The first reauthorization of the Generic Drug User Fee Amendments (GDUFA II) was signed into law by President Trump on August 18, 2017, as part of the FDA Reauthorization Act of 2017 (FDARA) (P.L. 115-52). After a brief overview of significant GDUFA II changes and enhancements, this Strategic Perspective will summarize seven guidance documents issued by the FDA in October 2017 (two final and five draft) that are designed to assist industry in understanding and complying with GDUFA II.

**GDUFA II Changes and Enhancements**

Originally signed into law as part of the FDA Safety and Innovation Act (FDASIA) (P.L. 112-144) on July 9, 2012, GDUFA was designed to speed the delivery of safe and effective generic drugs to the public and improve upon the predictability of the review process. According to the Congressional testimony of Janet Woodcock, M.D., Director of the FDA’s Center for Drug Evaluation and Research, and the FDA’s GDUFA Reauthorization Performance Goals and Program Enhancements for Fiscal Years 2018-2022 (the GDUFA II Commitment Letter), GDUFA II performance goals and enhancements for fiscal years 2018 through 2022 include:

- **Faster review of priority ANDAs.** In GDUFA II, standard abbreviated new drug applications (ANDAs) will continue to be reviewed within 10 months of submission, but priority ANDAs will be reviewed within eight months of submission. To help ensure the more aggressive eight month timeline for each priority review, the applicant will have to submit a pre-submission facility correspondence (PFC) listing all of the facilities that will require FDA inspection at least two months prior to the date of ANDA submission.

- **Establishment of pre-ANDA program.** To reduce the number of cycles to approval, particularly for complex products, GDUFA II establishes a pre-ANDA program, consisting of a product development meeting, pre-submission meeting, and mid-review-cycle meeting.

- **ANDA review enhancements.** Instead of communicating deficiencies at the end of the review, at a point when it is too late for an applicant to fix them, GDUFA II will use “real time” communications to allow corrections to be made in the current review cycle.

- **Drug Master File (DMF) review.** The review program for DMFs, submissions from active pharmaceutical ingredient (API) manufacturers providing confidential information about facilities, processes, or articles used to manufacture, process, package, or store drugs, are enhanced under the GDUFA II Commitment Letter.

- **Facility assessments.** Under GDUFA II, the FDA will issue guidance and conduct outreach to foreign regulators on the risk-based selection model and take steps to support exports, enhance the speed and transparency of communications regarding facility assessments, and update its existing, publicly-available facility compliance status database.

- **Accountability and reporting.** In GDUFA II, enhanced infrastructure and analytics will increase transparency and accountability and strengthen program management and resource use. The FDA will expand GDUFA program reporting on a monthly, quarterly, and annual basis, enabling Congress, the industry, and stakeholders to gauge the generic drug program’s performance.

- **Program size commensurate with ANDA workload.** Because the number of ANDA submissions received substantially exceeded projections in GDUFA I, the FDA and the generic drug industry agreed that user fees
should total $493.6 million annually, adjusted for inflation, to maintain productivity and implement proposed improvements under GDUFA II.

Modification of user fee structure. To maintain program stability, the FDA and industry agreed to shift toward annual program fees: firms that sponsor one or more approved ANDAs will pay an annual fee, while ANDA sponsors making changes to an already approved ANDA through a prior approval supplement (PAS) will not pay a fee.

Treatment of small businesses. No facility or ANDA sponsor will be charged an annual fee until an ANDA in which it is listed is approved. The annual program fee will be based on the number of approved ANDAs owned by the firm and affiliates. Contract manufacturing organizations (CMOs) hired by ANDA sponsors to manufacture their generic drugs will pay one-third the annual facility fee paid by ANDA holders.

October 2017 GDUFA II Guidance

Since the October 1, 2017, effective date, the FDA has issued two final and five draft guidance documents to assist industry in understanding and complying with GDUFA II. Summaries of the two final guidance documents follow:

1. **ANDA Submissions—Prior Approval Supplements.** This guidance clarifies how the FDA will handle a PAS and amendments to a PAS for an ANDA subject to the GDUFA performance metric goals. Specifically, it describes how the GDUFA II performance metric goals apply to a PAS subject to the refuse-to-receive (RTR) standards, a PAS that requires an inspection, a PAS for which an inspection is not required, and an amendment to a PAS. It also confirms that, effective October 1, 2017, ANDA applicants no longer are required to pay application fees when they submit a PAS.

2. **Completeness Assessments for Type II API DMFs.** This guidance is intended for holders of Type II API DMFs that are or will be referenced in an ANDA, an amendment to an ANDA, a PAS to an ANDA, or an amendment to a PAS. A Type II DMF may include drug substances, substance intermediates, and materials used in their preparation, or a drug product. A Type II DMF also can cover dosage form drugs manufactured under contract for another company that would file an ANDA. The guidance explains that DMF holders are required to pay a DMF fee when first authorizing the reference of their DMF in a generic application and that Type II API DMFs must undergo an FDA completeness assessment (CA). It makes recommendations about the information that should be included in the DMF to facilitate a GDUFA CA. It does not apply to Type II API DMFs used to support new drug applications (NDAs), biologics license applications (BLAs), other submissions that are not generic drug submissions, or any other types of DMFs.

The five draft guidance documents provide the following information:

1. **ANDA Submissions—Amendments to ANDAs.** This draft guidance explains how the review goals established as part of GDUFA II will apply to amendments to either ANDAs or PASs. Under GDUFA I, amendments were classified into a complex tier system. GDUFA II simplified the amendment review goals and no longer subjects them to a tier system; however, review goals continue to be dependent on several factors. In general, under GDUFA II, amendments are designated as either standard or priority, classified as major or minor, and receive a goal date based on the factors discussed in the draft guidance, including whether a preapproval inspection is needed.

2. **Formal Meetings between FDA and ANDA Applicants for Complex Products.** This draft guidance describes an enhanced pathway for discussions between the FDA and an applicant (or prospective applicant) preparing to submit an ANDA for a complex product to FDA. It provides information on requesting and conducting product development meetings, pre-submission meetings, and mid-review-cycle meetings with FDA.

3. **Requests for Reconsideration at the Division Level.** This draft guidance provides recommendations on the procedures for resolving scientific and regulatory issues or matters between the FDA and applicants of ANDAs that wish to pursue a request for reconsideration within the review discipline at the
division level or original signatory authority. As agreed to in the GDUFA II Commitment Letter, applicants may pursue a request for reconsideration within the review discipline at the division level. In addition, if an applicant requests a teleconference as part of its request to reclassify a major amendment or standard review status, the FDA will schedule and conduct the teleconference and decide 90 percent of such reclassification requests within 30 days of the date of the FDA’s receipt of the request for a teleconference. As stated in the Commitment Letter, this goal only applies when the applicant accepts the first scheduled teleconference date offered by the FDA (see FDA explains reconsideration processes for generic drug regulatory findings, October 12, 2017).

4. Post-Complete Response Letter (CRL) Meetings between FDA and ANDA Applicants. This draft guidance provides recommendations on post-CRL meetings between FDA and ANDA applicants for the purpose of clarifying deficiencies identified in a CRL to an ANDA. It is intended to provide procedures that will promote well-managed post-CRL meetings and help ensure that such meetings are scheduled and conducted in accordance with the time frames set forth in the GDUFA II Commitment Letter (see Post-complete response letter meeting requests clarified, October 16, 2017).

5. Assessing User Fees under GDUFA II. This draft guidance serves to provide an explanation about the new fee structure and types of fees for which entities are responsible. It describes the types of user fees authorized by GDUFA II, the process for submitting payments to the FDA, the consequences for failing to pay generic drug user fees, and the process for requesting a reconsideration of a user fee assessment. It also describes how the FDA determines affiliation for purposes of assessing generic drug user fees. The FY 2018 GDUFA II fees were published by the FDA on August 29, 2017 (82 FR 41026) (see GDUFA II’s user fees explained in draft guidance, October 30, 2017).

Conclusion

GDUFA II will not only will continue to provide user fees to the FDA to help fund its generic drug approval program, but will allow for even faster review of priority ANDAs, and enhancements to the pre-ANDA program, the DMF review program, facility assessments, and FDA accountability and reporting. GDUFA II also adjusts user fees to be commensurate with the overall ANDA workload, modifies the user fee structure to maintain a predictable fee base and better align program costs with the fee-paying ability of applicants, and takes small businesses concerns into account. The GDUFA II Commitment Letter and recent FDA guidance will be of considerable assistance to industry in understanding GDUFA II changes and complying with its new requirements.