Cures Act (Division A, P.L. 114-255) included sections that modified drug and device regulation, perhaps reducing the number of such provisions that were added to FDARA (P.L. 115-52).[9]

FDARA (P.L. 115-52) consists of nine titles; the first four authorize FDA to collect fees and use the revenue to support specified activities for the review of prescription brand-name drugs and biological products, medical devices, generic drugs, and biosimilar biological products.[10] FDARA Titles V through IX addressed a range of other policy issues including pediatric drugs and

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[6] FFDCA 736(f) and (g); FFDCA 738(h) and (i); FFDCA 744B(h) and (i); FFDCA 744H(e). Further details on each of these legal conditions are available in the FDA user fee financial reports: http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/FinancialReports/default.htm.

[7] Prescription drugs, FFDCA 736B(f)(5); medical devices, FFDCA 738A(b)(5); generic drugs, FFDCA 744C(f)(5); biosimilars, FFDCA 744I(f)(3).

[8] PDUFA: http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM511438.pdf; GDUFA: http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf and http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525236.pdf; MDUFA: http://www.fda.gov/downloads/ForIndustry/UserFees/MedicalDeviceUserFee/UCM526395.pdf and http://www.fda.gov/downloads/ForIndustry/UserFees/MedicalDeviceUserFee/UCM526532.pdf; BsUFA: http://www.fda.gov/ForIndustry/UserFees/BiosimilarUserFeeActBsUFA/default.htm. The summary document for MDUFA contains statutory language, and the summary document for GDUFA contains the new fee structure.

[9] For more information, see CRS Report R44720, The 21st Century Cures Act (Division A of P.L. 114-255).

[10] For more information, see CRS Report R42680, *The Food and Drug Administration Safety and Innovation Act (FDASIA, P.L. 112-144)*.

devices, reauthorizations and improvements related to drugs, device inspection and regulatory improvements, generic drug access, and a set of miscellaneous provisions.

User Fees and the FDA Budget

FDA's budget has two funding streams: annual appropriations (i.e., discretionary budget authority, or BA) and industry user fees.[11] In FDA's annual appropriation, Congress sets both the total amount of appropriated funds and the amount of user fees that the agency is authorized to collect and obligate for that fiscal year. FDA's *total program level* increased from $3.832 billion in FY2012 to $4.745 billion in FY2017. Although congressionally appropriated funding increased by 11% over that time period, user fee revenue increased more than 47%. In FY2017, user fees accounted for 41% of FDA's *total program level*.[12] **Appendix B** provides information on the relative proportion of costs supported by user fee revenue and appropriations for each of the four user fee programs. The following paragraphs look at the funding for each of the four human medical product user fee programs individually.

Prescription drug user fees were first collected in FY1993 and have comprised an increasing proportion of the FDA's budget that is focused on prescription drug regulation. In FY2007, prescription drug user fees provided 56% of the PDUFA program total costs (appropriations provided 44%); in FY2016 (from the most recent financial report available), user fees covered 72% of PDUFA program total costs (appropriations covered 28%).[13] While most of PDUFA revenue supports activities managed by Center for Drug Evaluation and Research (CDER), PDUFA revenue also contributes to other FDA organizational components that support the PDUFA program, including Center for Biologics Evaluation and Research (CBER), the Office of Regulatory Affairs (ORA), and FDA headquarters.[14]

Medical device user fees were first collected in FY2003 and have comprised an increasing proportion of FDA's budget that is focused on device regulation. In FY2007, medical device user fees accounted for 17% of the MDUFA program total costs, compared with 36% in FY2016.[15] While most of MDUFA revenue supports activities managed by Center for Devices and Radiological Health (CDRH), MDUFA revenue also contributes to other parts of FDA that support the MDUFA program including CBER, ORA, and FDA headquarters.[16]

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[11] For more information about the FDA budget generally, and a discussion of user fees within the budget, see CRS Report R44576, *The Food and Drug Administration (FDA) Budget: Fact Sheet*.

[12] User fee amounts reflect what the congressional committees have authorized FDA to collect and spend that fiscal year. However, there is generally variation between the enacted amount and the amount that is spent from user fees. The amounts in the "Actual" column in the FDA *Justification of Estimates for Appropriations Committees* (CJ) reflect the amount spent from PDUFA fees, corresponding to the columns labeled "Obligations" and "Amount spent from ... fees" in the FDA user fee financial reports.

[13] FDA, *FY2016 PDUFA Financial Report*, Table 8: PDUFA Program—Historical Trend of Total Costs by Funding Source as of September 30 of each Fiscal Year, p. 13, at https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/FinancialReports/PDUFA/UCM550408.pdf.

[14] Ibid., Table 7: PDUFA Program—Historical Trend of Total Costs by Organization as of September 30 of Each Fiscal Year, p. 12.

[15] FDA, *FY2016 MDUFA Financial Report*, Table 7: MDUFA Program—Historical Trend of Total Costs by Funding Source as of September 30 of each Fiscal Year, p. 12, at https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/FinancialReports/MDUFMA/UCM550429.pdf.

[16] Ibid., Table 6: MDUFA Program—Historical Trend of Total Costs by Organization as of September 30 of Each Fiscal Year, p. 11.

In FY2013, the first year generic drug user fees were collected, user fees accounted for 45% of the GDUFA program total costs compared with 76% in FY2016.[17] While most of GDUFA fee revenue supports activities managed by CDER, GDUFA revenue also contributes to other FDA components that support the GDUFA program, including CBER, ORA, and FDA headquarters.[18]

In FY2013, the first year biosimilar user fees were collected, user fees accounted for 0% of the BsUFA program total costs compared with 29% in FY2016.[19] While most of BsUFA revenue supports activities managed by CDER, BsUFA revenue also contributes to other parts of FDA that support the BsUFA program, including CBER, ORA, and FDA headquarters.[20]

Medical Product User Fee Programs

PDUFA

Prior to marketing, a manufacturer must submit a new drug application (NDA) to FDA, demonstrating the drug's safety and effectiveness. FDA scientific and regulatory personnel review the NDA and prepare written assessments in several categories—medical, chemistry, statistical, pharmacology, clinical pharmacology and biopharmaceutics, risk assessment and risk mitigation, proprietary name, patient labeling—and then decide whether or not to approve the drug.[21]

In 1992, PDUFA (later called PDUFA I) gave FDA the authority to collect fees from the pharmaceutical industry and use the revenue to support "the process for the review of human drug applications."[22] That five-year authority, which covered both NDAs and biologics license applications (BLAs),[23] has been renewed on five subsequent occasions, by PDUFA II (1997), PDUFA III (2002), PDUFA IV (2007), PDUFA V (2012), and PDUFA VI (2017). PDUFA I authorized FDA to use the fee revenue to fund the "process for the review of human drug applications" and defined what that process encompassed. Congress has amended that definition to expand the scope of activities covered by PDUFA. PDUFA I covered activities that fit within the time window from when a manufacturer submits an NDA or a BLA until FDA makes its decision on that application, (e.g., review of applications, letters from FDA to applicants outlining deficiencies in their applications, and facility inspections). With additions within PDUFA II, III, and IV, FDA may now use PDUFA fees for activities during a drug's preclinical development,

[17] FDA, *FY2016 GDUFA Financial Report*, Table 7: GDUFA Program—Historical Trend of Total Costs by Funding Source as of September 30 of Each Fiscal Year, p. 10, at https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/FinancialReports/GDUFA/UCM550655.pdf.

[18] Ibid., Table 6: GDUFA Program—Historical Trend of Total Costs by Organization as of September 30 of Each Fiscal Year, p. 10.

[19] FDA, *FY2016 BsUFA Financial Report*, Table 6: BsUFA Program—Historical Trend of Total Costs by Funding Source as of September 30 of Each Fiscal Year, p. 10, at https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/FinancialReports/BsUFA/UCM550369.pdf.

[20] Ibid., Table 5: BsUFA Program—Historical Trend of Total Costs by Organization as of September 30 of Each Fiscal Year, p. 9.

[21] The listed categories are the sections of drug approval packages posted by FDA; for example, see the November 2016 files regarding Sanofi's Soliqua 100/33 (insulin glargine and lixisenatide), http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208673Orig1_toc.cfm.

[22] P.L. 102-571.

[23] A biologics license application (BLA) refers to an application submitted to FDA for the licensure of certain biological products under Section 351 of the Public Health Service Act (PHS Act).

clinical trials, and postapproval marketing periods, including postmarket safety activities such as adverse-event data-collection systems, and requirements relating to postapproval studies, labeling changes, and risk evaluation and mitigation strategies.

Each five-year authorization sets a total amount of fee revenue for the first year and provides a formula for annual adjustments to that total based on inflation and workload changes. PDUFA VI sets an annual base revenue of $878.6 million for FY2018, to be adjusted as specified.[24] It also modifies the inflation adjustment; replaces the workload adjustment with a capacity planning adjuster; eliminates the final year adjustment provisions and establishes an annual operating reserve adjustment; adds an additional direct cost adjustment; and specifies additional dollar amounts for each year.[25]

PDUFA I through V had required that three types of fees each contribute one-third of the fee revenue every year: application fee and annual establishment and product fees.[26] PDUFA VI established a new user fee structure, eliminating the product and establishment fees, and adding a *program fee*. It continued the *application fee*, while eliminating the fee for a supplemental application. PDUFA VI requires that user fees be waived or reduced under certain circumstances (e.g., if necessary to protect the public health or if the applicant is a small business submitting its first human drug application). Under the new law, 80% of the total prescription drug user fee revenue comes from program fees and 20% from application fees:

- *Application fee*: A drug's sponsor (usually the manufacturer) must pay a fee each time it submits an NDA or a BLA for FDA review.
- *Program fee*: The sponsor must pay an annual program fee for each prescription drug product that is identified in an approved application.[27]

MDUFA

Medical devices are used to diagnose, treat, monitor, or prevent a disease or condition in a patient. FDA describes medical devices as ranging "from simple tongue depressors and bedpans to complex programmable pacemakers with micro-chip technology and laser surgical devices."[28] FDA classifies devices based on their risk to the patient: low-risk devices are class I, moderate-risk are class II, and high-risk are class III.

The FFDCA requires premarket review for moderate- and high-risk devices. There are two main paths manufacturers can use to bring a device to market. One path consists of conducting clinical studies and submitting a premarket approval (PMA) application that includes evidence providing reasonable assurance that the device is safe and effective. A successful PMA process results in

[24] See CRS Report R44864, *Prescription Drug User Fee Act (PDUFA): 2017 Reauthorization as PDUFA VI* for details of the various adjustments.

[25] See CRS Report R44864 *Prescription Drug User Fee Act (PDUFA): 2017 Reauthorization as PDUFA VI* for details of the various adjustments.

[26] Each manufacturer was required to pay an annual *establishment fee* for each of its manufacturing establishments, an annual *product fee* for each product that fits within PDUFA's definition, and an *application fee*.

[27] PDUFA VI adds the limitation that a person named as the applicant in an approved application cannot be assessed more than five program fees in a fiscal year for prescription drug products identified in such approved application.

[28] FDA, Medical Devices, "Is the Product a Medical Device," at http://www.fda.gov/medicaldevices/deviceregulationandguidance/overview/classifyyourdevice/ucm051512.htm.

device *approval*. As of June 2017, 94% of PMAs accepted for filing in the first nine months of FY2017 were approved by FDA.[29]

The other path involves submitting a 510(k) notification demonstrating that the device is substantially equivalent to a device already on the market (a predicate device) that does not require a PMA. The 510(k) process is unique to medical devices and, if successful, results in FDA *clearance*. The 510(k) process is less costly and time-consuming than the PMA path. Substantial equivalence (SE) is determined by comparing the performance characteristics of a new device with those of a predicate device. Demonstrating SE does not usually require safety and effectiveness data from a clinical trial. As of June 2017, 85% of 510(k)s accepted for review in the first nine months of FY2017 were determined to be substantially equivalent.[30]

Congress gave FDA the authority to collect user fees from the medical device industry in 2002 and renewed that authority three times: MDUFA II (2007), MDUFA III (2012), and MDUFA IV (2017). Low-risk medical devices (class I) and a small number of moderate-risk (class II) medical devices are exempt from premarket review and payment of the associated fee. Of the unique devices that are listed by manufacturers with FDA in FY2016, about 63% were exempt from premarket review, 35% entered the market via the 510(k) process, and 1% entered via the PMA process.[31] Small businesses—those with gross receipts below a specified amount—pay reduced premarket review fees and have some fees waived altogether.

In addition to premarket review fees, there are also fees for when a manufacturer requests approval of a significant change in the design or performance of a device approved via the PMA pathway; these are called PMA supplements. The original 2002 user fee law had only authorized FDA to collect fees for premarket review, such as for PMA applications, PMA supplements, or 510(k) notifications. MDUFA II added two types of annual fees in order to generate a more stable revenue stream for the agency: establishment registration fees, paid by most device establishments registered with FDA; and product fees, paid for high-risk (class III) devices for which periodic reporting is required. MDUFA II also added two additional types of application fees[32] and substantially lowered all existing application fee amounts. MDUFA III changed the definition of "establishment subject to a registration fee," increasing the number paying the fee.

Under MDUFA I through III, user fee revenue could be used only for activities associated with premarket review of medical devices. MDUFA IV fees will fund postmarket surveillance of medical devices by collecting real-world evidence from different sources (such as registries, electronic health records, and other digital sources) via the National Evaluation System for health Technology (NEST).[33]

MDUFA fee amounts are set as a percentage of the PMA fee, or base fee. The law sets both the base fee amount for each fiscal year, and the percentage of the base fee that constitutes most other fees. MDUFA IV changed the 510(k) fee from 2% of the PMA fee to 3.4% of the PMA fee, added a new fee (de novo classification request, 30% of the PMA fee), and changed the 510(k) fee paid by small businesses (from 50% of the PMA fee to 25%).[34] The law requires the total revenue

[29] MDUFA III Performance Report, September 7, 2017, p. 28 at https://www.fda.gov/downloads/ForIndustry/UserFees/MedicalDeviceUserFee/UCM575208.pdf.

[30] Ibid., p. 203.

[31] Email from Division of Analysis and Program Operations, Office of Compliance, CDRH/FDA, May 23, 2016.

[32] The two applications are (1) the 30-Day Notice, used by a manufacturer to request modifications in manufacturing procedures, and (2) the 513(g) application, used by a manufacturer to request information on device classification.

[33] For further information about NEST, see CRS Report R42130, *FDA Regulation of Medical Devices*.

[34] For more information, see CRS Report R44517, *The FDA Medical Device User Fee Program: MDUFA IV Reauthorization*.

amount be adjusted by an inflation adjustment; the base fee is increased accordingly to generate the inflation-adjusted total revenue amount. The establishment fee may be increased as necessary so that total fees collected for the fiscal year generates the total adjusted revenue amount.

- *Application fee:* The sponsor of a medical device must pay a fee for each submission (e.g., PMA, a 510(k), de novo classification request, supplement).
- *Establishment fee*: Sponsors whose establishment meets the MDUFA definition must pay an annual registration fee.
- *Periodic reporting fee*: Certain class III device sponsors must pay an annual fee.

GDUFA

Since the Hatch-Waxman amendments to the FFDCA in 1984,[35] FDA has approved generic drugs, allowing safe and effective alternatives to brand-name prescription drugs. Because the brand-name sponsor has already submitted evidence to FDA supporting a drug's safety and effectiveness based on clinical trial data, the sponsor of a generic drug may ask FDA to rely on those data. Rather than submit data from animal studies, clinical studies, and bioavailability, the generic sponsor must show that the generic product is bioequivalent to the brand-name product in an abbreviated new drug application (ANDA). FDA also requires the generic sponsor to submit to reviews of chemistry, manufacturing, controls, labeling, and testing. Because the generic sponsor does not have the expense of product development or animal or human clinical trials, it can offer its product at a lower price than the brand-name sponsor does for its product. Due to an increase in the number of ANDAs submitted to FDA for review, and an increase in the number of foreign facilities making generic drugs, prior to GDUFA, the agency lacked the resources to keep pace, resulting in a backlog of submitted ANDAs.

Prior to the passage of GDUFA I, generic drug companies submitting ANDAs were not subject to user fees from FDA nor were they included in the scope of activities covered by PDUFA fees.[36] GDUFA I authorized FDA to collect fees from generic drug companies to supplement the cost of certain human generic drug activities: review of ANDAs and drug master files (DMFs);[37] approval, deficiency, and complete response letters; facility inspections; monitoring or research; postmarket safety activities; and regulatory science. In exchange, FDA committed to meeting certain performance goals and to taking a "first action" by the end of FY2017 on 90% of the backlog applications that were submitted pre-GDUFA and still pending on October 1, 2012. A May 2017 Government Accountability Office (GAO) report found that "as of December 31, 2016, FDA had acted on 92% of the 4,743 applications in the backlog pending review as of October 1, 2012, exceeding its GDUFA [I] goal."[38] GDUFA I set a total amount of fee revenue for

[35] The Drug Price Competition and Patent Term Restoration Act of 1984 (P.L. 98-417), often referred to as the Hatch-Waxman Act, amended the FFDCA to allow a generic drug manufacturer to submit an abbreviated NDA (ANDA) to the FDA for premarket review. In the ANDA, the generic company establishes that its drug product is chemically the same as the already approved drug and thereby relies on the FDA's previous finding of safety and effectiveness for the approved drug.

[36] For more information, see CRS Report R44703, *Generic Drugs and GDUFA Reauthorization: In Brief*.

[37] A Drug Master File (DMF) is a voluntary submission to the FDA that 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. The information contained in the DMF may be used to support an Investigational New Drug Application (IND), an NDA, an ANDA, another DMF, an Export Application, or amendments and supplements to any of these; however, it cannot be used as a substitute for an IND, NDA, ANDA, or export application.

[38] U.S. Government Accountability Office, Generic Drug User Fees: Application Review Times Declined, but FDA Should Develop a Plan for Administering Its Unobligated User Fees, GAO-17-452, May 2017, https://www.gao.gov/

the first year and provided a formula for annual adjustments to that total based on inflation and workload changes. It established a one-time backlog fee for ANDAs pending as of October 1, 2012.

GDUFA II creates a new generic drug applicant program fee, to be paid annually, which is tiered based on the number of approved ANDAs an applicant owns. It eliminates the prior approval supplement (PAS) fee and specifies that fees for foreign generic drug and active pharmaceutical ingredient (API)[39] facilities will be $15,000 higher than for domestic facilities. The new law sets the total fee revenue for FY2018 at $493,600,000 and specifies the amount to be derived from each fee type: 35% from the new generic drug applicant program fees, 33% from ANDA fees, 5% from DMF fees, 20% from generic drug facilities, and 7% from API facilities.

- *Drug Master File fee*: The sponsor of a Type II API DMF in a generic drug submission must pay an annual fee for each DMF.
- *Application fee*: The sponsor of an ANDA must pay a fee for each submission.
- *Facility fee*: Generic drug manufacturers must pay an annual fee for each manufacturing establishment.
- *Program fee*: The sponsor of an ANDA must pay an annual fee based on the number of approved ANDAs the sponsor owns.

BsUFA

A biologic drug is made from living organisms.[40] Compared with conventional chemical drugs, biologic drugs are relatively large and complex molecules. A biosimilar is a therapeutic drug that is similar but not structurally identical to the brand-name biologic drug made by a pharmaceutical or biotechnology company. Biologics and biosimilars frequently require special handling and processing to avoid contamination (by microbes or other unwanted substances) and are usually administered to patients via injection or infused directly into the bloodstream. For these reasons, biologics often are referred to as specialty drugs.

The cost of specialty drugs, including biologics, can be very high. The introduction of biosimilars in 2006 in Europe has reduced prices for biologics overall.[41] Marketing biosimilars in the United States became possible in March 2010 when Congress established a new regulatory authority for FDA. Congress created an abbreviated licensure pathway for biological products demonstrated to be "highly similar" (biosimilar) to, or "interchangeable" with, an FDA-licensed biological product. This new authority, the Biologics Price Competition and Innovation Act (BPCIA) of 2009, was enacted as Title VII of the Affordable Care Act (ACA, P.L. 111-148). Authority to collect user fees was provided by the Biosimilar User Fee Act of 2012 (BsUFA I, Title IV of FDASIA, P.L. 112-144).

assets/690/685453.pdf.

[39] An API is defined as a substance, or a mixture when the substance is unstable or cannot be transported on its own, intended to be used as a component of a drug and to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the human body; or a substance intended for final crystallization, purification, or salt formation, or any combination of those activities (FFDCA §744A(2)).

[40] For more information, see CRS Report R44620, *Biologics and Biosimilars: Background and Key Issues*.

[41] In some cases, the biosimilar price is 33% below the brand-name price (IMS Health, The Impact of Biosimilar Competition, June 2016, p. 4, http://ec.europa.eu/growth/tools databases/newsroom/cf/itemdetail.cfin?item_id=8854).

Use of the fees collected under BsUFA I and BsUFA II is specified in law to include, among other things, activities necessary for the review of submissions in connection with biosimilar product development and the review of biosimilar product applications.[42] BsUFA II sets the total fee revenue amount for FY2018 at $45,000,000 and establishes that the total revenue amounts for FY2019 through FY2022 will be based on a formula that takes into account the annual base revenue for the fiscal year, a new inflation adjustment, a new capacity planning adjustment, and the operating reserve for the fiscal year. The law removes the establishment fee and replaces it with a new biosimilar biological product program fee, stipulating that product sponsors shall not be assessed more than five biosimilar biological product program fees for a fiscal year per application. BsUFA II removes the supplement application fee and changes the application fee by no longer reducing the application fee by the cumulative amount of previously paid fees for the product. As under BsUFA I, the biosimilar application fee may be waived for the first such application from a small business, defined as an entity, including affiliates, with fewer than 500 employees that does not have an approved drug or biosimilar product introduced into commerce. BsUFA II fees are as follows:

- *Initial product development fee:* The sponsor of a biosimilar must pay a fee for development meetings with FDA.
- *Annual product development fee*: The sponsor of a biosimilar must also pay an annual fee while the biosimilar is in the development program.
- *Reactivation fee*: A sponsor that discontinues participation in the biosimilar development program must pay a reactivation fee to resume development.
- *Application fee*: The sponsor must pay a fee each time it submits a new biosimilar application.
- *Program fee*: The sponsor of a biosimilar biological product application must pay an annual program fee.

Selected CRS Products
Related to FDA Regulation of Human Medical Products

CRS Report R41983, *How FDA Approves Drugs and Regulates Their Safety and Effectiveness*

CRS Report R42130, *FDA Regulation of Medical Devices*

CRS Report R42680, *The Food and Drug Administration Safety and Innovation Act (FDASIA, P.L. 112-144)*

CRS Report R44517, *The FDA Medical Device User Fee Program: MDUFA IV Reauthorization*

CRS Report R44576, *The Food and Drug Administration (FDA) Budget: Fact Sheet*

CRS Report R44620, *Biologics and Biosimilars: Background and Key Issues*

CRS Report R44703, *Generic Drugs and GDUFA Reauthorization: In Brief*

CRS Report R44720, *The 21st Century Cures Act (Division A of P.L. 114-255)*

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

CRS Report R44961, *FDA Reauthorization Act of 2017 (FDARA, P.L. 115-52)*

[42] FFDCA §744G(9) and (13).

Appendix A. FDA Human Medical Product User Fee Programs

Table A-1. FDA Human Medical Product User Fee Programs

Prescription Drugs, Medical Devices, Generic Drugs, and Biosimilars

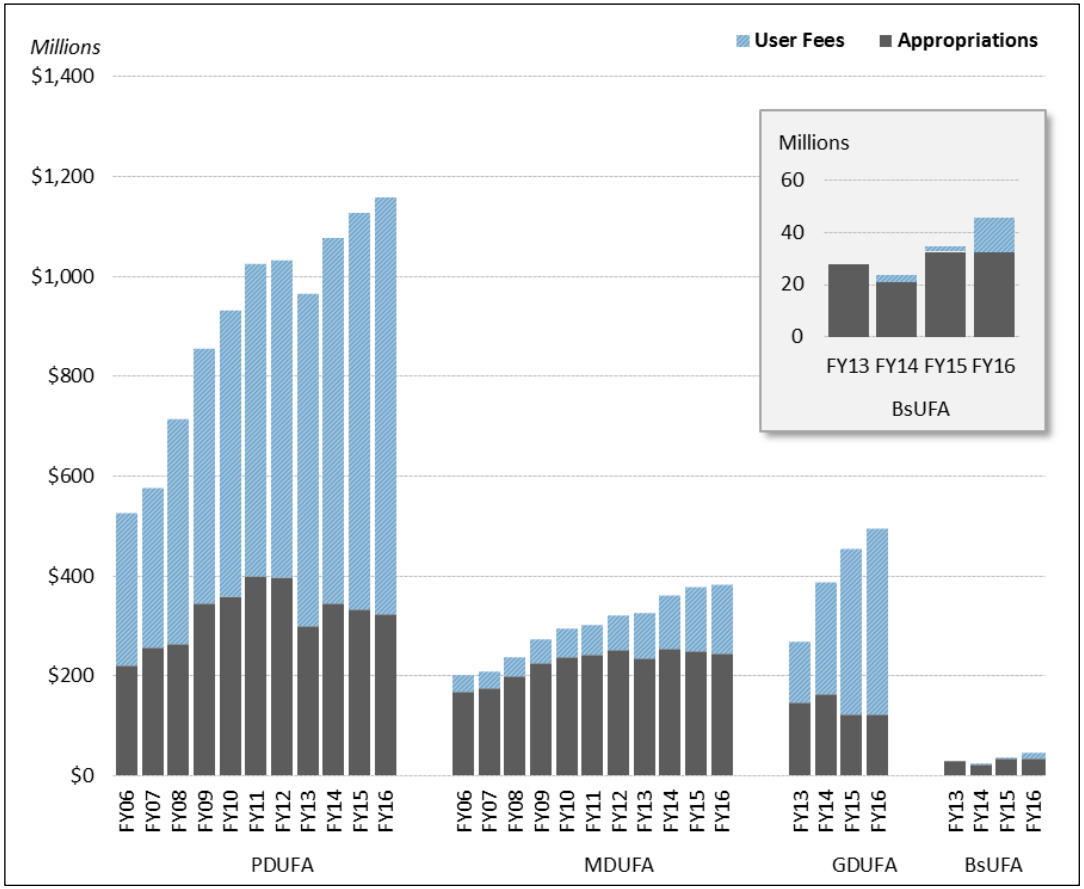
	PDUFA		MDUFA		GDUFA		BsUFA	
Original authorizing legislation	Prescription Drug User Fee Act of 1992 (P.L. 102-571)		Medical Device User Fee and Modernization Act of 2002 (P.L. 107-250)		Generic Drug User Fee Amendments of 2012 (Title III of FDASIA, P.L. 112-144)		Biosimilar User Fee Act of 2012 (Title IV of FDASIA, P.L. 112-144)	
Number of authorizations	6		4		2		2	
Sections in FFDCA	735, 736, 736B		737, 738, 738A		744A, 744B, 744C		744G, 744H, 744I	
Percent of program budget paid by user fees in FY2016	72%		36%		76%		29%	
Total FTEs in FY2016	4,125		1,616		1,765		174	
Fee schedule for FY2018	Application w/ clinical data	$2,421,495	PMA, PDP, PMR, BLA	$310,764	ANDA	$171,823	Initial BPD	$227,213
			BLA efficacy supplement	$310,764	DMF	$47,829	Annual BPD	$227,213
	Application w/o clinical data	$1,210,748	Panel-track supplement	$233,073	API domestic facility	$45,367	Reactivation	$454,426
			De novo class. request	$93,229	API foreign facility	$60,367	Application w/ clinical data	$1,746,745
			180-day supplement	$46,615	FDF domestic facility	$211,087		
	Program	$304,162	Real-time supplement	$21,753	FDF foreign facility	$226,087	Application fee w/o clinical data	$873,373
			510(k) submission	$10,566	Program large	$1,590,792	Program	$304,162
			30-Day Notice	$4,972	Program medium	$636,317		
			Classification fee	$4,195	Program small	$159,079		
			Periodic report	$10,877				
			Establishment fee	$4,624				

Source: FY2016 FDA User Fee Financial Reports at https://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/FinancialReports/default.htm; 82 FR 43247, *PDUFA Rates for FY2018*, September 14, 2017; 82 FR 41032, *MDUFA Rates for FY2018*, August 29, 2017; 82 FR 43242, *BsUFA Rates for FY2018*, September 14, 2017; 82 FR 41028, *GDUFA Rates for FY2018*, August 29, 2017.

Notes: ANDA, abbreviated new drug application; API, active pharmaceutical ingredient; BLA, biologics license application; BPD, biosimilar biological product development; DMF, drug master file; FDASIA, FDA Safety and Innovation Act; FDF, final dosage form; FFDCA, Federal Food, Drug, and Cosmetic Act; FTE, full-time equivalent (employees); NDA, new drug application; PDP, product development protocol; PMA, premarket approval application; PMR, postmarket report; w/, with; w/o, without.

Appendix B. User Fees and Appropriations

Figure B-1.FDA Human Medical Product User Fee Programs: Total Costs, by Funding Source



Sources: Graphic created by CRS using data from FY2015 and FY2016 FDA User Fee Financial Reports at https://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/FinancialReports/default.htm; PDUFA Financial Report, Table 8, p. 13; MDUFA Financial Report, Table 7, p. 12; GDUFA Financial Report, Table 7, p. 10; BsUFA Financial Report, Table 6, p. 10.

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