The Generic Drug User Fee Amendments (GDUFA): Background and Reauthorization

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SUMMARY

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The Generic Drug User Fee Amendments (GDUFA): Background and Reauthorization

The Food and Drug Administration (FDA) regulates the safety, effectiveness, and quality of drugs—both brand name and generic—pursuant to its authorities under the Federal Food, Drug, and Cosmetic Act (FFDCA). Throughout this report, the term *brand-name drug* refers to a drug that is approved under a new drug application (NDA) submitted pursuant to section 505(b) of the FFDCA. The term *generic drug* refers to a drug that is approved under an abbreviated new drug application (ANDA) submitted pursuant to FFDCA Section 505(j). FDA must approve an NDA or ANDA before a drug may be marketed in the United States.

FDA Regulation of Generic Drugs

When filing an ANDA, a generic drug applicant relies on FDA's previous determination of safety and effectiveness for the reference listed drug (RLD, typically the brand-name drug) rather than conducting its own preclinical and clinical investigations to prove safety and effectiveness. Although a generic is considered a "copy" of the RLD, it may differ in certain characteristics (e.g., shape, inactive ingredients, packaging). A generic that is approved under an ANDA is presumed to be therapeutically equivalent to the RLD. Because the generic is expected to produce the same clinical effect and has the same safety profile (when administered under the conditions in the labeling) as the RLD, it can be substituted for the RLD without the intervention of the prescriber.

Funding of Generic Drug Regulation

FDA regulation of generic drugs is funded through a combination of annual discretionary appropriations from the General Fund of the Treasury and user fees paid by the generic pharmaceutical industry. Prior to the enactment of the Generic Drug User Fee Amendments (GDUFA), FDA lacked the resources to keep pace with the increasing number of ANDAs submitted for review and foreign facilities making generic drugs, which led to a backlog of submitted ANDAs pending FDA review.

To increase predictability and efficiency in ANDA review and to bring uniformity to inspection schedules, in 2012, GDUFA (now referred to as GDUFA I) was enacted as Title III of the FDA Safety and Innovation Act (FDASIA; P.L. 112-144). GDUFA I gave FDA an additional source of revenue—user fees paid by generic drug companies—to support FDA generic drug review and related activities. In exchange for fee revenue, FDA agreed to meet certain performance goals, as negotiated by the agency and generic drug industry. GDUFA I was set to expire on September 30, 2017, and was subsequently reauthorized as GDUFA II by Title III of the FDA Reauthorization Act (FDARA; P.L. 115-52). GDUFA II is set to expire on September 30, 2022, unless reauthorized.

Scope of This Report

This report describes (1) the FDA process for review and approval of generic drugs, (2) the statutory framework that governs how FDA assesses and collects generic drug fees, (3) the impact of GDUFA on FDA application review time and the agency's budget, and (4) the GDUFA reauthorization process and considerations for Congress.

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Introduction

The Food and Drug Administration (FDA) regulates the safety, effectiveness, and quality of drugs—both brand name and generic—pursuant to its authorities under the Federal Food, Drug, and Cosmetic Act (FFDCA). Throughout this report, the term *brand-name drug* refers to a drug that is approved under a new drug application (NDA) submitted pursuant to section 505(b) of the FFDCA.[1] The term *generic drug* refers to a drug that is approved under an abbreviated new drug application (ANDA) submitted pursuant to FFDCA Section 505(j).[2] FDA must approve an NDA or ANDA before a drug may be marketed in the United States.

A company interested in marketing a new *brand-name drug* in the United States must submit an NDA to FDA for approval. Federal law and regulations specify the required contents of an NDA, including full reports of safety and effectiveness derived from preclinical (animal) and clinical (formally designed, conducted, and analyzed studies of human subjects) investigations.[3] Clinical investigations generally occur in three phases and can be the most expensive aspect of drug development.

In contrast, when filing an ANDA, a *generic drug* applicant relies on FDA's previous determination of safety and effectiveness for the reference listed drug (RLD,[4] typically the brand-name drug) rather than conducting its own preclinical and clinical investigations to prove safety and effectiveness.[5] A generic drug generally contains the same active ingredient in the same dosage form, strength, and route of administration as the RLD. While a generic is considered a "copy" of the RLD, it may differ in certain characteristics (e.g., shape, inactive ingredients, packaging). A generic that is approved under an ANDA is presumed to be therapeutically equivalent to the RLD. Because the generic is expected to produce the same clinical effect and has the same safety profile (when administered under the conditions in the labeling) as the RLD, it can be substituted for the RLD without the intervention of the prescriber.[6]

FDA regulation of generic drugs is funded through a combination of annual discretionary appropriations from the General Fund of the Treasury and user fees paid by the generic pharmaceutical industry. Prior to the enactment of the Generic Drug User Fee Amendments (GDUFA), FDA lacked the resources to keep pace with an increasing number of ANDAs submitted for review and foreign facilities making generic drugs, which resulted in a backlog of submitted ANDAs.

In 2012, GDUFA (now referred to as GDUFA I) was enacted as Title III of the FDA Safety and Innovation Act (FDASIA; P.L. 112-144). GDUFA I gave FDA an additional source of revenue—user fees paid by generic drug companies—to support FDA generic drug review and related

[1] FFDCA §505(b) [21 U.S.C. §355(b)].

[2] FFDCA §505(j) [21 U.S.C. §355(j)].

[3] FFDCA §505(b) [21 U.S.C. §355(b)] and 21 C.F.R. §314.50. See also CRS Report R41983, *How FDA Approves Drugs and Regulates Their Safety and Effectiveness*.

[4] The reference listed drug (RLD) is typically a brand-name drug but may be a generic. It is called the RLD because an ANDA (or a 505(b)(2) NDA) *refers* to the clinical data in the RLD's approved application. 21 C.F.R. §314.3(b).

[5] FDA, "Determining Whether to Submit an ANDA or a 505(b)(2) Application," Guidance for Industry, May 2019, p. 2, https://www.fda.gov/media/124848/download.

[6] 21 C.F.R. §314.3(b) defines *therapeutic equivalents* as "approved drug products that are pharmaceutical equivalents for which bioequivalence has been demonstrated, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling." See also FDA, "Determining Whether to Submit an ANDA or a 505(b)(2) Application," Guidance for Industry, p. 3.

activities.[7] In exchange for fee revenue, FDA agreed to meet certain performance goals, as negotiated by the agency and generic drug industry. GDUFA I was set to expire on September 30, 2017, and was subsequently reauthorized as GDUFA II by Title III of the FDA Reauthorization Act (FDARA; P.L. 115-52). GDUFA II is set to expire on September 30, 2022, unless reauthorized.

This report describes (1) the FDA process for review and approval of generic drugs, (2) the statutory framework that governs how FDA assesses and collects generic drug fees, (3) the impact of GDUFA on FDA application review time and the agency's budget, and (4) the GDUFA reauthorization process and considerations for Congress.

FDA Review and Approval of Generic Drugs

FDA reviews and approves generic drugs under an abbreviated pathway created by the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act; P.L. 98-417). This section focuses on the FDA review process and does not discuss intellectual property rights for pharmaceutical products (i.e., patents and regulatory exclusivities), which are addressed in other CRS reports.[8]

Submission of ANDAs

Federal law and regulations specify the required contents of an ANDA. Among other things, an ANDA must include information and data demonstrating that the generic version is pharmaceutically equivalent to the RLD (i.e., it contains the same active ingredients in the same strength, dosage form, and route of administration) and bioequivalent to the RLD (i.e., the active ingredient of the generic becomes available at the site of action at the same rate and to same extent as that of the RLD).[9] FDA has issued various guidance documents, both general and product specific, that clarify expectations for demonstrating bioequivalence between a generic drug and the RLD. An ANDA may not be submitted if new clinical investigations are necessary to establish the generic drug's safety and effectiveness.[10]

An ANDA must include proposed labeling for the generic drug, which must be the same as that for the RLD, with some exceptions.[11] The ANDA also must provide information about the generic's chemistry, manufacturing, and controls to ensure that the manufacturer can make the drug correctly and consistently.[12] As part of the ANDA review process, FDA typically inspects the

[7] P.L. 112-144, Title III. See CRS Report R42680, *The Food and Drug Administration Safety and Innovation Act (FDASIA, P.L. 112-144).*

[8] See, for example, CRS Report R46679, *Drug Prices: The Role of Patents and Regulatory Exclusivities*.

[9] FFDCA §505(j)(2) [21 U.S.C. §355(j)(2)] and 21 C.F.R. §314.94. *Bioequivalence* is defined as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study" (21 C.F.R. §314.3). Bioequivalence testing may be conducted in vivo (inside a living organism) or in vitro (outside a living organism), depending on the drug (21 C.F.R. §320.24(a)).

[10] FDA, "Determining Whether to Submit an ANDA or a 505(b)(2) Application," Guidance for Industry, p. 3.

[11] FFDCA §505(j)(2)(A)(v) [21 U.S.C. §355(j)(2)(A)(v)].

[12] 21 C.F.R. §314.94(a)(9).

facilities where the finished drug and its active pharmaceutical ingredient (API) are manufactured.[13]

An applicant may submit a petitioned ANDA for a generic drug that differs from the RLD in certain respects, such as dosage form, route of administration, strength, or active ingredient (in a product with more than one active ingredient) and for which studies are not necessary to establish the safety and effectiveness of the proposed generic.[14] To do so, an applicant would first submit a suitability petition to FDA requesting permission to submit an ANDA for a generic that differs from an RLD; if FDA approves the petition, the applicant may then submit an ANDA with the change.

FDA Review of ANDAs

ANDAs are submitted for review to the Office of Generic Drugs (OGD) and the Office of Pharmaceutical Quality (OPQ), both of which reside within FDA's Center for Drug Evaluation and Research (CDER). The OGD Division of Filing Review first determines whether an ANDA is sufficiently complete to allow FDA review. If OGD finds that the ANDA is not acceptable for review—for example, if it contains certain deficiencies—FDA guidance states that the agency will refuse to receive (RTR) the ANDA. The applicant may resubmit the ANDA with additional information.[15] If the deficiencies are minor and easily remedied, FDA may allow the applicant to correct the deficiencies or amend the ANDA at the agency's discretion.[16] If the deficiencies are not corrected within a specified amount of time (usually a week), FDA guidance indicates that the agency will RTR the ANDA. FDA considers RTR to be an indicator of poor application quality.[17]

Once an ANDA is accepted for filing (i.e., "received"), the first cycle of review begins. FDA staff in three disciplines review ANDAs:

- **Bioequivalence:** the OGD Office of Bioequivalence assesses whether the generic is bioequivalent to the RLD.
- **Labeling:** the OGD Division of Labeling Review assesses whether the generic's proposed labeling matches that of the RLD.
- **Quality:** the CDER OPQ evaluates the chemistry, manufacturing, and controls information to ensure drug quality.[18]

Within each of these disciplines, primary and secondary reviewers review an ANDA. The primary reviewers evaluate whether the ANDA meets the regulatory requirements with respect to the specific discipline of the office (e.g., bioequivalence), and the secondary reviewers are to "assess

[13] FDA, Chapter 46—New Drug Evaluation, Program 7346.832, Pre-approval Inspections, Implementation date: September 16, 2019, p. 9, https://www.fda.gov/media/121512/download.

[14] FFDCA §505(j)(2)(C) [21 U.S.C. §355(j)(2)(C)], 21 C.F.R. §314.93. FDA. "Determining Whether to Submit an ANDA or a 505(b)(2) Application," Guidance for Industry, May 2019, p. 3.

[15] GAO, "Generic Drug Applications: FDA Should Take Additional Steps to Address Factors That May Affect Approval Rates in the First Review Cycle," August 2019, GAO-19-565, p. 7, https://www.gao.gov/assets/710/700779.pdf.

[16] FDA, "ANDA Submissions –Refuse-to-Receive Standards," Guidance for Industry, December 2016, p. 3, https://www.fda.gov/media/86660/download.

[17] FDA, "OGD UPDATE: Welcome to much more than GDUFA II," Kathleen Uhl, Director Office of Generic Drugs, September 7, 2017, p. 16, https://www.fda.gov/media/115887/download.

[18] GAO, "Generic Drug Applications: FDA Should Take Additional Steps to Address Factors That May Affect Approval Rates in the First Review Cycle," pp. 7-8.

that assessment" to ensure quality and consistency in the technical assessment and communication with the applicant.[19] Division directors serve as a resource to reviewers for consultation on novel, complex, or high-risk products, among other things.[20]

As mentioned above, as part of an ANDA, applicants must demonstrate that they can consistently produce a quality drug product. To ensure that this is the case, FDA staff conduct quality assessments and inspections of the facilities named in the ANDA, such as those that manufacture the API and the finished drug product. CDER, with participation from the FDA Office of Regulatory Affairs (ORA), considers whether a preapproval inspection is needed, whereas ORA, with CDER participation, conducts the inspections.[21] In certain cases, a preapproval inspection may not be necessary, for example, if FDA determines that the agency has sufficient information about the facility. Upon completion of an inspection or other information review, ORA provides to CDER's Office of Compliance either an "approve" recommendation, if no significant issues were identified, or a "withhold" recommendation, if there are significant issues that would affect the ability of the facility to perform.[22]

FDA allows applicants to respond to deficiencies identified in an ANDA during the review process. For example, the agency may send an information request (IR) letter to the applicant requesting additional information or clarification to assist reviewers. In addition, FDA issues discipline review letters (DRLs) to applicants during the mid-point of the review cycle to identify any potential deficiencies that would affect ANDA approval.[23] IRs and DRLs are intended to promote efficiency and effectiveness in the review process, minimize the number of review cycles, and increase FDA's overall rate of approval. Issuance of an IR or DRL does not stop the clock for a given review cycle. If a response to an IR or DRL contains information that requires a more thorough review, FDA may reclassify the submission as an amendment and assign a new goal date for that amendment.[24]

FDA's goal in the first cycle is to review and act on certain priority ANDAs *within 8 months of submission* and other ANDAs *within 10 months of submission*. These review goals have been agreed upon between FDA and the generic drug industry under the GDUFA II Commitment Letter.[25] FDA aims to act on a priority ANDA *within 8 months* if the applicant has submitted a complete and accurate Pre-Submission Facility Correspondence two months prior to ANDA submission. This gives FDA at least 60 days to determine whether a facility inspection is necessary and to begin inspection planning prior to receiving the ANDA.[26] If the applicant has not submitted such correspondence, the agency's goal is to act on the priority ANDA *within 10 months*. FDA has issued and subsequently updated a Manual of Policies and Procedures (MAPP)

[19] FDA, MAPP 5241.3, "Good Abbreviated New Drug Application Assessment Practices," pp. 5-8, https://www.fda.gov/media/110017/download.

[20] FDA, MAPP 5241.3, "Good Abbreviated New Drug Application Assessment Practices," p. 9.

[21] FDA, Chapter 46—New Drug Evaluation, Program 7346.832, Pre-approval Inspections, p. 9.

[22] Ibid., p. 28.

[23] FDA, "Information Requests and Discipline Review Letters Under GDUFA" Guidance for Industry, December 2017, p. 2, https://www.fda.gov/media/109915/download.

[24] Ibid., pp. 4-5.

[25] FDA, "GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years FY2018-2022," https://www.fda.gov/media/101052/download.

[26] FDA, "ANDAs: Pre-Submission of Facility Information Related to Prioritized Generic Drug Applications (Pre-Submission Facility Correspondence)," Draft Guidance, November 2017, https://www.fda.gov/media/105794/download.

that describes which ANDAs will be prioritized for review, including ANDAs related to drug shortages and ANDAs related to public health emergencies.[27]

Upon completing review of an ANDA, FDA sends one of three action letters to the applicant: an approval letter, a tentative approval letter, or a complete response letter.[28] An approval letter signifies that FDA has approved the generic drug in the ANDA for marketing, while a tentative approval letter means that the ANDA meets the regulatory requirements for approval but cannot receive final approval due to unexpired patents or regulatory exclusivities.[29] A complete response letter describes the deficiencies that FDA has identified in an ANDA that must be addressed before it can be approved.[30] Following receipt of a complete response letter, an applicant may submit an amendment that addresses the deficiencies.[31] This submission would trigger a new review cycle, during which FDA would review the changes. Subsequent review cycles can take between 3 and 10 months each (see **Table A-1**), depending on whether the amendments made to the ANDA are major or minor, designated as priority or standard, and whether an inspection is required.[32]

Modification of Approved ANDAs

Generally, any modification to an approved ANDA must be reported to FDA, and certain modifications require FDA approval prior to distribution of the generic drug with the change. The type of regulatory submission required depends on the potential of the change "to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product."[33]

Major changes to an approved ANDA require submission and approval of a prior approval supplement (PAS). More specifically, a PAS is used to request a modification to an approved ANDA that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as it may relate to its safety or effectiveness. This includes changes in the API, finished drug product, production process, quality controls, equipment, or facilities named in an approved ANDA.[34] Certain manufacturing changes may trigger the need for an FDA inspection prior to approval of a PAS.

Moderate changes—for example, a labeling modification that adds or strengthens a contraindication, warning, or adverse reaction—require submission of a changes-being-effected

[27] FDA, Manual of Policies and Procedures (MAPP) 5240.3, "Prioritization of the Review of Original ANDAs, Amendments, and Supplements," revised January 30, 2020, https://www.fda.gov/media/89061/download.

[28] FDA, "Information Requests and Discipline Review Letters Under GDUFA," p. 3.

[29] 21 C.F.R. §314.3(b).

[30] Ibid.

[31] FDA, "ANDA Submissions—Amendments to Abbreviated New Drug Applications Under GDUFA," Guidance for Industry, July 2018, p. 3, https://www.fda.gov/media/89258/download.

[32] FDA, "ANDA Submissions—Amendments to Abbreviated New Drug Applications Under GDUFA," Guidance for Industry, July 2018, https://www.fda.gov/media/89258/download. See also GAO, "Generic Drug Applications: FDA Should Take Additional Steps to Address Factors That May Affect Approval Rates in the First Review Cycle," p. 2.

[33] 21 C.F.R. §314.70(b), (c), and (d). FDA, "ANDA Submissions –Prior Approval Supplements Under GDUFA," Guidance for Industry, October 2017, https://www.fda.gov/media/89263/download.

[34] FFDCA §744A(11) [21 U.S.C. §379j–41(11)]. 21 C.F.R. § 314.70(b). FDA, "Changes to an Approved NDA or ANDA," Guidance for Industry, April 2004, p. 24, https://www.fda.gov/files/drugs/published/Changes-to-an-Approved-NDA-or-ANDA.pdf.

(CBE) supplement.[35] A drug incorporating such labeling change may be distributed upon FDA receipt of the CBE supplement (called a "CBE-0 supplement").[36] However, some moderate changes, including modifications to a drug's container closure system, require submission of a CBE supplement at least 30 days prior to distribution of the product with the change (called a "CBE-30 supplement").[37] Minor changes, such as editorial changes in the labeling, may be submitted to FDA in annual reports.[38]

Generic Drug User Fees

Although the Hatch-Waxman Act has been considered successful in boosting generic drug competition, the law has increased the number of ANDAs and other regulatory submissions to FDA, thus increasing the agency's workload. The number of manufacturing facilities has also increased, particularly those located outside of the United States. As a result, both FDA's review workload and the resources needed to complete foreign facility inspections have grown.[39] These factors have resulted in delayed review and approval of generic drugs. In March 2012, the median review time for an ANDA was approximately 31 months, and FDA had a backlog of more than 2,500 ANDAs.[40] ANDAs were approved in one review cycle less than 1% of the time.[41]

To increase predictability and efficiency in ANDA review and bring uniformity to inspection schedules, in 2012, GDUFA I was enacted, authorizing FDA to assess and collect user fees from generic drug companies to support generic drug review and related activities.[42] The fees enabled FDA to hire additional scientists and support staff to facilitate ANDA review, as well as inspectors to conduct generic facility inspections. In exchange for fee revenue, FDA agreed to meet certain performance goals, as negotiated by the generic drug industry and agency. GDUFA I, initially set to expire on September 30, 2017, was reauthorized as GDUFA II by the FDA Reauthorization Act of 2017 (FDARA).[43] GDUFA II is set to expire on September 30, 2022.[44]

GDUFA Framework

As described below, the statutory provisions governing GDUFA specify how FDA may use generic drug fees. Each five-year authorization has set a total amount of fee revenue for the first year, provided a formula for annual adjustments to that total based on inflation, specified the fee

[35] 21 C.F.R. §314.70(c). FDA, "Changes to an Approved NDA or ANDA," Guidance for Industry, p. 25.

[36] 21 C.F.R. §314.70(c)(6). FDA, "ANDA Submissions –Prior Approval Supplements Under GDUFA," p. 4.

[37] 21 C.F.R. §314.70(c)(3). FDA, "ANDA Submissions –Prior Approval Supplements Under GDUFA," p. 3.

[38] 21 C.F.R. §314.70(d). FDA, "Changes to an Approved NDA or ANDA," Guidance for Industry, p. 26.

[39] Statement of Janet Woodcock, MD, Director, CDER, FDA, before the Senate Committee on Health, Education, Labor, and Pensions, "FDA User Fee Agreements: Strengthening FDA and the Medical Products Industry for the Benefit of Patients," March 29, 2012, p. 22.

[40] Ibid.

[41] Statement of Janet Woodcock, MD, Director of CDER, FDA, before the House Committee on Energy and Commerce, Subcommittee on Health, "Generic Drug User Fee Act Reauthorization (GDUFA II)," 115th Cong., 1st sess., March 2, 2017, p. 4.

[42] P.L. 112-144, Title III. See CRS Report R42680, *The Food and Drug Administration Safety and Innovation Act (FDASIA, P.L. 112-144).*

[43] P.L. 115-52, Title III. See CRS Report R44961, *FDA Reauthorization Act of 2017 (FDARA, P.L. 115-52).*

[44] P.L. 115-52, §305.

types that contribute to the total revenue, and required that certain legal conditions be satisfied in order for FDA to collect user fees.

Covered Activities

GDUFA fees may be used for allowable activities and expenses, as specified in statute. Specifically, FDA may use the fee revenue to fund "human generic drug activities," which include the following:

- review of generic drug submissions (e.g., ANDAs and drug master files [DMFs]);[45]
- issuance of letters (e.g., approval and complete response letters);
- inspections of generic drug facilities;
- monitoring of research conducted in connection with review of generic drug submissions;
- postmarket safety (e.g., activities related to adverse event reporting); and
- regulatory science activities related to generic drugs.[46]

The FFDCA defines "resources allocated for human generic drug activities" as expenses for FDA officers, employees, contractors, and advisory committees; information management and computer resources; facilities, furniture, equipment, materials and supplies;[47] and the collection of user fees and resources accounting.[48]

GDUFA II did not modify the definitions of "human generic drug activities" or "resources allocated for human generic drug activities," thus maintaining the GDUFA I scope of allowable activities and expenses that fees could support.

Revenue and Fee Adjustments

GDUFA I set a total fee revenue amount of $299 million for the first year of the program (FY2013) and provided a formula for annual fee adjustment based on inflation.[49] The revenue amount was based on the assumption that FDA would receive 750 ANDAs per year, with ANDAs being the primary workload driver of the generic drugs program. However, in the first four years of the GDUFA program, FDA received, on average, 1,000 ANDAs per year.[50] In addition, GDUFA I provided for a final year adjustment in FY2017 to increase fees to provide for up to three months of operations.

To account for FDA's growing workload, GDUFA II increased the total fee revenue for the first year of the program (FY2018) to $493.6 million, to be adjusted annually for inflation, as

[45] A Drug Master File (DMF) is a voluntary submission to 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, for example, may be used to support an ANDA; however, it cannot be used as a substitute for an ANDA.

[46] FFDCA §744A(9) [21 U.S.C. §379j–41(9)].

[47] Beginning October 1, 2023, the costs of resources shall include only expenditures for leasing and necessary scientific equipment. FFDCA §744B(e)(2) [21 U.S.C. §379j–42(e)(2)].

[48] FFDCA §744A(12) [21 U.S.C. §379j–41(12)].

[49] P.L. 112-144, Title III. See CRS Report R42680, *The Food and Drug Administration Safety and Innovation Act (FDASIA, P.L. 112-144).*

[50] FDA, "GDUFA II Fee Structure Summary," https://www.fda.gov/media/101064/download.

specified.[51] GDUFA II also provided for a final year adjustment, in FY2022, to increase fees to provide for up to three months of operations.[52]

Fee Types

GDUFA I had required that the following types of fees each contribute to the fee revenue every fiscal year:[53]

- ANDA/PAS fee (24%): One-time fee paid by the sponsor of an ANDA or PAS upon submission of the application. The PAS fee was half the ANDA fee.[54]
- DMF fee (6%): One-time fee paid by a person that owns a Type II API DMF when the DMF is first referenced in a generic drug submission (i.e., an ANDA, an amendment to an ANDA, a PAS, or an amendment to a PAS). A Type II API DMF contains information about the processes and facility making an API.
- Generic drug finished dosage form (FDF) facility fee (56%): Fee paid annually by a person that owns a facility identified in a generic drug submission that is either pending or approved to produce a FDF of a human generic drug.
- API facility fee (14%): Fee paid annually by a person that owns a facility that is identified (1) in a generic drug submission that is pending or approved to produce an API of a human generic drug, or (2) in a Type II API DMF referenced in a generic drug submission.

Under GDUFA I, FDA was allowed to charge foreign facilities between $15,000 to $30,000 more per facility than domestic facilities, depending on the agency's annual calculations concerning relative costs of foreign and domestic inspections. A facility that qualified as both an API and FDF facility was subject to both fees.[55] A contract manufacturing organization (CMO) producing generic drugs on behalf of the ANDA sponsor was subject to the full FDF fee. In addition, GDUFA I established a one-time backlog fee for ANDAs pending as of October 1, 2012.

GDUFA II modified the fee structure (see **Table 1**). In particular, GDUFA II created a new generic drug applicant program fee, eliminated the PAS fee, and provided that fees for foreign FDF and API facilities are $15,000 higher than for domestic facilities.[56] Under GDUFA II, a facility that qualifies as both an API and FDF facility is subject to the FDF fee only.[57] A CMO

[51] FFDCA §744B(b)(1) & (c)(1) [21 U.S.C. §379j–42(b)(1) & (c)(1)].

[52] FFDCA §744B(c)(2) [21 U.S.C. §379j–42(c)(2)].

[53] P.L. 112-144, Title III. See also FDA, "GDUFA II Fee Structure Summary," https://www.fda.gov/media/101064/download.

[54] As an example of how FDA calculates individual fee amounts, for FY2015, FDA determined that the inflation-adjusted target revenue was $312,224,000. As specified under GDUFA I, ANDA and PAS fees were to make up 24% of this total (i.e., $74,934,000, rounded to the nearest thousand dollars). FDA then estimated how many full application equivalents (FAEs) would be submitted in FY2015, assuming ANDAs count as one FAE and PASs count as one-half an FAE. FDA determined, based on submissions from previous years, that 1,276 FAEs would be subject to the application fee in FY2015. FDA then divided the fee revenue amount to be derived from application fees ($74,934,000) by the 1,276 FAEs, resulting in an ANDA fee of $58,730 (rounded to the nearest ten dollars) and a PAS fee of $29,370 (i.e., half the ANDA fee).

[55] P.L. 112-144, Title III. See also FDA, "GDUFA II Fee Structure Summary," https://www.fda.gov/media/101064/download.

[56] FFDCA §744B(b)(2)(C) [21 U.S.C. §379j–42(b)(2)(C)].

[57] FFDCA §744B(a)(4)(iii) [21 U.S.C. §379j–42(a)(4)(iii)].

manufacturing generic drugs on behalf of the ANDA sponsor is subject to one third of the FDF fee. GDUFA II specified the amount to be derived from each fee type as follows:

- Generic drug applicant program fee (35%): Annual fee paid by a person based on the number of approved ANDAs they own.
- ANDA fee (33%): One-time fee paid by the sponsor of an ANDA (but not a PAS) upon submission of the application.
- DMF fee (5%): same as under GDUFA I.
- Generic drug FDF facility fee (20%): Fee paid annually by a person that owns a facility identified in a generic drug submission that is approved (but not pending) to produce an FDF of a human generic drug.
- API facility fee (7%): Fee paid annually by a person that owns a facility that is identified (1) in a generic drug submission that is approved (but not pending) to produce an API of a human generic drug, or (2) in a Type II API DMF referenced in a generic drug submission.[58]

This restructuring was intended to shift the burden toward annual program fees.[59] (The volume of applications fluctuates from year to year, whereas the amount of facilities and approved ANDA holders is relatively stable over time.)

Table 1. GDUFA I Versus GDUFA II Fee Structures

Fee Type	GDUFA I (FY2013-FY2017)	GDUFA II (FY2018-FY2022)
One-Time Fees		
• Application fee	24%	33%
ANDA	*(Full application fee)*	*(Full application fee)*
PAS	*(50% of application fee)*	*N/A*
• DMF fee	6%	5%
Annual Fees		
• API facility fee	14%	7%
• FDF facility fee	56%	20%
• CMO facility fee	Same as FDF	33% of the FDF Facility Fee
• Program Fee	N/A	35%
Small (1-5 ANDAs)	*N/A*	*(10% of program fee)*
Medium (6-19 ANDAs)	*N/A*	*(40% of program fee)*
Large (20+ ANDAs)	*N/A*	*(Full program fee)*

Source: P.L. 112-144, Title III, FFDCA §744B [21 U.S.C. §379j–42], and FDA, "GDUFA II Fee Structure Summary," https://www.fda.gov/media/101064/download.

Notes: ANDA = abbreviated new drug application, API = active pharmaceutical ingredient, CMO = Contract Manufacturing Organization, DMF = drug master file, FDF = Finished Dosage Form, GDUFA = Generic Drug User Fee Amendments, N/A= not applicable, PAS = Prior Approval Supplement. An entity may not be subject to every fee. For example, an API facility may be subject to the API facility fee and the DMF fee, but not the program or ANDA fees.

[58] FFDCA §744B(b)(2) [21 U.S.C. §379j–42(b)(2)].

[59] FDA, "GDUFA II Fee Structure Summary," https://www.fda.gov/media/101064/download.

Conditions ("Triggers")

A key element of GDUFA is that user fees are to supplement congressional appropriations, not replace them. The law has included three limiting conditions, known as "triggers," to enforce this goal. Specifically, FDA may collect and use fees only if

- FDA's overall Salaries and Expenses direct appropriation (excluding user fees) equals or exceeds the agency's FY2009 Salaries and Expenses appropriation (excluding user fees), multiplied by the adjustment factor applicable to the fiscal year involved;[60]
- the fee amounts are specified in that fiscal year's appropriations act;[61] and
- the agency spends at least $97 million (multiplied by the adjustment factor for the applicable fiscal year) from appropriated funds (excluding user fees) for the review of generic drug applications.[62]

GDUFA II did not modify these conditions.

GDUFA Impact on FDA Performance and Budget

In each fiscal year for which user fees are collected, FDA is required to submit to Congress a performance report on the agency's progress in meeting the performance goals specified in the GDUFA II Commitment Letter,[63] as well as a fiscal report on the use of fees collected by the agency.[64] Further, in each fiscal year for which GDUFA fees are collected, FDA must submit a corrective action report to Congress, which includes (1) for GDUFA II, goals that have been met and recommendations on how FDA can improve and streamline the ANDA review process, and (2) for GDUFA II, goals that have not been met, a justification and description of the circumstances under which ANDA review goals were missed, and a description of efforts FDA has made to improve the agency's ability to meet such goals.[65]

Further, in the GDUFA II Commitment Letter, FDA has agreed to publish quarterly and monthly performance reports that provide various metrics, such as the number of ANDAs approved or tentatively approved in a specific period of time and the mean and median time to approval.[66] FDA also agreed to publish a GDUFA five-year financial plan no later than the second quarter of FY2018 and to update that plan no later than the second quarter of each subsequent fiscal year.[67]

[60] FFDCA §744B(h)(1) [21 U.S.C. §379j–42(h)(1)].

[61] FFDCA §744B(i)(2)(A)(i) [21 U.S.C. §379j–42(i)(2)(A)(i)].

[62] FFDCA §744B(i)(2)(A)(ii) [21 U.S.C. §379j–42(i)(2)(A)(ii)].

[63] FFDCA §744C(a)(1) [21 U.S.C. §379j–43(a)(1)]. The GDUFA II Commitment Letter specifies the metrics that FDA has agreed to publish in its annual performance reports, for example, the "number of product development, pre-submission and mid-review cycle meetings requested, granted, denied and conducted, by face to face or in writing" and the "number of applications received, refused to receive, and average time to receipt decision." See "GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years FY2018-2022," pp. 23-24.

[64] FFDCA §744C(b) [21 U.S.C. §379j–43(b)].

[65] FFDCA §744C(c) [21 U.S.C. §379j–43(c)].

[66] "GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years FY2018-2022," p. 22.

[67] Ibid. See also "User Fee Five-Year Financial Plans," https://www.fda.gov/about-fda/user-fee-reports/user-fee-five-year-financial-plans.

Performance[68]

ANDA approval times provide a measure of GDUFA's effectiveness in meeting its primary goal: reducing the time between a manufacturer's submission of an ANDA and FDA's approval decision. As mentioned above, FDA's goal is to act on 90% of certain priority ANDAs within 8 months of receipt of the application and all other ANDAs within 10 months.[69] As of September 30, 2019, FDA had met 100% of its FY2019 goal for 8-month review and 97% percent of the FY2019 goal for 10-month review.[70] However, these review goals apply to the first cycle of review, and most ANDAs undergo multiple cycles of review prior to approval. Thus, as described below, ANDA review times often exceed these timelines.

In FY2020, FDA approved or tentatively approved 909 ANDAs, 138 (15%) of which were approved on the first cycle of review (see **Figure 1**).[71] FDA did not consistently report on the number of first review cycle approvals in its annual performance reports prior to FY2018. However, FDA estimates that from FY2013 to FY2017, it took an average of three review cycles for ANDA approval.[72] In August 2019, the Government Accountability Office (GAO) reported that 12% of the ANDAs reviewed by FDA from FY2015 through FY2017 were approved or tentatively approved in the first cycle.[73] Prior to the enactment of the GDUFA I in 2012, ANDAs were approved in one review cycle less than 1% of the time.[74]

[68] This section focuses on ANDAs and does not provide metrics on other regulatory submissions (e.g., PAS, amendments, complete response letters). FDA's annual, monthly, and quarterly reports provide additional metrics on the agency's workload and performance.

[69] FDA, "GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years FY2018-2022," p. 4.

[70] FDA, "FY2019 Performance Report to Congress for the Generic Drug User Fee Amendments," https://www.fda.gov/media/138924/download.

[71] FDA, "Activities Report of the Generic Drugs Program (FY 2020) Monthly Performance," accessed January 15, 2021, https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/activities-report-generic-drugs-program-fy-2020-monthly-performance.

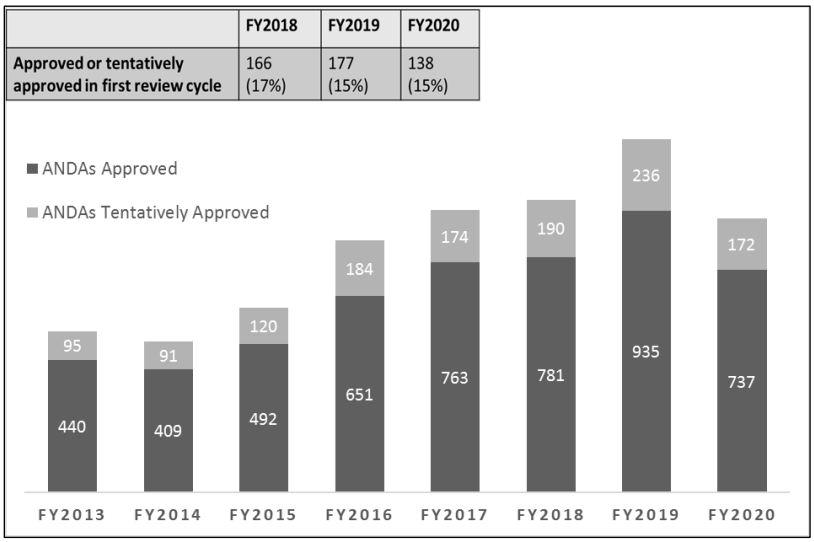
[72] GAO, "Generic Drug Applications: FDA Should Take Additional Steps to Address Factors That May Affect Approval Rates in the First Review Cycle," August 2019, p. 2, GAO-19-565, https://www.gao.gov/assets/710/700779.pdf.

[73] GAO, "Generic Drug Applications: FDA Should Take Additional Steps to Address Factors That May Affect Approval Rates in the First Review Cycle," p. 10.

[74] Statement of Janet Woodcock, MD, Director of CDER, FDA, before the House Committee on Energy and Commerce, Subcommittee on Health, March 2, 2017, p. 4.

Figure 1. ANDA Approvals Under GDUFA I and II

FY2013-FY2020



Source: CRS, based on the following FDA resources: Activities Reports of the Generic Drugs Program Monthly Performance (for each of FY2018-FY2020), Activities Report of the Generic Drug Program (for each of FY2013-FY2017), and the Annual Performance Report to Congress for the Generic Drug User Fee Amendments (for each of FY2013-FY2019).

In the performance report for FY2019 (the most recent year for which an annual report is available), for ANDAs received in FY2019 (i.e., the FY2019 receipt cohort), the *mean approval time* was *281 days* (median 296 days) and the *mean tentative approval time* was *350 days* (median 350 days).[75] The mean and median number of review cycles to approval and tentative approval, respectively, was one. These numbers reflect only those ANDAs that were either approved or tentatively approved at the time the report was prepared. As such, these numbers reflect the earliest and fastest submissions reaching approval. More up-to-date figures for FY2019 are expected in future reports.[76]

FDA also publishes quarterly reports, which provide review times for each quarterly action cohort in a fiscal year. In the second quarter of FY2021 (January 2021-March 2021), the *mean ANDA approval time* was *31.55 months* (median 22.80 months) and the *mean tentative approval time* was *33.76 months* (median 30.93 months).[77]

In addition to aiming to meet certain review performance goals (specified in **Table A-1**), in the GDUFA II Commitment Letter, FDA indicated it would take additional actions to introduce more predictability and timeliness to the review of generic drugs. Pursuant to the Commitment Letter, for example, FDA has issued regulatory and product-specific guidance documents for industry,[78] held public workshops to facilitate the development of generic drugs, and worked to increase

[75] FDA, "FY2019 Performance Report to Congress for the Generic Drug User Fee Amendments," p. 37.

[76] Ibid.

[77] Activities Report of the Generic Drugs Program | GDUFA II Quarterly Performance, current as of April 20, 2021, https://www.fda.gov/industry/generic-drug-user-fee-amendments/activities-report-generic-drugs-program-gdufa-ii-quarterly-performance. These numbers reflect a snapshot in time and may change based on refreshed counts in FDA's tracking systems.

[78] FDA, "GDUFA Guidances and MAPPs," https://www.fda.gov/industry/generic-drug-user-fee-amendments/gdufa-guidances-and-mapps.

communication with applicants during the review cycle. In addition, FDA has established a Pre-ANDA program for complex generic drugs, which includes product development, presubmission, and mid-review cycle meetings to help clarify regulatory expectations early in product development and during ANDA review.[79] FDA has issued the "Good [ANDA] Assessment Practices" MAPP, which establishes good assessment practices for FDA staff in order to increase operational efficiency and effectiveness.[80] To complement this MAPP, FDA has issued the draft guidance for industry "Good ANDA Submission Practices," which identifies common, recurring deficiencies that may lead to delay in ANDA approval and provides recommendations on how to avoid these deficiencies. Both documents have the stated goal of decreasing the number of review cycles.[81] Moreover, FDA has taken additional policy actions intended to complement the GDUFA II efforts; for example, issuance of the Drug Competition Action Plan, which, among other things, aimed to reduce "gaming of regulatory requirements."[82]

Budget

In FY2013, the first year generic drug user fees were collected, user fees accounted for 45% of the GDUFA program total costs compared with 72% in FY2019 (see **Figure 2**).[83] While most GDUFA fee revenue supports activities managed by CDER, GDUFA revenue also contributes to other FDA components that support the GDUFA program, including the Center for Biologics Evaluation and Research, ORA, and FDA headquarters.[84]

[79] FDA, "Pre-ANDA Program & Complex Generic Products," https://www.fda.gov/industry/generic-drug-user-fee-amendments/pre-anda-program-complex-generic-products.

[80] FDA, MAPP 5241.3, "Good Abbreviated New Drug Application Assessment Practices," effective January 3, 2018, https://www.fda.gov/media/110017/download.

[81] FDA, "Good ANDA Submission Practices," Draft Guidance for Industry, January 2018, https://www.fda.gov/media/110689/download.

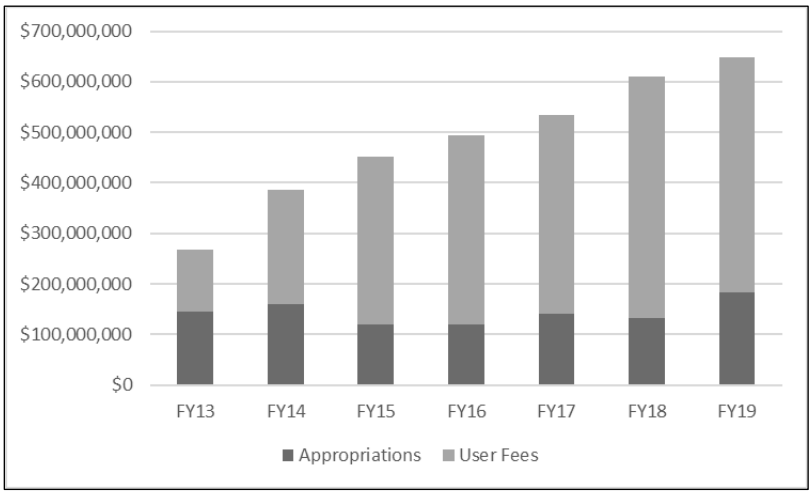
[82] FDA, "FDA Public Meeting Generic Drug User Fee Amendments (GDUFA) of 2017," July 21, 2020, p. 40, https://www.fda.gov/media/141309/download.

[83] FDA, FY2019 GDUFA Financial Report, Table 8: Historical Generic Drug User Fee Obligations by Funding Source as of September 30 of Each Fiscal Year, p. 16, at https://www.fda.gov/media/139343/download.

[84] FDA, FY2019 GDUFA Financial Report, Table 9: Historical Trend of Total FTEs Utilized by Organization as of September 30 of Each Fiscal Year, p. 16.

Figure 2. GDUFA Program: User Fees and Appropriations

Total Costs, by Funding Source



Source: Created by CRS using data from FDA GDUFA Financial Reports at https://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/FinancialReports/default.htm.

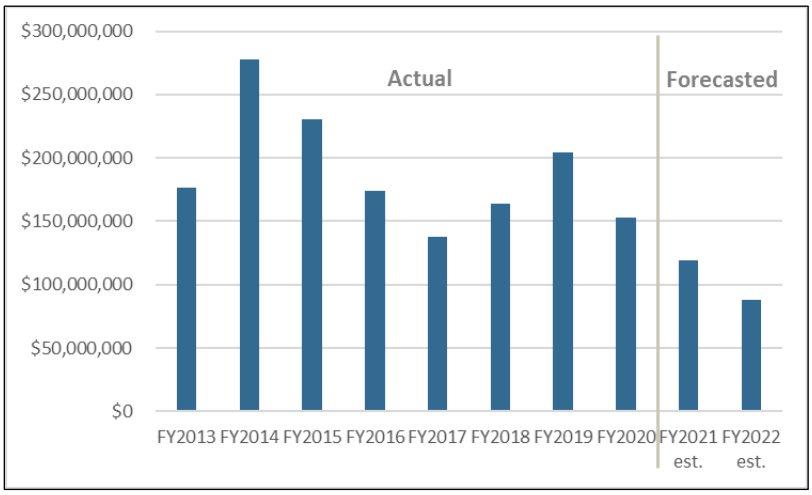
Once appropriated, GDUFA fees remain available until expended and any fees not obligated in the fiscal year for which they were appropriated and collected may be carried over into subsequent fiscal years. According to FDA, maintaining a carryover balance helps mitigate the risk of under collecting fees and the risk of a lapse in appropriations (e.g., a government shutdown).[85] The agency considers funding for 8 to 12 weeks of operations ($82 million to $122 million in FY2022) to be a sufficient carryover balance. Under GDUFA I, some industry representatives reportedly expressed concern that the GDUFA carryover balance was too large and, thus, whether the user fees too high.[86] While the carryover balance fell in the first few years of GDUFA II, the balance increased in FY2019 (see **Figure 3**). FDA indicated that the increase in FY2019 was "primarily driven by challenges in hiring new staff for the program, underspending in operations, and an increase in available non-user fee appropriations."[87]

[85] FDA, "Five-year Financial Plan Fiscal Years 2018-2019-2020-2021-2022," 2021 Update for the GDUFA Program, p. 13, https://www.fda.gov/media/147060/download.

[86] Derrick Gingery, "Generic Drug User Fee Projections Complicated By Shifting Personnel Costs," *Pink Sheet*, December 4, 2020.

[87] FDA, *FY2019 GDUFA Financial Report*, p. 14.

Figure 3. GDUFA Program Carryover, Actual and Forecasted



Source: The FY2014-FY2016 amounts are from the FY2017 GDUFA financial report, the FY2017 amount is from the FY2019 GDUFA financial report, and FY2018-FY2022 amounts are from the "Five-year Financial Plan Fiscal Years 2018-2019-2020-2021-2022," 2021 update.

Notes: In addition to the carryover amounts reflected in this figure, FDA maintains a set-aside, which varies from year to year, to provide for future year refunds. This amount generally is designated as unavailable for use.

Reauthorization and Considerations for GDUFA III

The FFDCA specifies the process for GDUFA III reauthorization, requiring FDA to consult with specified congressional committees (i.e., the House Energy and Commerce Committee and Senate Committee on Health, Education, Labor and Pensions), scientific and academic experts, health care professionals, representatives of patient and consumer advocacy groups, and the generic drug industry.[88] FDA is required to hold a public meeting prior to beginning negotiations with the generic drug industry,[89] as well as to hold discussions with representatives of patient and consumer advocacy groups at least once every month during negotiations with the generic drug industry.[90] The meeting minutes of the negotiation sessions with the generic drug industry must be made public on the FDA website.[91] After negotiations with the generic drug industry, FDA must present the agreed-upon goals and recommendations to the abovementioned committees and publish them in the *Federal Register* with a public comment period. FDA also must hold a public meeting to present its views on the goals and recommendations and, pursuant to public comment, revise the recommendations as necessary.[92] The revised recommendations must be transmitted to Congress by January 15, 2022, along with a summary of views and comments received on the recommendations and changes made in response to those views and comments.[93]

[88] FFDCA §744C(f)(1) [21 U.S.C. §379j–43(f)(1)].
[89] FFDCA §744C(f)(2) [21 U.S.C. §379j–43(f)(2)].
[90] FFDCA §744C(f)(3) [21 U.S.C. §379j–43(f)(3)].
[91] FFDCA §744C(f)(6) [21 U.S.C. §379j–43(f)(6)].
[92] FFDCA §744C(f)(4) [21 U.S.C. §379j–43(f)(4)].
[93] FFDCA §744C(f)(5) [21 U.S.C. §379j–43(f)(5)].

The GDUFA III reauthorization process began with a public meeting held in July 2020, followed by a 30-day comment period.[94] Beginning in September 2020, FDA has held negotiation sessions with industry and meetings with patient and consumer advocacy groups; minutes of the meetings are available on the FDA website.[95]

Considerations for GDUFA III[96]

GDUFA II was intended to facilitate faster access to generic drugs, with two major objectives: (1) reducing the number of review cycles and (2) increasing approvals of safe, high-quality, and lower-cost generic drugs.[97] As discussed below, these objectives may remain priorities under GDUFA III, given that most ANDAs continue to undergo multiple cycles of review prior to approval. In addition, FDA has voiced concerns about recurring drug shortages, particularly focusing on manufacturing disruptions and quality issues as contributing factors.[98] As explained below, certain drugs, including sterile injectable generics, may be particularly susceptible to shortages.

Multiple Review Cycles

Available data indicate that first-cycle ANDA approvals remain low,[99] although they have increased since GDUFA I was enacted. As mentioned above, prior to the enactment of GDUFA I in 2012, ANDAs were approved in one review cycle less than 1% of the time.[100] In FY2020, about 15% of ANDAs were approved or tentatively approved in the first cycle.

In August 2019, GAO published a report that analyzed FDA data on ANDAs that were first submitted to and reviewed by FDA in FY2015 through FY2017. As part of its study, GAO reviewed documentation from the first review cycle for a subset of 35 ANDAs submitted to FDA in FY2017 and FY2018. GAO reported that 12% of ANDAs reviewed from FY2015 through FY2017 were approved in the first cycle.[101] In addition, GAO identified the following specific

[94] FDA, "Public Meeting on the Reauthorization of the Generic Drug User Fee Amendments (GDUFA)," https://www.fda.gov/drugs/public-meeting-reauthorization-generic-drug-user-fee-amendments-gdufa-07212020-07212020.

[95] FDA, "GDUFA III Reauthorization Negotiation Sessions," https://www.fda.gov/drugs/development-approval-process-drugs/gdufa-iii-reauthorization-negotiation-sessions, and "GDUFA Reauthorization Stakeholder Meetings," https://www.fda.gov/industry/generic-drug-user-fee-amendments/gdufa-reauthorization-stakeholder-meetings.

[96] This is not a comprehensive discussion of all issues under considerations during GDUFA III negotiations.

[97] FDA, "FDA Public Meeting Generic Drug User Fee Amendments (GDUFA) of 2017," July 21, 2020, p. 40, https://www.fda.gov/media/141309/download.

[98] FDA, "Statement on FDA's new report regarding root causes and potential solutions to drug shortages," October 29, 2019, https://www.fda.gov/news-events/press-announcements/statement-fdas-new-report-regarding-root-causes-and-potential-solutions-drug-shortages.

[99] This in contrast to approval of new drug applications and biologics license applications under the Prescription Drug User Fee Act (PDUFA). According to the FY2019 PDUFA performance report, preliminary data show that the percentage of priority (6-month review goal) and standard (10-month review goal) applications filed in FY2018 and approved during the first review cycle was 89% and 61%, respectively; see https://www.fda.gov/media/138325/download.

[100] Statement of Janet Woodcock, MD, Director of CDER, FDA, before the House Committee on Energy and Commerce, Subcommittee on Health, March 2, 2017, p. 4.

[101] GAO, "Generic Drug Applications: FDA Should Take Additional Steps to Address Factors That May Affect Approval Rates in the First Review Cycle," August 2019, GAO-19-565, https://www.gao.gov/assets/710/700779.pdf.

factors that may have contributed to whether an application received approval in the first review cycle:

- **Sufficiency of the ANDA.** This includes completeness of the application and the applicant's understanding of regulatory requirements. FDA will RTR an incomplete ANDA, and ANDAs that receive RTR are less likely to receive a first-cycle approval.[102] Less experienced applicants were more likely to produce lower-quality ANDAs compared to applicants with relatively more experience.[103]
- **Drug quality deficiencies.** Drug quality deficiencies, including those related to manufacturing facilities, were the most common deficiencies that remained at the end of the first review cycle, based on GAO's review of the documentation for the subset of 35 ANDAs, 26 of which were not approved in the first cycle.[104]
- **Type of drug.** Certain drug characteristics, including route of administration and complexity, may affect first-cycle approval. GAO found that between FY2015 and FY2017, FDA reviewed ANDAs for 41 ophthalmic drugs (i.e., drugs administered through the eye) and 20 transdermal drugs (i.e., drugs administered through the skin), none of which received approval in the first cycle. In contrast, of the 205 reviewed ANDAs for topical drugs (i.e., drugs administered to the skin with limited systemic absorption), 25% (52 ANDAs) received first-cycle approval.[105]
- **Priority review designation.** GAO found that first-cycle approval rates were lower for ANDAs for first generics (typically granted priority review) than for ANDAs with no priority designation. This may be because applicants have a financial incentive to be the first to file an ANDA for a first generic, potentially rushing and submitting a lower-quality application as a result.[106] In contrast to first generics, other priority-designated ANDAs—such as those responding to a drug shortage or public health emergency—had higher first-cycle approval rates than nonpriority ANDAs.[107]

GAO notes in the report that FDA has taken various actions to increase the rate of first-cycle ANDA approvals, for example, issuing regulatory and product-specific guidance, communicating with applicants during the review cycle, and assisting applicants with development of complex generics. FDA has taken actions to improve consistency among agency reviewers by creating review templates and working to increase reviewers' and applicants' understanding of industry

[102] FDA, "OGD UPDATE: Welcome to much more than GDUFA II," Kathleen Uhl, Director Office of Generic Drugs, September 7, 2017, pp. 12-16, https://www.fda.gov/media/115887/download.

[103] GAO, "Generic Drug Applications: FDA Should Take Additional Steps to Address Factors That May Affect Approval Rates in the First Review Cycle," p. 11.

[104] Ibid., p. 12.

[105] Ibid., pp. 12-14.

[106] The first applicant to submit a substantially complete ANDA that makes a paragraph IV certification with respect to the RLD's unexpired patents may obtain 180 days of exclusivity (FFDCA §505(j)(5)(B)(iv) [21 U.S.C. §355(j)(5)(B)(iv)]. For additional information, see CRS Report R46679, *Drug Prices: The Role of Patents and Regulatory Exclusivities*.

[107]GAO, "Generic Drug Applications: FDA Should Take Additional Steps to Address Factors That May Affect Approval Rates in the First Review Cycle," pp. 14-15.

practices and FDA review standards.[108] However, generic applicants noted that inconsistencies among FDA reviewers continue to exist and may influence first-cycle approvals.

Generic Drug Quality and Manufacturing

Although generic drug manufacturers must comply with current good manufacturing practices (CGMPs), few incentives exist for drug manufacturers to engage in mature quality management systems that go beyond CGMPs.[109] FDA has indicated that quality issues are the most common immediate causes of drug manufacturing interruptions, which can result in shortages.[110] Sterile injectable generic drugs are particularly susceptible to shortages for various reasons, including low profitability and lack of incentive for manufacturers to invest in manufacturing quality and redundant capacity.[111] Concerns about manufacturing quality and shortages have been compounded by the COVID-19 pandemic, which has limited FDA's ability to conduct facility inspections, particularly foreign inspections.[112]

FDA has proposed policy initiatives to improve manufacturing quality and prevent drug shortages. For example, in July 2015, FDA had proposed a voluntary quality metrics program in which the agency would request submission of certain quality metrics (e.g., "the number of lot release and stability tests conducted for the product") from owners and operators of certain human drug establishments.[113] This information was intended to be used to "further develop the FDA's risk-based inspection scheduling, to identify situations in which there may be a risk for drug supply disruption, to improve the efficiency and effectiveness of establishment inspections, and to improve FDA's evaluation of drug manufacturing and control operations."[114] Subsequently in November 2016, FDA issued a revised draft guidance describing the initial phase of the quality metrics program as voluntary. However, the revised draft guidance further indicated that after evaluating the results of the voluntary phase of the quality metrics program in 2018, the agency intended to "initiate notice and comment rulemaking under existing statutory authority to develop a mandatory quality metrics reporting program."[115] Several pharmaceutical industry groups submitted comments to the docket in opposition of FDA's proposal, calling it burdensome and raising questions about FDA's authority to implement such a mandatory program.[116] Based on

[108] Ibid., pp. 16-19.

[109] Mature quality management systems refers to robust manufacturing systems that go beyond compliance with CGMPs, which FDA considers to be a minimum threshold. Such mature systems may include deploying advanced quality control techniques to prevent quality problems and thus disruptions in manufacturing. See Testimony of Dr. Janet Woodcock, "Securing the U.S. Drug Supply Chain: Oversight of FDA's Foreign Inspection Program," U.S. Congress, House Committee on Energy and Commerce, Subcommittee on Oversight and Investigations, 116th Congress, 1st session, December 10, 2019, https://energycommerce.house.gov/committee-activity/hearings/hearing-on-securing-the-us-drug-supply-chain-oversight-of-fda-s-foreign.

[110] FDA, "Drug Shortages: Root Causes and Potential Solutions," published October 2019 and updated February 2020, p. 76, https://www.fda.gov/media/131130/download.

[111] Ibid., pp. 21-22.

[112] GAO, Statement of Mary Denigan-Macauley, Director, Health Care, "Drug Safety: FDA's Future Inspection Plans Need to Address Issues Presented by COVID-19 Backlog," GAO-21-409T, March 4, 2021, https://www.gao.gov/assets/gao-21-409t.pdf. FDA, "FDA Public Meeting Generic Drug User Fee Amendments (GDUFA) of 2017," July 21, 2020, p. 33.

[113] FDA, "Request for Quality Metrics; Notice of Draft Guidance Availability and Public Meeting; Request for Comments," 80 *Federal Register* 44973, July 28, 2015.

[114] Ibid.

[115] FDA, "Submission of Quality Metrics Data; Draft Guidance for Industry; Availability; Request for Comments," 81 *Federal Register*, November 25, 2016.

[116] See, for example, a presentation by David Gaugh, R.Ph., GPhA (the Generic Pharmaceutical Association, now the

input from the pharmaceutical industry, in June 2018, FDA announced two voluntary programs, the Quality Metrics Feedback Program and the Quality Metrics Site Visit Program.[117] FDA has not yet finalized its quality metrics guidance.

In addition, FDA has supported and encouraged the adoption of advanced manufacturing technologies (i.e., technologies that may improve drug quality, reduce shortages, and speed time to market).[118] One example of an advanced manufacturing technology is continuous manufacturing, which refers to a nonstop process that is conducted largely within the same facility and eliminates hold times between steps. This technology differs from the traditionally used batch manufacturing process, which involves multiple discrete steps during which a material may be stored in and shipped to multiple facilities for further processing, requiring additional time and equipment, and potentially degrading sensitive ingredients.[119] The Association for Accessible Medicines (AAM, the generic industry trade group), however, has indicated that continuous manufacturing may not be practical for some generic products, particularly low-volume products that are manufactured once or twice a year, and may require significant financial investment.[120]

Concluding Comments

GDUFA II is set to expire on September 30, 2022. The GDUFA III reauthorization process began on July 21, 2020, with a public meeting, during which FDA officials indicated that there is "still work to be done to further enhance efficiency, transparency, and gain more first-cycle approvals."[121] Congress may consider whether to consult with FDA and the generic drug industry on ways to further increase efficiency and timeliness and reduce delays in the review process.

Further, user fee legislation historically has been used to address related FDA policy concerns. GDUFA I was enacted as part of FDASIA, which made broader reforms to FDA's regulatory policy. While FDASIA did not directly address generic drug review (outside of GDUFA), the law did amend FDA's drug inspection framework, requiring the agency to conduct surveillance inspections of both domestic and foreign manufacturing establishments on a risk-based schedule.[122] Prior to FDASIA, FDA was required to inspect domestic establishments every two

Association for Accessible Medicines), regarding the Quality Metrics Public Meeting, August 24, 2015, posted to FDA-2015-D-2537-0036 on October 22, 2015, https://www.regulations.gov/document/FDA-2015-D-2537-0036.

[117] FDA, "Modernizing Pharmaceutical Quality Systems; Studying Quality Metrics and Quality Culture; Quality Metrics Feedback Program," 83 *Federal Register* 30748, June 29, 2018, and "Quality Metrics Site Visit Program for Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research Staff; Information Available to Industry 2018," 83 *Federal Register* 30751, June 29, 2018.

[118] FDA, "FDA Public Meeting Generic Drug User Fee Amendments (GDUFA) of 2017," July 21, 2020, p. 70; "Accelerating the Adoption of Advanced Manufacturing Technologies to Strengthen Our Public Health Infrastructure," current as of January 15, 2021, https://www.fda.gov/news-events/fda-voices/accelerating-adoption-advanced-manufacturing-technologies-strengthen-our-public-health; "Advanced Manufacturing," current as of January 16, 2021, https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/advanced-manufacturing.

[119] FDA, "Modernizing the Way Drugs Are Made: A Transition to Continuous Manufacturing," current as of May 17, 2017, https://www.fda.gov/drugs/news-events-human-drugs/modernizing-way-drugs-are-made-transition-continuous-manufacturing.

[120] Comments from the Association for Accessible Medicines (AAM) to Docket No. FDA-2017-N-3615: Administering the Hatch-Waxman Amendments: Ensuring a Balance Between Innovation and Access; Public Meeting, Request for Comments, November 17, 2017, pp. 18-19.

[121] FDA, "GDUFA II: Overview of Goals and Accomplishments, GDUFA III Public Meeting 7/21/2020," by Maryll W. Toufanian, Director of the Office of Generic Drug Policy, p. 47, https://www.fda.gov/media/141309/download.

[122] P.L. 112-144. §705. See also CRS Report R46507, *FDA's Role in the Medical Product Supply Chain and*

years, with no comparable requirement for foreign establishments. GDUFA II was enacted as Title III of FDARA, which also included provisions related to ANDA prioritization, facility reinspection, and review transparency.[123] In this context, Congress may consider using user fee reauthorization to address broader FDA-related policy concerns.

Considerations During COVID-19.

[123] P.L. 115-52, Title VIII "Improving Generic Drug Access." See CRS Report R44961, *FDA Reauthorization Act of 2017 (FDARA, P.L. 115-52)*.

Appendix A. GDUFA II Review Performance Goals

Table A-1. Review Performance Goals

ANDAs, ANDA amendments, PASs, and PAS amendments

Submission Type	Standard	Priority
Original ANDAs	Act on 90% within 10 months of ANDA submission	Act on 90% within • 8 months if preapproval inspection is required and complete and accurate PFC is submitted 2 months prior to submission, • 10 months if preapproval inspection is required and PFC is not submitted 2 months prior
Major ANDA amendments	Act on 90% within • 8 months if preapproval inspection not required, • 10 months if preapproval inspection is required	Act on 90% within • 6 months if preapproval inspection not required, • 8 months if preapproval inspection is required and complete and accurate PFC is submitted 2 months prior to submission, • 10 months if preapproval inspection is required and PFC is not submitted 2 months prior
Minor ANDA amendments	Act on 90% within 3 months of submission date	Act on 90% within 3 months of submission date
PASs	Act on 90% within • 6 months if preapproval inspection not required, • 10 months if preapproval inspection required.	Act on 90% within • 4 months if preapproval inspection not required, • 8 months if preapproval inspection is required and complete and accurate PFC is submitted 2 months prior to submission, • 10 months if preapproval inspection is required and PFC is not submitted 2 months prior

Submission Type	Standard	Priority
PAS major amendments	Act on 90% within • 6 months if preapproval inspection not required, • 10 months if preapproval inspection required.	Act on 90% within • 4 months if preapproval inspection not required, • 8 months if preapproval inspection is required and complete and accurate PFC is submitted 2 months prior to submission, • 10 months if preapproval inspection is required and PFC is not submitted 2 months prior
PAS minor amendments	Act on 90% within 3 months of submission date	Act on 90% within 3 months of submission date

Source: Table created by CRS based on the "GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years FY2018-2022," https://www.fda.gov/media/101052/download.

Notes: ANDA = abbreviated new drug application, PAS = prior approval supplement, PFC = Pre-Submission Facility Correspondence.

Appendix B. Acronyms Used in This Report

AAM	Association for Accessible Medicines
ANDA	Abbreviated New Drug Application
API	Active Pharmaceutical Ingredient
CBE	Changes Being Effected
CDER	Center for Drug Evaluation and Research
CGMP	Current Good Manufacturing Practice
CMO	Contract Manufacturing Organization
DMF	Drug Master File
DRL	Discipline Review Letter
FDA	Food and Drug Administration
FDAAA	FDA Amendments Act of 2007
FDARA	FDA Reauthorization Act of 2017
FDASIA	FDA Safety Innovation Act of 2012
FDF	Finished Dosage Form
FFDCA	Federal Food, Drug, and Cosmetic Act
FTC	Federal Trade Commission
GAO	Government Accountability Office
GDUFA	Generic Drug User Fee Amendments
IR	Information Request
MAPP	Manual of Policies and Procedures
NDA	New Drug Application
OGD	Office of Generic Drugs
OPQ	Office of Pharmaceutical Quality
ORA	Office of Regulatory Affairs
PAS	Prior Approval Supplement
PDUFA	Prescription Drug User Fee Act
RLD	Reference Listed Drug
RTR	Refuse to Receive

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