

GDUFA II Public Comments

Introduction and Background

The Generic Drug User Fee Amendments of 2012 (GDUFA) authorizes the Food and Drug Administration (FDA) to collect user fees for the review of certain generic human drug applications and associated Type II active pharmaceutical ingredient (API) drug master files (DMFs), and to conduct associated inspections. GDUFA was authorized as part of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA). Authority for the GDUFA program expires on September 30, 2017. In preparation for GDUFA II, FDA began the reauthorization process with a public meeting on June 15, 2015. Following the meeting, a docket was open for 30 days for the public to submit written comments. In October 2015, FDA began negotiations with industry and monthly discussions with patient and consumer groups concurrently to determine proposed recommendations for the next GDUFA program. These discussions concluded in August 2016. Minutes of these meetings are posted on FDA's website at <http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm476940.htm>.

The provisions of the 2012 authorization of GDUFA also include the following requirements:

- (4) PUBLIC REVIEW OF RECOMMENDATIONS.—After negotiations with the generic drug industry, the Secretary shall—*
- (A) present the recommendations developed under paragraph (1) to the congressional committees specified in such paragraph;*
 - (B) publish such recommendations in the Federal Register;*
 - (C) provide for a period of 30 days for the public to provide written comments on such recommendations;*
 - (D) hold a meeting at which the public may present its views on such recommendations; and*
 - (E) after consideration of such public views and comments, revise such recommendations as necessary.*
- (5) TRANSMITTAL OF RECOMMENDATIONS.—Not later than January 15, 2017, the Secretary shall transmit to the Congress the revised recommendations under paragraph*

(4), a summary of the views and comments received under such paragraph, and any changes made to the recommendations in response to such views and comments.

FDA has complied with these requirements. Following administrative review and clearance, FDA posted the package of proposed recommendations at <http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf>. FDA held a public meeting on October 21, 2016, to accept public comments on the proposed package. The public docket subsequently closed on November 16, 2016. The transcript of the public meeting and the written comments submitted to the docket can be found on FDA's website at <http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm444958.htm>. This document provides a summary of the views and comments received at the October 21st public meeting and the 15 written comments submitted to the public docket. Following its review of the public comments, FDA has determined that no changes to the originally proposed recommendations are necessary, and we intend to send the recommendations to Congress in accordance with the procedures in section 744C(d)(5).

Summary of Public Comments

FDA acknowledges general support for the GDUFA II agreement from the public, including patient and consumer advocates, health care industry groups, and the generic drug industry. For example, there is wide support for proposals that would reduce review cycles and support timely approvals and access to high quality, affordable generic drugs, including complex generic drug products. Specific comments, including those making proposals or expressing support for, or concern regarding, the GDUFA II agreement, are noted below.

Submission Review Performance Goals (Section I of GDUFA II Commitment Letter)

For GDUFA II, FDA proposes two major changes to the submission review goals. First, all Abbreviated New Drug Applications (ANDAs) and ANDA amendments would fall within a single, consolidated review goals scheme to simplify and streamline program administration, promote review efficiency, and ensure that “no submission is left behind.” Second, GDUFA II would create faster review goals for priority submissions. For an ANDA, standard review would be 10 months from submission and priority review would be 8 months from submission. Priority review would be available for submissions that FDA considers to be public health priorities pursuant to the Center for Drug Evaluation and Research (CDER) Manual of Policies and Procedures (MAPP) 5240.3 Rev. 2, “Prioritization of the Review of Original ANDAs, Amendments, and Supplements.”¹

Stakeholders are supportive of these proposals; however, one national health organization questioned the feasibility of some of the proposed submission review goals, such as reviewing 90 percent of priority major ANDA amendments within 6 months (if a preapproval inspection is not required). We note that review goals became more rigorous each year of GDUFA I, that FDA has met or exceeded all GDUFA I review goals to date, that many review goals would stay the same from the last year of GDUFA I through GDUFA II, and that impactful changes to review goals were generally targeted towards faster review of priority submissions, which constitute a relatively small portion of our overall workload and are especially important to public health.

¹<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM407849.pdf>

ANDA Review Transparency and Communications Enhancements (Section II of GDUFA II Commitment Letter)

The purpose of the proposed GDUFA II ANDA review transparency and communications enhancements is to improve predictability and transparency, promote the efficiency and effectiveness of the review process, minimize the number of review cycles necessary for approval, increase the overall rate of approval, and facilitate greater consumer access to generic drugs.

A pharmacy company expressed support for the proposed review transparency and communications enhancements but said more should be done about “a backlog of more than 5,000” ANDAs. We note that there are approximately 2,200 ANDAs—not over 5,000 ANDAs—at FDA, that substantially all of them (except for very recent submissions) are under active review, and that GDUFA II would provide resources commensurate with FDA’s ANDA workload.

Pre-ANDA Program and Subsequent Mid-Review-Cycle Meetings for Complex Products (Section III of GDUFA II Commitment Letter)

The purpose of the proposed GDUFA II pre-ANDA program for complex products is to clarify regulatory expectations for prospective applicants early in product development, help applicants develop more complete submissions, promote a more efficient and effective review process, and reduce the number of review cycles to obtain ANDA approval of complex products.

Four comments specifically expressed support for the newly proposed pre-ANDA program. Specifically, a pharmacy company suggested the pre-ANDA program could help applicants develop more complete submissions for complex products. This company expressed support for FDA’s efforts to increase first-cycle approvals. (In total, five comments explicitly

agreed that the proposed GDUFA II agreement would support first-cycle approvals). The company also suggested increasing the availability of product-specific guidance could help manufacturers meet approval requirements more rapidly. An industry organization highlighted the importance of FDA's commitment to issue product-specific guidance for 90 percent of new chemical entity New Drug Applications that are approved on or after October 1, 2017, at least 2 years prior to the earliest lawful ANDA filing date, and agreed FDA should strive for approval of ANDAs in the first review cycle. A consumer advocacy group suggested the pre-ANDA program would help clarify regulatory expectations early in the generic drug development process and thus reduce review cycles. FDA notes that the pre-ANDA program and other elements of the GDUFA II Commitment Letter were developed for this very purpose. Finally, a company in the generic drug industry expressed appreciation for the enhanced pathway for complex products set forth in the GDUFA II Commitment Letter.

Facilities (Section V of GDUFA II Commitment Letter)

FDASIA eliminated long-standing minimum inspection frequency requirements and directed FDA instead to inspect drug facilities globally on the basis of risk. Industry sources have asserted that the transition to a new paradigm has been commercially disruptive for the regulated industry, which over time had developed procedures and expectations based on the old model. While facility assessment cuts across multiple FDA drug programs, GDUFA II contains several proposals on facility-related enhancements targeted to generic industry-specific challenges.

To mitigate export related challenges identified by U.S.-based API manufacturers, FDA would issue a guidance explaining the risk-based site selection model, undertake outreach to foreign regulators on the risk-based site selection model, and support the export of safe and

effective pharmaceutical products by the U.S.-based pharmaceutical industry, including through the issuance of communications conveying the current compliance status of U.S. manufacturing facilities to foreign regulators. One consumer advocacy group commented that it believed this guidance will help FDA communicate facility issues that could prevent ANDA and Prior Approval Supplement (PAS) approval.

To mitigate ANDA sponsor concerns regarding the transparency and speed of facility assessment and its impact on ANDA approvability and product launch, FDA would communicate outstanding facility issues that could prevent approval of an ANDA or PAS through an Information Request, Discipline Review Letter, or Complete Response Letter, and communicate to the facility owner final inspection classifications that do not negatively impact approvability of any pending application within 90 days of the end of the inspection. In addition, FDA would provide updates to and seek feedback from industry stakeholders regarding facility assessment. These enhancements would occur in Fiscal Years (FY) 2018 and 2019.

To enhance transparency concerning the compliance status of GDUFA self-identified facilities and sites, FDA would update its existing, publicly available database beginning in FY 2019. An organization representing hospitals and other providers commented that these transparency enhancements are welcomed by its providers.

Enhanced Accountability and Reporting (Section VI of GDUFA II Commitment Letter)

FDA proposes accountability and reporting enhancements to provide more robust internal capacity and workload analysis. These enhancements include developing a modernized time reporting approach in GDUFA II that will support accurately determining resource needs for the human generic drug review program. Further, FDA will contract with an independent third party

to provide financial transparency and help ensure that GDUFA user fee resources are administered, allocated, and reported in an efficient and transparent manner.

FDA received three comments that pertain to this section of the GDUFA Commitment Letter. One consumer advocacy group expressed support of the proposed commitment to timely perform regular assessment of progress on GDUFA goals and the allocation of user fees. A national health organization stated that public health advocates need more information on the amount of time required for FDA to review and act on applications. FDA notes that our proposed accountability and reporting enhancements are intended to provide this type of information. Finally, an industry organization highlighted that GDUFA I underestimated the human generic drug program's workload. The organization urged FDA to adopt human resource processes that provide the necessary resources and staff to support the timely approval of safe generic drug products. The Agency notes that the proposed accountability and reporting enhancements include more robust resource management planning, a modernized time-reporting system, and analysis both internally and by third-party experts. The activities we undertake will provide more detail on resource utilization and allocation necessary to meet the negotiated performance goals.

GDUFA User Fees

FDA proposes an improved user fee structure that will provide funding commensurate with overall program workload, shift the fee burden more toward annualized fees in order to maintain a predictable fee base and better align fee responsibility with program costs and fee-paying ability, and provide fee relief for small businesses and new market entrants.

Ten comments made specific statements with respect to GDUFA user fees. One national health organization expressed concern that the Agency receives inadequate appropriations and

that GDUFA user fees may not be sufficient for the Agency to meet the GDUFA goals or fulfill our public health mission. A healthcare professional expressed concern that the user fees may not be sufficient for FDA's operations. The same national health organization expressed support for the user fee structure, which the commenter said will provide a more stable source of funding and provide relief for small businesses. A consumer advocacy group agreed that the annual ANDA holder program fee in the proposed user fee structure will provide a more stable, predictable funding stream and urged FDA to ensure that the user fees are sufficient to address an increase in our workload. FDA recognizes the challenge of workload prediction and resource management. However, we note that, despite these challenges, we met or exceeded all of our goals in GDUFA I. Additionally, the introduction of an ANDA holder program fee will, as the comments indicated, provide a more stable source of funding that will help mitigate the effects of fluctuations in application fee collections.

Two private organizations with an interest in APIs expressed concern over the user fee structure. Their comments indicated that the API facility fee should be based on revenue, with lower-revenue companies paying a lower API facility fee. One of these commenters expressed support, describing as an improvement, our proposal that no facility or ANDA sponsor be charged an annual fee until an ANDA in which it is listed is approved. A third commenter made a more general statement that smaller companies should pay a lower GDUFA fee. This commenter also stated that a waiver should not be offered to smaller companies. Revenue-based fees were discussed extensively during GDUFA negotiations and in the small business workgroup.

We found that it would be challenging to administer a revenue-based program. For example, a company might meet various "small business" definitions, yet the same company

may have significant support—e.g., in the form of venture capital—or may be connected to a larger, higher-revenue company. Further, deciding which companies fit into a particular revenue tier is time- and resource-intensive, and the process of making this determination is a burden both for industry (who would have to produce information) and for FDA (who would have to process and verify the information). The small business workgroup—comprised of representatives from FDA and industry—concluded that the traditional models of small business support were neither the best nor most efficient way to provide targeted fee relief to small businesses and new market entrants. The workgroup discussions fed into a broader fee dialogue that yielded some new proposed mechanisms for fee relief in GDUFA II; specifically, through (1) the tiered ANDA-holder program fee; (2) a lower fee for Contract Manufacturing Organizations, which we found tend to be smaller businesses; and (3) our proposal that no facility or ANDA sponsor be charged an annual fee until an ANDA in which it is listed is approved.

One company from the generic drug industry expressed concern that the ANDA-holder program fee will have a negative impact on smaller generic drug companies and result in an increase in the cost of generic drugs. This company offered as options the following changes to the proposed fee structure: (1) increasing the allocated percentage of revenue derived from facility fees; (2) instituting a program fee where the entire amount to be collected in a particular fiscal year is divided by the number of approved ANDAs to obtain an amount to be paid per approved ANDA; and (3) shifting the tier levels.

We believe that the proposed fee structure achieves a reasonable balance between providing FDA with predictable, adequate funding for our human generic drug review program, dividing fee responsibilities equitably across different segments of the generic drug industry, and

providing relief for small businesses. The fee revenue percentages were the result of exhaustive negotiations between the four industry trade groups with the help of FDA as a facilitator. The second proposal, which amounts to a product fee, was summarily dismissed by one of the industry trade groups. Finally, the bounds of the ANDA tiers were the result of extensive research by FDA and industry, and ultimately proposed by the industry trade group that represents ANDA holders in all three tiers.

With respect to small businesses, six comments indicated that the proposed user fee structure is an improvement compared to the user fee structure under GDUFA I.

Other Comments

Numerous commenters provided input for FDA to consider as it implements the recommendations. An industry association that strongly supports the proposed agreement urged FDA, when implementing GDUFA II, to carefully consider potential unintended consequences, streamline and improve the submission review process, and focus on process improvements that will increase submission approvability. FDA notes that the proposed agreement is designed to streamline and improve the submission review process, increase submission completeness, and ultimately increase the rate of approvals.

In addition, four commenters (a health professional, an academic, an industry organization, and a national health organization) urged FDA to maintain its safety and quality standards when implementing GDUFA II. FDA strongly agrees it is critical to maintain safety and quality standards. The proposed GDUFA II agreement would not alter them.

Commenters also provided input concerning regulatory policy issues that are outside the scope of the proposed GDUFA II agreement, which focuses on review goals and program enhancements. For example, some commenters provided input on FDA policies concerning drug

shortages, specific regulatory science grants, regulatory science policy concerning complex products, and prioritization of the review of submissions that the Agency considers to be public health priorities.

Finally, a national health organization and a consumer advocacy group expressed concern that user fees give rise to at least an appearance of impropriety due to the regulated industry paying FDA. We note that these concerns attach principally to the statute concerning user fees, and are not directed uniquely at the proposed GDUFA II agreement. In addition, improving the timeliness, transparency, and predictability of submission review, and broadening access to quality affordable generic medicines, clearly benefits American consumers. The user fee program would not change FDA's standards for safety and quality. User fee review goals are negotiated so that the performance is stated in terms of target timelines within which FDA will make a decision, not the outcome of that decision. User fees are administered by a separate and distinct FDA organizational unit; reviewers continue to focus exclusively on scientific and technical review of submissions. These and other features of the proposed agreement are designed to ensure that FDA always serves the interest of public health with integrity and public confidence.

Conclusion

The feedback provided throughout the GDUFA reauthorization process has given FDA a better understanding of the concerns and priorities held by a diverse group of public stakeholders. This feedback was the basis for a number of proposals in the GDUFA II agreement that will reduce review cycles and support timely approvals and access to high quality, affordable generic drugs, including complex generic drug products.