APhA
American Pharmacists Association

Via Electronic Submission to: www.regulations.gov

December 12, 2021

Dockets Management Staff (HFA–305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Generic Drug User Fee Amendments; Public Meeting; Request for Comments (Docket No. FDA-2020-N-1459)

Dear Food and Drug Administration staff:

The American Pharmacists Association (APhA) is pleased to submit our comments to the Food and Drug Administration (FDA) on the "Generic Drug User Fee Amendments; Public Meeting; Request for Comments"[1] and the GDUFA III draft commitment letter.[2] Founded in 1852, APhA is the largest association of pharmacists in the United States representing the entire pharmacy profession. APhA members practice in community pharmacies, hospitals, long-term care facilities, specialty pharmacies, community health centers, physician offices, ambulatory clinics, managed care organizations, hospice settings, and government facilities. Our members strive to improve medication use, advance patient care, and enhance public health.

APhA believes that FDA has made good progress on GDUFA II's goals. The agency has improved the efficiency of the generic drug review and approval process and increased consumer access to high-quality, safe and effective, and affordable generic drugs. In FY 2021 alone, there have been:

- 670+ Approvals; 150+ Tentative Approvals
- 90+ first generics
- 1850+ Complete Response Letters (CRLs)
- 4700+ Information Requests (IRs) and Discipline Review Letters (DRLs)

[1] FDA. Generic Drug User Fee Amendments; Public Meeting; Request for Comments. 86 FR 60049. October 29, 2021. Available at: https://www.govinfo.gov/content/pkg/FR-2021-10-29/pdf/2021-23499.pdf
[2] FDA. GDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROGRAM ENHANCEMENTS FISCAL YEARS 2023-2027 (hereinafter "Commitment Letter"). Available at: https://www.fda.gov/media/153631/download

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- 550+ Drug Master File (DMF) Reviews[3]

In addition, FDA reached the milestone of 100+ cumulative Competitive Generic Therapy (CGT) approvals.[4]

The availability of affordable, quality generic drugs is critical to patient health and results in significant cost savings. According to the Association for Accessible Medicines (AAM), in 2019, generic drugs accounted for 90% of prescriptions in the United States, but only 20% of the costs.[5] In 2019 alone, generic drugs saved the U.S. health care system $313 billion[6], and nearly $2.2 trillion over the past 10 years.[7] In order to continue to reap the benefits of generic drugs, FDA must build upon the successes of GDUFA II.

APhA appreciated the opportunity to share our perspective during the GDUFA III stakeholder meetings and offers the following comments on the draft Commitment Letter:

SUBMISSION ASSESSMENT PERFORMANCE GOALS (pp. 4 - 11)

APhA is pleased to see that FDA has exceeded the 90% performance level under GDUFA II for several submission types:

- FDA agreed to review and act on standard original ANDAs within 10 months of the date of ANDA submission. As of September 30, 2020, FDA has met 98% of the FY 2020 goals for these applications.

- FDA agreed to review and act on priority original ANDA submissions with an 8-month goal date if the applicant submits a Pre-Submission Facility Correspondence (PFC) 2 months prior to the date of ANDA submission and the PFC is found to be complete and accurate and remains unchanged. As of September 30, 2020, FDA has met 93% of the FY 2020 goals for these applications.

[3] FDA. Public Meeting on the Reauthorization of Generic Drug User Fee Amendments (GDUFA III) (hereinafter "GDUFA III Public Meeting"). Nov. 16, 2021. Slide 14, accessed on Dec. 8, 2021 at: https://www.fda.gov/media/154305/download
[4] Id.
[5] Association for Accessible Medicines (2020). Securing Our Access & Savings: 2020 Generic Drug & Biosimilars Access & Savings in the U.S. Report, p. 16, accessed on Dec. 2, 2021 at https://accessiblemeds.org/sites/default/files/2020-09/AAM-2020-Generics-Biosimilars-Access-Savings-Report-US-Web.pdf
[6] Id.
[7] Id. at p. 18.

- FDA agreed to review and act on standard prior approval supplements (PASs) within 6 months of the date of submission if no inspection is needed. As of September 30, 2020, FDA has met 99% of the FY 2020 goals for these applications.[8]

There is room for improvement in first review cycle approvals, however. A 2019 GAO report found that FDA only approved 12% of generic drug applications in the first review cycle in FYs 2015-2017.[9] On average, applications went through 3 review cycles before approval, delaying the generic drug's arrival to market.[10] APhA supports initiatives included in the Commitment Letter that will improve first cycle approvals, such as increased communications and meetings between FDA and generic drug manufacturers; the Imminent Action pathway; the issuance/updating of guidances and Manuals of Policies and Procedures (MAPPs); and other program enhancements. In order to track FDA's performance, APhA also supports the extensive monthly, quarterly, and annual reporting metrics detailed in the Commitment Letter.[11]

ANDA Assessment Transparency and Communications Enhancements (pp. 12 – 16)

APhA supports the ANDA assessment program enhancements related to Information Requests (IRs), Discipline Review Letters (DRLs), Imminent Actions, and communications regarding deficiencies and actions, including post-CRL teleconferences and post-CRL Scientific Meetings detailed in the Commitment Letter. These program enhancements are designed to improve predictability and transparency, promote the efficiency and effectiveness of the review process, minimize the number of assessment cycles necessary for approval, increase the overall rate of approval, and facilitate greater access to generic drug products.

Suitability Petitions (pp. 21 - 22)

APhA supports FDA's commitment to enhance the review and response times for suitability petitions, including the commitment to conduct a completeness assessment within 21 days after receipt of the original petition or the receipt of the IR response. APhA particularly appreciates the agency's commitment to prioritize the review of suitability petitions for a drug that:

a. could mitigate or resolve a drug shortage and prevent future shortages;

[8] FY 2020 Performance Report to Congress for the Generic Drug User Fee Amendments, p. 9; accessed on Dec. 2, 2021 at https://www.fda.gov/media/151618/download
[9] GAO (Aug. 2019): GENERIC DRUG APPLICATIONS: FDA Should Take Additional Steps to Address Factors That May Affect Approval Rates in the First Review Cycle; p. 10, accessed on Dec. 8, 2021 at https://www.gao.gov/assets/710/700779.pdf
[10] Id.
[11] Commitment Letter at pp. 42-44.

b. address a public health emergency;
c. is for a new strength of a parenteral product that could aid in eliminating pharmaceutical waste or mitigating the number of vials needed per dose; or
d. is subject to special review programs under the President's Emergency Plan for AIDS Relief (PEPFAR).

Product-Specific Guidance (pp. 23 – 25)

APhA supports FDA's commitment to continue to issue product-specific guidances (PSG) identifying the methodology for generating the evidence needed to support ANDA approval, especially for Complex Products. APhA also supports the PSG performance metrics; increased transparency of PSGs under development; the prioritization of PSGs based on industry requests and public input; and the opportunity for an applicant or prospective applicant who has already commenced an in vivo bioequivalence study to request a PSG Teleconference and follow-up meeting when a new or revised PSG is published. The PSG Teleconference and PSG Meeting will enable the applicant to obtain FDA's feedback on the potential impact of the new or revised PSG on its development program, as well as discuss its development approach to ensure compliance with the relevant statutes and regulations.

Meetings (pp. 25 – 29)

To improve ANDA assessment efficiency, APhA supports the following types of meetings included in the Commitment Letter:

- A *pre-ANDA submission Product Development Meeting* (pp. 25 – 26) to provide a forum for scientific exchange on specific issues in which FDA will provide targeted advice regarding an ongoing ANDA development program.

- A *Pre-Submission Meeting* (pp. 26 – 27) to present unique or novel data or information that will be included in the ANDA submission.

- A *Mid-Cycle Review Meeting* or an *Enhanced Mid-Cycle Review Meeting* for complex generic product applicants who were granted a Product Development Meeting, in order to:

- Mid-Cycle Review Meeting (pp. 27 – 28): ask for the FDA's rationale for any deficiency identified in the mid-cycle DRL(s), and/or to ask questions related to FDA's assessment of the data or information in the ANDA.

- Enhanced Mid-Cycle Review Meeting (p. 28): ask questions related to a proposed scientific path to address possible deficiencies identified in the mid-cycle DRL(s). The applicant may ask questions about potential new data or information to address any possible deficiencies.

- A *Post-CRL Scientific Meeting* (pp. 28-29) to provide an applicant scientific advice on possible approaches to address deficiencies identified in a CRL related to establishing equivalence.

DMF ASSESSMENT PROGRAM ENHANCEMENTS (pp. 30 – 33)

As discussed at the GDUFA III Public Meeting, Drug Master Files (DMFs) remain a challenge for ANDA applicants because on average a DMF holder's response time to FDA questions exceeds 3 months, limiting the ability for the DMF to be adequate in one review cycle.[12] For this reason, APhA supports the program enhancements included in the Commitment Letter which are intended to facilitate timely DMF assessment. These include the following, among others:

- DMF Review Prior to ANDA Submission (pp. 31 – 32)

  - A DMF holder may submit a request for assessment 6 months prior to the planned submission date for: 1) an original ANDA, 2) an ANDA amendment containing a response to a CRL, or 3) an amendment seeking approval of an ANDA that previously received a tentative approval.

  - A DMF holder may submit a request for assessment 6 months prior to the planned submission date for a Post Approval Supplement (PAS) to add a new Active Pharmaceutical Ingredient (API) source, provided that:

    a. The PAS is for a drug product that could help mitigate or resolve a drug shortage and prevent future shortages; or

[12] FDA. Public Meeting on the Reauthorization of Generic Drug User Fee Amendments (GDUFA III). Nov. 16, 2021. Slide 31, accessed on Dec. 8, 2021 at: https://www.fda.gov/media/154305/download

b. The PAS is for a drug product that could help address a public health emergency.

- Teleconferences to Clarify DMF First Cycle Assessment Deficiencies (pp. 30 – 31)

  - FDA will grant and conduct teleconferences when requested to clarify deficiencies in first cycle DMF deficiency letters.

- Off-Cycle Review of Solicited DMF Amendments (pp. 32 – 33)

  - FDA will assess solicited DMF amendments related to original ANDAs and PASs upon receipt even if the original ANDA or PAS is not currently under assessment.

  - FDA will issue a MAPP on the prioritization of FDA assessment of solicited DMF amendments on or before June 30, 2024.[13]

  - FDA will ensure that DMF assessment comments submitted to the DMF holder are issued at least in parallel with the issuance of review comments relating to the DMF for the ANDA.

- Unsolicited DMF Amendments

  - FDA will assist with coordination of an unsolicited amendment to avoid introducing delays to the ANDAs the DMF supports.[14]

- API-Excipient Mixtures

  - FDA will issue guidance clarifying the regulatory status of API-excipient mixtures for GDUFA purposes.[15]

FACILITIES (pp. 33 – 38)

[13] Commitment Letter at p. 41.
[14] GDUFA III Public Meeting at Slide 31.
[15] Commitment Letter at p. 41.

APhA supports commitments designed to address deficiencies identified during facility inspections. These include:

- Improved Communications
  - Notification to the applicant through an IR, DRL or CRL that issues exist with preapproval inspection of a facility or site.
  - Monthly updating of the publicly available Inspection Classification Database.
- Post-Warning Letter Meetings
  - ANDA applicants may request a meeting with FDA to seek the Agency's feedback on the applicant's plan to remediate facility deviations identified in a warning letter.
  - FDA will issue guidance regarding the Post-Warning Letter Meeting process, including recommendations on items facilities should submit as part of a meeting request.
- Reinspection Metrics
  - FDA will reinspect a domestic facility within 4 months of the letter to the facility granting the applicant's reinspection request, and within 8 months for an international facility.
- Reclassification of Facility-Based Major CRL Amendments[16]
  - FDA will grant the request to reclassify the Facility-Based Major CRL Amendment to minor if FDA determines that none of the following are necessary to complete the assessment of the amendment:
    i. A facility inspection

[16] Id. at pp. 17-18.

ii. Use of alternate tools for facility assessment
iii. Continued assessment of inspection deficiency responses

- FDA will make a decision on a request for reclassification of a Facility-Based Major CRL Amendment within 30 days from the date of submission for priority amendments and within 60 days for standard amendments.

- FDA will issue a MAPP on the process for Reclassification of Facility-Based Major CRL Amendments on or before June 30, 2024.[17]

Continued Enhancement of User Fee Resource Management (pp. 38 - 41)

For FY 2020, FDA had total budgetary resources for the GDUFA program of $697.4 million (including carryover balance), spent $540.7 million for the generic drug review process,[18] and carried a cumulative balance of $152.7 million forward for future fiscal years.[19] The FY 2022 estimates are $656.4 million in total budgetary resources (including carryover balance), $568.7 million in total expenses,[20] and an $87.6 million carryover balance.[21] In GDUFA III, it will be critical for FDA to continue to be a good steward of its financial resources. We urge FDA to continue its activities to mature the Agency's resource capacity planning (RCP) function, including utilization of modernized time reporting to support enhanced management of GDUFA resources and implementation of the Capacity Planning Adjustment (CPA).

Accordingly, APhA supports FDA's commitments to:

- publish an implementation plan that will describe how RCP and time reporting will continue to be utilized during GDUFA III;

- conduct and publish a third-party assessment of the RCP capability by the end of FY 2025; and

[17] Id. at p. 41.
[18] Food and Drug Administration: FIVE-YEAR FINANCIAL PLAN Fiscal Years 2018-2019-2020-2021-2022 2021 Update FOR THE GENERIC DRUG USER FEE AMENDMENTS PROGRAM, p. 8; accessed on Dec. 7, 2021 at https://www.fda.gov/media/147060/download
[19] Id. at p. 9.
[20] Id. at p. 8.
[21] Id. at p. 9.

- publish a GDUFA 5-year financial plan with annual updates and convene an annual public meeting to discuss the 5-year financial plan and FDA's progress in implementing modernized time reporting and resource management planning.

Improving the Hiring of Review Staff (p. 41)

APhA supports the GDUFA III Commitment Letter's focus on hiring and retaining highly qualified review staff. Specifically, APhA supports FDA's intention to hire 128 staff for the generic drug review program in FY 2023 and confirm progress in the hiring of GDUFA III staff in the GDUFA 5-year financial plan.

GUIDANCE AND MAPPS (p. 41)

To provide direction to ANDA applicants, APhA supports FDA's intention to draft or modify relevant MAPPs to reflect the commitments and goals in the GDUFA III Commitment Letter, including, but not limited to directing project managers, assessors, and other assessment program staff to actively work towards an action for ANDA's with missed or extended goal dates and revise MAPP 5200.12 Communicating ANDA Review Status Updates with Industry to include communications related to imminent action on or before April 30, 2023. APhA also supports FDA's plan to issue a Federal Register Notice on or before April 30, 2023 to solicit public comment on the content of Appendix A in the guidance for Industry titled *ANDA Submissions – Amendments to ANDA under GDUFA* (July 2018). FDA will use evaluations and/or training to assure consistency in ANDA amendment classification.

Additional APhA Recommendations

Improve Drug Safety

The recalls of generic angiotensin II receptor blockers (ARBs) due to nitrosamine contamination[22] have highlighted the importance of ensuring drug safety. To protect patient health, APhA urges FDA to include continuous quality improvement measures and safety oversight in GDUFA III. A larger proportion of generic drug user fees should be directed to postmarket surveillance. Performing active, diligent postmarketing pharmacovigilance is critical for proactively identifying possible areas of concern for medications and ensuring the ongoing safety of medications post-approval. In addition to safety surveillance, FDA should direct more resources towards hiring and training investigators. To the extent possible, foreign inspections should be unannounced. In addition, FDA should put in place better data systems for tracking the source of drugs when problems arise.

Address Drug Shortages and Strengthen the Pharmaceutical Supply Chain

APhA appreciates the inclusion of provisions in the Commitment Letter to address drug shortages. APhA calls for widespread development of redundancy and risk mitigation strategies by manufacturers of inactive and active ingredients on a facility and product basis to ensure reliable and consistent availability of safe and high-quality drugs. APhA also urges greater transparency, accuracy, and timeliness of information and notification to health care professionals regarding drug shortages and anticipated shortages, product quality and manufacturing issues, supply disruption, and recalls.

APhA recognizes the monumental task that FDA has in implementing the Drug Supply Chain Security Act (DSCSA), which impacts many generic drug products. We recommend that GDUFA III include funding to provide FDA with resources to appropriately and adequately develop standards, processes, and data systems to implement the DSCSA by the 2023 statutory deadline and support the maintenance, enforcement, and surveillance for compliance with the requirements.

Foster Competition and Lower Drug Prices

While drug pricing is outside the purview of FDA, APhA welcomes any steps FDA can take in GDUFA III that will promote competition and lead to lower drug prices. For example, APhA

[22] FDA Updates and Press Announcements on Angiotensin II Receptor Blocker (ARB) Recalls (Valsartan, Losartan, and Irbesartan) (Nov. 2019); accessed on Dec. 8, 2021 at https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan

supports the competitive generic therapy (CGT) pathway established by the FDA Reauthorization Act (FDARA) for drugs with "inadequate generic competition."[23] At the request of the applicant, FDA may expedite the development and review of an ANDA for a drug designated as a CGT.

In addition to the CGT pathway, APhA appreciates the establishment of FDA's webpage on the CREATES Act implementation and how generic drug applicants can request a Covered Product Authorization (CPA) from FDA for reference listed drugs (RLDs) subject to a Risk Evaluation and Mitigation Strategy (REMS) with elements to assure safe use (ETASU).[24]

Finally, APhA recommends that GDUFA III include funding to continue to educate patients and health care providers, including pharmacists, on the benefits of generic drugs in order to further increase their uptake.

Conclusion

APhA appreciates the opportunity to submit these comments on the draft GDUFA III Commitment Letter. We look forward to continuing to work with FDA, Congress, and other stakeholders as the reauthorization process continues. If you have any questions or need additional information, please feel free to contact Karin Bolte, Director, Health Policy at kbolte@aphanet.org or (202) 558-2727.

Sincerely,

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[23] Food and Drug Administration Reauthorization Act of 2017 (FDARA), P.L. 115-52.
[24] Food and Drug Administration, Access to Product Samples: The CREATES Act, accessed on Dec. 8, 2021 at https://www.fda.gov/drugs/guidance-compliance-regulatory-information/access-product-samples-creates-act