APhA
American Pharmacists Association

Via Electronic Submission to: www.regulations.gov

October 28, 2021

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

Re: Docket No. FDA-2021-N-0891: Reauthorization of the Prescription Drug User Fee Act; Public Meeting; Request for Comments

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 "Reauthorization of the Prescription Drug User Fee Act; Public Meeting; Request for Comments"[1] and the PDUFA VII 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 supports PDUFA's goal of providing additional revenues so that FDA can hire more staff, improve systems, and establish a better managed human drug review process to make important therapies available to patients sooner without compromising FDA's high standards for safety, efficacy, and quality. APhA appreciated the opportunity to share our perspective during the PDUFA VII stakeholder meetings and offers the following comments on the draft commitment letter:

[1] FDA. Reauthorization of the Prescription Drug User Fee Act; Public Meeting; Request for Comments. 86 FR 47316. August 24, 2021. Available at: https://www.govinfo.gov/content/pkg/FR-2021-08-24/pdf/2021-18094.pdf
[2] FDA. PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2023 THROUGH 2027 (hereinafter "commitment letter"). Available at: https://www.fda.gov/media/151712/download

Review Performance Goals (pp. 4-6)

APhA believes that FDA has made good progress on PDUFA VI's goals. For FY 2019, FDA met or exceeded the 90 percent performance level for 11 of the 12 review performance goals.[3] In its FY 2020 PDUFA Performance Report to Congress, FDA stated that it has the potential to meet or exceed all 12 review performance goals for FY 2020.[4]

There is room for improvement in first review cycle approvals, however. Preliminary data show that the percentage of priority and standard applications filed in FY 2019 and approved during the first review cycle were 73 percent and 68 percent, respectively.[5] APhA supports initiatives included in the commitment letter that will improve first cycle approvals, such as increased communications and meetings between FDA and product sponsors.

New Molecular Entity (NME) Milestones and Postmarketing Requirements (PMRs) (pp. 12 – 14)

As the commitment letter notes, postmarketing requirements (PMRs) are critically important to ensuring "the timely availability of information on the safety and efficacy of therapies to the United States public."[6] Accordingly, APhA supports the commitment letter's inclusion of pre-approval process enhancements and guidelines to improve the consistency and predictability of FDA communications about required postmarketing studies, including the study purpose, critical study design elements including type of study and study population, timelines for discussions and engagement on the PMR for the remainder of the review cycle, and for 505(o)(3) PMRs the specific serious risk.

With regard to the proposed establishment of a process for sponsors to request release of PMRs, APhA urges FDA to exercise caution before releasing sponsors from their PMR commitments. To ensure transparency, APhA recommends that the commitment letter include post-approval review of existing PMRs as part of the PDUFA-tracked metrics.

[3] FDA. FY 2020 PERFORMANCE REPORT TO CONGRESS for the Prescription Drug User Fee Act. P. 8. Available at: https://www.fda.gov/media/151602/download
[4] Id.
[5] Id at p. 7.
[6] FDA. Commitment Letter. P. 12. Available at: https://www.fda.gov/media/151712/download

Review of Proprietary Names to Reduce Medication Errors (pp. 17 – 18)

In order to reduce patient and pharmacist confusion and protect the public health, APhA strongly supports FDA's efforts to reduce medication errors related to look-alike and sound-alike proprietary names and such factors as unclear label abbreviations, acronyms, dose designations, and error-prone label and packaging design. Therefore, APhA welcomes the commitment letter's inclusion of performance goals for FDA to review proprietary name submissions in order to address potential issues as soon as possible. We encourage inclusion of pharmacists and pharmacy organizations in the discussions related to these performance goals.

Meeting Management Goals (pp. 20 – 27)

As noted above, APhA supports initiatives included in the commitment letter that will improve first cycle approvals, such as increased communications and meetings between FDA and product sponsors. This includes the expansion from CBER to CDER of the INitial Targeted Engagement for Regulatory Advice on CBER/CDER ProducTs (INTERACT) meetings, the new Type D Meeting, and meeting follow-up questions in the form of a "Request for Clarification." Specifically:

- INTERACT meetings will enable sponsors with novel questions and those for which there is no existing FDA guidance to seek pre-IND advice and guidance from FDA.

- The new Type D meeting will enable sponsors to receive FDA input on a narrow set of questions such as a follow-up question that raises new issues after a formal meeting. Type D meetings will be limited to no more than 2 focused topics and questions that require input from no more than 3 disciplines or Divisions.

- Formalization of "Requests for Clarification" will enable sponsors to submit follow-up questions to clarify FDA's feedback in a written response only (WRO) or something captured in meeting minutes.

APhA also supports FDA's commitment to hold a public workshop and issue guidance on meeting management and communication best practices.

Advancing Development of Drugs for Rare Diseases (pp. 29 – 34)

Over 90 percent of rare diseases still do not have an FDA-approved treatment.[7] For these reasons, APhA supports the provisions included in the commitment letter that are designed to facilitate the development and timely approval of drugs and biologics for rare diseases. Among others, these initiatives include the following:

- support for the hiring of significant numbers of new CDER and CBER staff;
- incorporation of CDER and CBER's Rare Diseases staff into review teams;
- training of CDER and CBER review staff related to development, review, and approval of drugs for rare diseases;
- outreach to industry, patient groups, and other stakeholders;
- reporting on the activities and success of the rare disease programs in the PDUFA annual performance report; and
- establishment of the Rare Disease Endpoint Advancement (RDEA) pilot program.

The RDEA pilot program will seek to advance rare disease drug development programs by providing a mechanism for sponsors to collaborate with FDA throughout the efficacy endpoint development process.

Advancing Development of Drug-Device and Biologic-Device Combination Products Regulated by CBER and CDER (pp. 34 - 35)

Use-Related Risk Analysis (URRA) and human factor (HF) validation studies are important to evaluating the user interface of a drug-device or biologic-device combination product to eliminate or mitigate use-related hazards that may affect the safe and effective use of the combination product. APhA supports the new procedures and timelines for URRA and HF validation study protocols, as well as guidance included in the commitment letter that are designed to advance the development of combination products.

Advancing Real-World Evidence for Use in Regulatory Decision-Making (pp. 36 – 38)

APhA commends FDA for its commitment to advancing the use of real-world evidence (RWE) in regulatory decision-making. We appreciate the publishing of FDA's *Framework for FDA's*

[7] National Organization for Rare Disorders (NORD). NORD Remarks at FDA's Rare Disease Day Meeting February 24, 2020. Available at: NORD-2020-Comments-at-FDA-RDD-Meeting.pdf (rarediseases.org)

Real-World Evidence Program,[8] and its draft guidances on *Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics*,[9] and *Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products*.[10] APhA is pleased to see FDA's intent to build upon this momentum by establishing a pilot *Advancing RWE Program* as part of its PDUFA VII commitments. The proposed process to submit RWE proposals and gain direct feedback from the FDA through up to four meetings has merit. A potential challenge is that participation is contingent upon sponsors' agreement with the FDA about public disclosure of elements of the RWE proposal.

As FDA implements the *Advancing RWE Program*, APhA urges the agency to include pharmacists as a key stakeholder in this process because pharmacists are highly accessible healthcare providers and have been collecting, analyzing, and using RWE in their practice settings for many years.

Enhancing the Incorporation of the Patient's Voice in Drug Development and Decision-Making (pp. 38–39)

As part of PDUFA VII, APhA supports the continued development of approaches and processes for incorporating the patient's voice, experiences, and patient reported outcomes (PROs) in drug development and regulatory decision-making. We welcome publication of the first two patient-focused drug development (PFDD) guidance documents addressing how stakeholders can collect and submit patient experience data and other relevant information from patients and caregivers for medical product development and regulatory decision-making.[11] APhA urges FDA to include pharmacists as a core member of the integrated review teams during drug development and application review where a sponsor intends to use patient input and PROs as part of the development program. In addition, APhA urges FDA to consider how PROs reported to pharmacists can be incorporated, as pharmacists are easily accessible to patients and

[8] FDA. Framework for FDA's Real-World Evidence Program. December 2018. Available at: https://www.fda.gov/media/120060/download

[9] FDA. Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics Draft Guidance for Industry. May 2019. Available at: https://www.fda.gov/media/124795/download

[10] FDA. Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products Draft Guidance for Industry. September 2021. Available at: https://www.fda.gov/media/152503/download

[11] FDA. Patient-Focused Drug Development: Collecting Comprehensive and Representative Input: Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders. June 2020. Available at: https://www.fda.gov/media/139088/download; Patient-Focused Drug Development: Methods to Identify What Is Important to Patients: Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders DRAFT GUIDANCE. October 2019. Available at: https://www.fda.gov/media/131230/download

collect PRO data through the provision of pharmacy services such as medication therapy management, disease management, and patient counseling.

Enhancing Drug Development Tools Qualification Pathway for Biomarkers (pp. 42 – 43)

APhA supports advances in the utilization of biomarkers and pharmacogenomic markers. As part of the patients' health care team, many pharmacists integrate pharmacogenomics into their practices to achieve optimal medication use, outcomes, and safety. As medications have become more complex and personalized, patient counseling and education regarding medication regimens are imperative to successful patient outcomes. Pharmacists have more medication-related education and training than any other health care provider, making them best suited to provide medication-related consults and services based on a patient's genomic information.

In PDUFA VII, APhA supports the FDA's commitment to enhancing the drug development tools qualification pathway for biomarkers. In addition, APhA supports the inclusion of pharmacogenomic analysis in the drug development, approval, and postmarketing surveillance processes. APhA also encourages FDA and stakeholders to consider incentives to support enhanced coordination of care with pharmacists to ensure adequate patient access to education and ongoing support to improve medication adherence, safety, patient self-management, and understanding.

Enhancement and Modernization of the FDA Drug Safety System (pp. 43 – 47)

<u>Optimization of the Sentinel Initiative</u>

APhA commends the commitment letter's focus on enhancing, implementing, and integrating the Sentinel and BEST (Biologics Effectiveness and Safety) Systems in FDA drug safety activities by sustaining the high quality and large quantity of data available, allowing continued application of advanced methods for determining when and how those data are utilized, and ensuring comprehensive training of review staff on the use of Sentinel and BEST. However, APhA believes that a larger proportion of PDUFA VII user fees should be directed to these initiatives. The Sentinel program plays a critical role in providing proactive surveillance through a distributed data approach that cannot be replaced by the Adverse Event Reporting System (AERS), Risk Evaluation and Mitigation Strategies (REMS), or other surveillance systems that retroactively collect data.

In addition to continued implementation and integration of the Sentinel program into FDA's drug safety activities, APhA appreciates FDA's plans to:

- communicate with sponsors and the public regarding general methodologies for Sentinel queries;

- publish on its website an update on facilitation of public and sponsor access to Sentinel's distributed data network to conduct safety surveillance;

- post study results, study parameters, and analysis code online;

- analyze and report on the use of Sentinel for regulatory purposes, e.g., in the contexts of labeling changes, PMRs, or PMCs; and

- report on spending for the Sentinel Initiative in the annual PDUFA Financial Report.

Pregnancy Safety

APhA supports FDA's commitment to develop a consistent approach for assessing the outcomes of pregnancies in women exposed to drugs and biological products and clarifying the optimal use and value of pregnancy registries and electronic healthcare data for assessing pregnancy safety. Specifically, FDA will:

- Develop a framework describing how data from different types of post-market pregnancy safety studies might optimally be used;

- By September 30, 2023, hold a public workshop on post-market safety studies in pregnant women to facilitate determination of the ideal post-market study design(s);

- By September 30, 2024, conduct five demonstration projects to address knowledge gaps about performance characteristics of different study designs; and

- By September 30, 2027, develop a guidance or Manual of Policies and Procedures (MAPP)/Standard Operating Procedures and Policies (SOPP) as appropriate to implement a standardized process for determining necessity and type of pregnancy post-market safety studies including PMRs.

Use of Real-World Evidence – Negative Controls

APhA also supports FDA's development of new methods to support causal inference in Sentinel/BEST that could address product safety questions and advance understanding of how

RWE may be used for studying effectiveness through the use of negative controls as stated in the commitment letter.

Enhancements related to Product Quality Reviews, Chemistry, Manufacturing, and Controls (CMC) Approaches, and Advancing the Utilization of Innovative Manufacturing Technologies (pp. 48 – 53)

CMC Approaches

Recognizing that drug development programs eligible for accelerated clinical development (i.e., those that address a serious disease or condition with unmet medical needs) might not result in more timely approval if Chemistry, Manufacturing, and Controls (CMC) development does not keep pace, the commitment letter includes several actions to address this issue. Specifically, FDA is committed to a series of deliverables (MAPP, CMC Development and Readiness Pilot (CDRP), Public Workshop, Strategy Document) intended to facilitate CMC readiness for products with accelerated clinical development. In addition, enhancement of the Four-Part Harmony CMC Information Request is meant to improve efficiency and clear communication of information requests and responses during application review. APhA supports the inclusion of these CMC initiatives in the commitment letter.

Inspections

With regard to inspections, APhA favors in-person inspections whenever possible as well as preserving the FDA's ability to conduct inspections without prior advance notice. However, the challenges of the COVID-19 pandemic forced the agency to use alternative inspection approaches, such as requesting records and other information from facilities/sponsors, using information and inspection reports shared by trusted foreign regulatory partners through mutual recognition agreements and confidentiality agreements, and alternative technology platforms. As FDA determines the role of these alternative inspection approaches post-COVID-19, APhA supports the commitment to issue a draft guidance that will allow for public comment. That said, APhA strongly supports and admires FDA's position as a global leader in inspection and surveillance and this position should be recognized and maintained in the recommendations in the draft guidance.

Enhancing CBER's Capacity to Support Development, Review, and Approval of Cell and Gene Therapy Products (pp. 53 – 56)

APhA supports FDA's intention to hire 228 new FTEs in CBER and other initiatives included in the commitment letter which are designed to support the development, review, and approval of cell and gene therapy products. New staff will focus on "direct review activities, indirect activities (e.g., policy, external outreach, postmarket safety), and supporting activities in the Cell and Gene Therapy Program (CGTP)."[12] In addition, the commitment letter includes numerous public stakeholder meetings and guidance on topics of interest including a PFDD meeting to better understand patient perspectives on gene therapy studies and products; novel and expedited methods and approaches on cell and gene therapy product development; and leveraging knowledge from across therapeutic contexts to facilitate cell and gene therapy development and review.

Continued Enhancement of User Fee Resource Management (pp. 57 - 58)

Changes in the PDUFA VI fee structure have improved the predictability of FDA funding, simplified user fee administration, and enhanced the flexibility of financial mechanisms to improve the management of PDUFA program funding. It is critical that FDA continues to be a good steward of its financial resources. APhA is encouraged by FDA's resource capacity planning (RCP) and modernized time reporting implementation to date. Moving forward, we urge FDA to fully enable its RCP capabilities and to continue to improve its Capacity Planning Adjustment (CPA) methodology to better assess the sustained workload and PDUFA resource needs.

Accordingly, APhA supports FDA's commitment to:

- publish an updated implementation plan that will describe how the agency's RCP function and time reporting will continue to be implemented during PDUFA VII;
- conduct a third-party assessment of the CPA; and
- publish an updated 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

[12] Commitment Letter, p. 53. Available at https://www.fda.gov/media/151712/download

RCP, including the continual improvement of the CPA and time reporting, and the integration of RCP in resource and operational decision-making processes.[13]

Improving FDA Hiring and Retention of Review Staff (p. 59)

PDUFA VI includes several commitments to improve the hiring and retention of critical review staff through modernization of FDA's hiring system, augmentation of hiring staff capacity and capabilities, creation of a dedicated function focused on staffing the program, reporting on hiring metrics, and a comprehensive and continuous assessment of hiring and retention. In April 2020, Booz Allen Hamilton published an Interim Hiring and Retention Assessment Report that noted continued deficiencies in FDA's recruiting, hiring, and retention functions.[14] While APhA appreciates the improvements FDA has made and the action plans the Agency has developed to address specific issues identified in the report, more progress needs to be made.

For this reason, APhA supports the PDUFA VII commitment letter's focus on hiring and retaining highly qualified review staff. Specifically, APhA supports FDA's:

- intention to hire 352 new FTEs over the course of PDUFA VII (228 in CBER and 123 in CDER), with hiring goals that will be tracked and hiring progress reported; and

- use of an independent contractor with expertise in assessing HR operations to conduct a targeted assessment of the hiring and retention of FDA staff working for the human drug review program.[15]

The goal is to improve hiring and retention by understanding factors both within and outside of FDA's control.

Information Technology and Bioinformatics Goals (pp. 60 – 64)

APhA supports initiatives included in the commitment letter to modernize FDA's information technology (IT) infrastructure to support PDUFA VII goals. These include:

- development of a Data and Technology Modernization Strategy;

[13] Id. at pp. 57-58.
[14] Booz Allen Hamilton. FDA Interim Hiring and Retention Assessment. April 13, 2020. Available at: https://www.fda.gov/media/138662/download
[15] Commitment Letter, p. 59.

- resources to accelerate CBER's data and technology modernization to facilitate an efficient review process;

- resources to complete the Electronic Submissions Gateway (ESG) transition to the cloud;

- demonstration projects to explore how cloud and cloud-based technologies could promote innovation in the drug development and regulatory review process; and

- resources to improve bioinformatics and computational biology capacity to strengthen FDA's ability to conduct and support reviews of submissions containing a variety of biological data such as Next Generation Sequencing.

Enhancing Use of Digital Health Technologies to Support Drug Development and Review (pp. 64 – 68)

As the medication experts on patient care teams, pharmacists are uniquely positioned to apply digital health technologies to optimize patient care outcomes. For example, pharmacists are currently collaborating with local clinics or through collaborative practice agreements (CPAs) with physicians and other providers to provide continuous glucose monitoring (CGM) services for patients with diabetes. In addition to CGM, current remote patient monitoring (RPM) services pharmacists are performing include the following:

- Blood Pressure Cuff (Auto-pair BP device connected to Phone or Hub)
- Weight Scale (Auto-pair Scale device connected to Phone or Hub)
- Pulse Oximeter (Auto-pair PulseOx device connected to Phone or Hub)
- Blood Glucometer (Auto-pair Glucometer device connected to Phone or Hub)
- International Normalized Ratio (INR) – anticoagulation monitoring

In addition to RPM services, APhA supports[16] pharmacists' provision of and billing for pharmacogenomics (PGx) counseling services and the new Remote Therapeutic Monitoring (RTM) codes that were proposed in the CY 2022 Medicare Physician Fee Schedule proposed

[16] APhA. Comments to CMS on the CY 2022 Payment Policies under the Physician Fee Schedule and Other Changes to Part B Payment Policies; Proposed Rule. September 13, 2021. Available at: https://www.pharmacist.com/DNNGlobalStorageRedirector.ashx?egsfid=AroSq_F5rL0%3d

rule.[17] These include monitoring musculoskeletal system status, respiratory system status, therapy (medication) adherence, and therapy (medication) response.

Given the explosion of digital health technologies and continued advancements in this space, APhA supports FDA's commitments to:

- Expand capacity and advance a digital health technology framework that will guide the use of digital health technology-derived data in regulatory decision-making for drugs and biological products;

- Establish a committee to promote consistency across centers on digital health technology-based policy, procedure, and analytic tool development;

- Convene public meetings or workshops on the use of digital health technologies in regulatory decision-making; identify at least three issue-focused demonstration projects to inform methodologies for digital health technology evaluation; and issue digital health technology-related guidances; and

- Enhance the agency's IT capabilities to support the review of digital health technology-generated data.

To ensure patient safety, APhA welcomes planned public meetings and guidances on detection of safety signals during continuous data acquisition and acceptable approaches to capturing and reporting adverse events in clinical trials using digital health technologies. APhA also supports planned guidance on regulatory considerations for Prescription Drug Use-Related Software that is distributed with a drug or integrated as part of a drug- or biologic-led combination product, as well as software that is distributed by an applicant independent of an approved product. Finally, APhA supports the issuance of guidance on the use of digital health technologies in traditional and decentralized clinical trials. As noted at FDA's September 28,

[17] Centers for Medicare and Medicaid Services. Medicare Program; CY 2022 Payment Policies under the Physician Fee Schedule and Other Changes to Part B Payment Policies; Proposed Rule (RIN 0938-AU42). July 23, 2021. Available at: https://www.govinfo.gov/content/pkg/FR-2021-07-23/pdf/2021-14973.pdf

2021 PDUFA VII public meeting[18] and in the PDUFA VII stakeholder meetings,[19] decentralized clinical trials can help to increase the diversity of trial participants.

Additional APhA Recommendation: Addressing Drug Shortages

APhA appreciates FDA's and the CDER Drug Shortage Staff's efforts to address our nation's drug shortage problem, including early notification requirements, expedited inspections and reviews of manufacturing sites, the establishment of an Agency Drug Shortages Task Force and stakeholder listening sessions, and the publication of FDA's report examining the root causes of drug shortages and potential solutions.[20]

Despite these advances, drug shortages continue to occur, especially in the context of COVID-19, where we have seen shortages of critical drugs used to treat COVID-19 patients. For this reason, APhA urges FDA to continue to focus on alleviating drug shortages as part of PDUFA VII. APhA calls for widespread development of redundancy and risk mitigation strategies in the manufacturing process 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.

Conclusion

APhA appreciates the opportunity to submit these comments on the draft PDUFA VII commitment letter. We look forward to continuing to work with FDA, Congress, and other stakeholders as the reauthorization process continues.

[18] FDA. Public Meeting on the Recommendations for Prescription Drug User Fee Act (PDUFA) Reauthorization. September 28, 2021. Available at: https://www.fda.gov/drugs/news-events-human-drugs/public-meeting-recommendations-prescription-drug-user-fee-act-pdufa-reauthorization-september-28

[19] FDA. PDUFA VII: Fiscal Years 2023 – 2027: Stakeholder Discussions on PDUFA VII Reauthorization. Content current as of 08/23/2021. Available at: https://www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-vii-fiscal-years-2023-2027?utm_medium=email&utm_source=govdelivery

[20] FDA. Drug Shortages: Root Causes and Potential Solutions. October 2019, Updated on 2/21/20. Available at: https://www.fda.gov/media/131130/download

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If you have any questions or need additional information, please feel free to contact Karin Bolte, Director, Health Policy at (202) 558-2727.

Sincerely,

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