Summary of views and comments received to Docket No. FDA-2021-N-0891 regarding proposed recommendations for PDUFA VII

Executive Summary

The Prescription Drug User Fee Act (PDUFA) authorizes the U.S. Food and Drug Administration (FDA or Agency) to collect user fees for the review of human drug applications (new drug applications (NDAs) submitted under 505(b) of the Federal Food, Drug, and Cosmetic Act and biologics license applications (BLAs) submitted under section 351(a) of the Public Health Service Act). The current authorization for PDUFA expires on October 1, 2022. To develop recommendations for the sixth reauthorization of PDUFA (PDUFA VII), FDA has followed the process described by the statute, including holding two public meetings with associated dockets for public comment, having monthly consultation meetings with public stakeholders (including patient and consumer advocates), and conducting negotiations with the regulated industry.

The statute further requires FDA to publish the recommendations in the *Federal Register* and hold a public meeting at which the public may present its views. This public meeting was held on September 28, 2021. FDA must then consider the public views and comments and revise such recommendations as necessary. When transmitting the recommendations to Congress, the Secretary must provide a summary of the public views and comments and any changes made to the recommendations in response to these views and comments. This document fulfills that requirement.

The process used to develop the recommendations for the reauthorization provided a significant opportunity for stakeholders and members of the public to express their views and priorities. FDA considers this input important to the shaping of the proposed recommendations for program enhancements.

Overall, the public docket comments received on the proposed set of recommendations reflect general support for the recommendations for reauthorization. Numerous groups expressed their support for many of the proposed PDUFA VII initiatives, pilot programs, goals, and commitments to further promote drug development and enhance the review of safety and efficacy of new therapeutic options. The most cited areas of support were for FDA's commitments related to enhancing the use of real-world evidence (RWE), supporting the Center for Biologics Evaluation and Research's (CBER's) anticipated review workload in innovative areas such as cell and gene therapy, advancing the adoption of digital health technologies (DHTs), and continuing to incorporate the patient voice.

A few commenters expressed reservations and concern about the program's use of fees on performance goals and in expediting review, saying that these appear to prioritize the speed of approval over safety for the public.

Many stakeholders also provided advice or other input for FDA to consider as it implements the recommendations. FDA appreciates the input and will consider these comments as it develops its implementation plans, to the extent they are consistent with reauthorization legislation that is passed into law. Some comments, such as those on broader program operations and specific

regulatory policies, are outside the scope of the PDUFA reauthorization discussions, which are focused on performance goals and procedures for the review of human drug applications. FDA will consider these views, as appropriate, but the Agency is unable to consider them as part of this user fee agreement's reauthorization recommendations.

Overall, given the general support expressed for the recommendations for the reauthorization of PDUFA, FDA has not made changes to the recommendations.

Introduction and Background

PDUFA authorizes FDA to collect user fees for the review of human drug applications. The current reauthorization of PDUFA (PDUFA VI) was part of the Food and Drug Administration Reauthorization Act of 2017. This authority expires on October 1, 2022. FDA began the reauthorization process, in preparation for PDUFA VII, with a public meeting held on July 23, 2020. Following the meeting, a *Federal Register* docket was open for 30 days for the public to submit written comments. In September 2020, FDA began concurrent negotiations with industry and monthly discussions with public stakeholders to determine the proposed recommendations for the next PDUFA program. The public stakeholders who participated included patient advocacy groups, consumer advocacy groups, healthcare professional groups, public policy advocacy groups, and scientific and academic experts. These discussions concluded in February 2021. Minutes of these meetings are posted on FDA's website at https://www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-vii-fiscal-years-2023-2027.

The provisions of PDUFA VI also include the following requirements:

(4) PUBLIC REVIEW OF RECOMMENDATIONS.—After negotiations with the regulated 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, 2022, 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 followed the process described in paragraph (4) and the Agency is publishing this summary in preparation for the transmittal of recommendations to Congress under paragraph (5).

Following administration review and clearance, FDA posted the package of proposed recommendations at https://www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-vii-fiscal-years-2023-2027 and published a *Federal Register* notice summarizing the proposed recommendations. FDA held a public meeting on September 28, 2021, to take public comment on the proposed package; a transcript and recording of that meeting can be found on FDA's website at https://www.fda.gov/drugs/news-events-human-drugs/public-meeting-recommendations-prescription-drug-user-fee-act-pdufa-reauthorization-september-28. The public docket for that meeting subsequently closed on October 28, 2021. The written comments submitted to the docket can be found on FDA's website at https://www.federalregister.gov/documents/2021/08/24/2021-18094/reauthorization-of-the-prescription-drug-user-fee-act-public-meeting-request-for-comments.

This document provides a summary of the 31 written comments submitted to the public docket before the close of the comment period which included comments from a variety of different groups: patient groups, consumer advocacy groups, pharmaceutical companies, trade groups, professional societies, and non-pharmaceutical companies like data vendors; two additional comments from consumer groups were submitted the day after the deadline, so they do not appear on the public docket, but FDA is also including them in this summary.

Following the Agency's review of the public comments, FDA has determined that no changes to the originally proposed recommendations are necessary, and FDA intends to send the recommendations to Congress in accordance with the procedures in section 736B(d)(5) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

Overview of Public Comments

Based on a review of the public input received in the docket, FDA has received widespread support for the PDUFA VII recommendations from a diverse range of stakeholders, including patient advocacy groups, professional and trade associations, academics, think tanks, and the regulated industry. In addition to the support for a variety of different commitments throughout the commitment letter, FDA received numerous recommendations and considerations that FDA should consider during the implementation.

The most supported sections of the commitment letter were for areas where there have been many advancements in drug development: namely in cell and gene therapy, RWE, and DHTs.

Broad support for cell and gene therapy and CBER review resources

Given FDA's anticipated influx of applications for new and innovative cell and gene therapies, many stakeholders were very supportive of the additional resources given toward supporting that upcoming review work and of the commitments in CBER's Capacity to Support Development, Review, and Approval of Cell and Gene Therapy Products section of the commitment letter. These commitments include a patient-focused drug development meeting, the development of guidances, and outreach to numerous public stakeholders, among many other activities (see pages 53-56).

Significant interest in advancing use of real-world evidence

Many commenters also supported the PDUFA VII agreement's commitment to advancing Real-World Evidence, citing RWE's potential to augment and complement traditional clinical trial data and better inform FDA's regulatory decision-making. The commitment letter describes the establishment of a new RWE pilot program (pages 36-38) as well as added resources to understand how RWE may be used to address product safety (pages 45-47). In addition to general support for these commitments, there were recommendations to ensure that health data and technology companies be included in RWE discussions and that RWE should not supplant the need for randomized controlled trials. One group expressed interest in RWE eventually playing a larger role in supporting new drug applications. FDA appreciates the input and will consider these comments as it develops its implementation plans, to the extent they are consistent with reauthorization legislation that is passed into law.

Continued incorporation of the patient voice

Patient-focused drug development and the inclusion of patient input continues to be a priority among stakeholders. Many stakeholders support FDA's continuation of the patient-focused drug development (PFDD) program (pages 38 – 39) and its related initiatives. Some recommendations from stakeholders included the consideration of caregivers' feedback alongside that of patients and general further enhancement to PFDD efforts like an emphasis on the patient representative program, additional guidances, and more expedited timelines for publishing guidances. FDA appreciates the input and will consider these comments as it develops its implementation plans, to the extent they are consistent with reauthorization legislation that is passed into law.

Importance of information technology (IT) modernization

FDA seeks to modernize in the fast-moving field of IT. As such, many commenters also supported the commitments (pages 60-68) to modernize FDA's IT and advance its use of cloud and DHTs. Some of these activities include, but are not limited to, modernizing CBER's IT systems and capabilities, conducting demonstration projects to explore cloud-based technologies, and publishing a guidance on the use of DHTs in traditional and decentralized clinical trials.

Emphasis on representation in clinical trials and clinical trial data

Many public stakeholders emphasized and highlighted the urgent need for clinical trials and clinical trial data to be more accessible and representative: by sex, by race, by age, by physical ability, by location, and by rarity of illness. Many of these stakeholders commented that FDA should consider this need as part of some of the PDUFA VII commitments. FDA appreciates the input and will consider these comments as it develops its implementation plans, to the extent they are consistent with reauthorization legislation that is passed into law.

Continuation of PDUFA VI regulatory decision tool pilot programs

To a lesser extent, various stakeholders supported the continuation of popular PDUFA VI pilot programs in PDUFA VII. Some commenters, for example, emphasized their continued support and desire for the complex innovative designs and model-informed drug development and the use of drug development tools qualification pathway for biomarkers programs (pages 40-43).

Support for new PDUFA VII pilot programs and initiatives like Split Real Time Application Review (STAR) and Rare Diseases Endpoint Advancement (RDEA)

There was support for some of the new pilot programs and initiatives established under PDUFA VII. For instance, some stakeholders highlighted support for the RDEA pilot (pages 30-34), which is to provide a mechanism for sponsors to collaborate with FDA throughout efficacy endpoint development to help advance rare disease drug development. Other organizations cited the STAR pilot (pages 14-17), a program for efficacy supplements that may shorten the time from complete submission to action by allowing for applications to be submitted in two parts, as an additional achievement. There were numerous specific comments and recommendations regarding how each of these new pilots and initiatives should be implemented; FDA appreciates the input and will consider these comments as it develops its implementation plans, to the extent they are consistent with reauthorization legislation that is passed into law.

Support for new Chemistry, Manufacturing, and Controls (CMC) section

Some commenters highlighted their support of the commitments in the new CMC section of the commitment letter (pages 48-53). This new section focuses on supporting communications on CMC issues during drug development, facilitating readiness of products with accelerated clinical development timelines, and advancing the implementation of innovative manufacturing technologies. In response to the section regarding alternative tools to assess facilities, one organization expressed their preference for maintaining in-person inspections. One group also requested additional clarification on the development of CMC guidances to account for issues pertinent to cell and gene therapy products. FDA appreciates the input and will consider these comments as it develops its implementation plans, to the extent they are consistent with reauthorization legislation that is passed into law.

Support for enhanced communications and new meeting types

Some stakeholders approved the meeting types and opportunities for communication with FDA, namely the Type D meetings and INTERACT (pages 20-27). While Type D meetings are focused on narrow sets of issues like follow-ups or questions that don't require extensive, detailed advice, INTERACT meetings are intended for novel questions and unique challenges early in drug development to help resolve an issue that might otherwise delay the initiation of an IND. Several stakeholders cautioned that these approaches should be used to enhance communications with FDA through face-to-face or teleconference meetings as opposed to written responses. FDA appreciates the input and will consider these comments as it develops its

implementation plans, to the extent they are consistent with reauthorization legislation that is passed into law.

Continued improvement in hiring and retaining FDA staff

Several commenters supported the commitments to improve hiring and retention of review staff, noting that, while improvements were made in PDUFA VI, more progress is needed in PDUFA VII. One stakeholder offered suggestions for the focus of the proposed assessment of hiring and retention, and another encouraged FDA to highlight its hiring needs publicly so external stakeholders are aware. FDA appreciates the input and will consider these comments as it develops its implementation plans, to the extent they are consistent with reauthorization legislation that is passed into law.

Support for procedural goals in the review of combination products

The new procedures and timelines for use-related risk analyses (URRAs) and human factors (HFs) studies (pages 34-35), which help mitigate use-related risk for combination products, were supported by two groups.

General support for PDUFA VII's drug safety commitments with some concern

Some stakeholders offered comments on the PDUFA VII commitments to enhance and modernize drug safety. One group offered support for the modernization and improvement of Risk Evaluation and Mitigation Strategy (REMS) assessments. Several stakeholders supported the optimization commitments for the Sentinel Initiative (Sentinel) (pages 43-47), particularly those focused on addressing questions of product safety and advancing the understanding of how RWE can be used for studying effectiveness. Two commenters encouraged FDA to share learnings from the demonstration projects described in those commitments. Another stakeholder, while supportive of the PDUFA VII commitments, suggested a greater proportion of PDUFA VII user fees should be allocated to the Sentinel Initiative and post-market safety activities. Two organizations noted that while user fees have been previously used to support Sentinel, they would like to see further transparency and reporting on the impact and benefit of the Sentinel system on FDA's regulatory actions and public health. FDA appreciates the input and will consider these comments as it develops its implementation plans, to the extent they are consistent with reauthorization legislation that is passed into law.

Comments on continued improvement of user fee management

Under PDUFA VII, FDA proposes to build on the PDUFA VI enhancements to user fee financial management by maturing the resource capacity planning (RCP) capability and promoting financial transparency. Two organizations expressed support for the user fee financial management commitments, with one group urging FDA to fully enable its RCP capabilities and to continue to improve its Capacity Planning Adjustment (CPA) methodology in PDUFA VII to better assess the sustained increases in workload and program resource needs.

Considerations for post-marketing requirements (PMRs) goals

One organization supported new process enhancements to PMRs but also cautioned FDA on releasing sponsors from PMR commitments (pages 12-14) and recommended that the commitment letter include the post-approval review of existing PMRs as a tracked metric. Another group noted that post-market enforcement of confirmatory trials should be better monitored and enforced, suggesting that enforcement should be a performance goal. FDA appreciates the input and will consider these comments as it develops its implementation plans, to the extent they are consistent with reauthorization legislation that is passed into law.

Concerns and issues over aspects of the PDUFA VII agreement

Comments and concerns over the agreement from a few stakeholders covered a variety of areas. Several groups criticized the long-standing practice of review goals, urging the FDA to prioritize the effectiveness and safety of drugs over speed. FDA would note that these review goals have been a part of the prior PDUFA agreements and are not unique to this PDUFA. Some of those groups also requested more transparency for the negotiations.

Two groups claimed the PDUFA VII commitment letter includes policy and regulatory changes without citing the specific policy or regulatory policy changes they refer to. FDA notes that, as mentioned in the kickoff public meeting, its regulatory policy is not a topic of conversation during reauthorization negotiations and, therefore, is not included in the proposed commitment letter.

Another commenter raised the issue of facility fees being too high for some smaller drug manufacturers; in response, one suggestion from another commenter was to adjust fees based on the size of the company.

In general, however, stakeholders have acknowledged the importance of the PDUFA program to ensure that FDA has the necessary resources and were appreciative of the opportunity for the Agency to seriously consider their feedback and input. Most of them highlighted PDUFA VII activities that were meaningful to the patients, members, and individuals they represent. FDA also appreciates the concerns, constructive feedback, and specific recommendations to better help the Agency meet its overall public health goal through its implementation of the PDUFA VII agreement.

Other comments

Several comments, regardless of their merit, were outside the scope of the PDUFA reauthorization discussions. These comments were on activities that either cannot be supported by PDUFA user fees under statute, encompass broader operations beyond the PDUFA program, or involve specific regulatory policies. FDA emphasized this scope consideration during the public meetings and at the other stakeholder consultation and negotiation meetings conducted throughout the process.

A sample of the out-of-PDUFA-scope comments received in the docket include the following recommendations: refining FDA's unapproved drug initiative, sharing supply chain information, expanding the Oncology Center of Excellence's Project Facilitate to other therapeutic areas, and pursuing early engagements with payers during drug development.

In addition, two advocacy organizations noted that voluntary REMS should not be relied upon for post-market safety yet made no specific reference to PDUFA VII's new commitments to establish more timely REMS reviews (pages 4 –44). One stakeholder suggested further advancement and adoption of human-specific translational models and tools in nonclinical testing. Another group recommended the creation of a new Center of Excellence for Rare Diseases.

To read more details on all the comments summarized above, FDA recommends visiting the publicly available docket at https://www.regulations.gov/docket/FDA-2021-N-0891.

Conclusion

The process for the reauthorization of PDUFA has benefited from significant opportunities for stakeholders to provide input into the recommendations. FDA greatly appreciates the significant and thoughtful input provided by stakeholders at the two public meetings and the monthly stakeholder consultation meetings, in addition to the docket comments described above. This input has helped FDA better understand and incorporate stakeholder perspectives and priorities, and this has ultimately contributed to a stronger set of proposed recommendations. Given the general support for the PDUFA VII agreement, while noting that FDA will take into consideration the recommendations to the new commitments' implementation, FDA has not made changes to those recommendations for the reauthorization of PDUFA.