

Executive Summary

The Prescription Drug User Fee Act (PDUFA) authorizes the Food and Drug Administration (FDA or the Agency) to collect user fees for the review of human drug applications. The current authorization for PDUFA expires on October 1, 2017. To develop recommendations for the reauthorization of PDUFA, FDA has followed the process described by statute, including two public meetings with associated dockets for public comment, monthly consultation meetings with public stakeholders including patient and consumer advocates, and 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 August 15, 2016. The FDA must then consider the public views and comments and revise such recommendations as necessary. When transmitting the recommendation to the Congress, the Secretary must provide a summary of the public views and comments and any changes made to the recommendations in response to the views and comments. This document fulfills that requirement.

The process used to develop the recommendations for the reauthorization included significant opportunity for stakeholders to provide their views and priorities. FDA considers this input important to the shaping of the proposed recommendations for program enhancements. As such, the comments received on the proposed set of recommendations reflect significant and wide-spread stakeholder support for the recommendations for reauthorization. Numerous groups expressed their support for PDUFA to enable FDA to continue to support the review of safety and efficacy of new therapeutic options while also supporting the development and innovation of regulatory science and regulatory decision tools. Numerous provisions received specific support from commenters; most notably among these were the commitments to support the incorporation of the patients' voice in drug development and decision-making.

A few commenters expressed a view that the recommendations did not appear to address their drug safety priorities. FDA notes, however, that the recommendations include important provisions and significant fee funding for substantial expansion of post-market safety and epidemiologic research and analysis to address drug safety issues (an added \$50 million to support this capability). FDA also notes that many of the other provisions including, for example, the regulatory science provisions will further strengthen its ability to assess the benefits and risk of drugs, of which safety is a primary consideration.

Many commenters provided advice or other input for FDA to consider as it implements the recommendations. FDA will consider these comments as it develops its implementations plans and appreciates the input. Some comments reflected priorities that are considered outside the scope of the PDUFA reauthorization process. FDA will consider these views as appropriate but is unable to incorporate them in the PDUFA reauthorization recommendations.

Given the wide-spread support expressed for the recommendations for the reauthorization of PDUFA, FDA has not made changes to the recommendations.

Introduction and Background

The Prescription Drug User Fee Act (PDUFA) authorizes the Food and Drug Administration (FDA) to collect user fees for the review of human drug applications. The reauthorization of PDUFA (PDUFA V) was part of the Food and Drug Administration Safety and Innovation Act of 2012. This authority expires on October 1, 2017. FDA began the reauthorization process, in preparation for PDUFA VI, with a public meeting held on July 15, 2015. Following the meeting, a docket was open for 30 days for the public to submit written comments. In September 2015, 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 2016. Minutes of these meetings are posted on FDA's website at

<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm446608.htm>

The provisions of the 2012 reauthorization of PDUFA 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, 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 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

<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm446608.htm> and published a Federal Register notice summarizing the proposed recommendations. FDA held a public meeting on August 15, 2016 to take public comment on the proposed package. The public docket subsequently closed on August 22, 2016. The transcript of the public meeting and the written comments submitted to the docket can be found on FDA's website at the same link provided earlier in this paragraph. This document provides a summary of 42 written comments submitted to the public docket before the close of the comment period (18 from patient groups, 2

from academics, 6 from healthcare professional organizations, 3 from industry groups, 1 from a non-profit policy group, 3 from consumer groups, and 9 from individuals). 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 736B(d)(5) of the Federal Food, Drug, and Cosmetic Act.

Summary of Public Comments

Based on a review of the public input received in the docket, FDA has received wide-spread support for the PDUFA VI agreement from the public, including from many of the stakeholder groups such as patient advocates, consumer advocates, healthcare professional groups, a non-profit policy group, individuals, and the regulated industry. Commenters noted the importance of the PDUFA program to ensuring continued strong commitment to the safety and efficacy of new and existing therapeutic options for the public. It was also noted that the recommendations support the needs of the FDA and the public, as well as those of the regulated industry. Support was expressed for FDA and industry's interest and willingness to invest in the next frontier of scientific discovery and medical therapy development. Commenters observed that the PDUFA program has been very successful, enabling FDA to achieve the best review times in the world while maintaining its high standards for safety and efficacy, and that the recommendation in PDUFA VI would enable significant progress on addressing some of the most pressing challenges in drug development. It was noted that PDUFA VI would vastly enhance the capacity to support analysis of safety and efficacy information from both clinical trials and in clinical experience. Many groups expressed their appreciation for the numerous opportunities to provide input into the process for developing the recommendations and that their input was taken seriously. It was also noted that many of the proposed enhancements in PDUFA VI would continue efforts to engage stakeholders through the inclusion of explicit opportunities to gather input from the public through public meetings and opportunities for public comment. Significant support was expressed for proposals related to incorporation of the patient's voice in drug-development and decision-making, exploration of approaches to incorporating the use of real world evidence, strengthening internal processes and systems to improve hiring and retention of key staff, and enhancing benefit-risk assessment in regulatory decision-making.

Patient groups that provided comments expressed near-universal and wide-ranging support for the proposed PDUFA VI package. Many patient groups commented that they appreciated the process FDA provided to allow for engagement through the two public meetings, the monthly stakeholder consultation meetings, and the docket. A few patient groups expressed some concern over the possible workload burden on review staff that may result from the new commitments, and that these new commitments may divert time and attention from existing review processes. FDA is confident that the level of resources provided for in PDUFA VI will enable it to achieve the proposed commitments while maintaining its review performance. Further, FDA notes that the proposed capacity planning adjustment, which FDA intends to establish by fiscal year 2021, will enable FDA to more optimally adjust annual target revenue to ensure the program is optimally resourced.

In addition, some consumer groups, while providing support for elements of PDUFA VI, also expressed concern that drug safety is not adequately prioritized in PDUFA VI, noting that, for example, only 2 of the 46 pages of the commitment letter are dedicated to post-market safety activities. FDA acknowledges that the number of pages and commitments devoted exclusively to post-market safety considerations are fewer than the number addressing broader drug safety considerations throughout the life cycle of a drug. The Agency notes that the PDUFA VI proposals nonetheless include important provisions and significant fee funding for substantial expansion of post-market safety and epidemiologic research and analysis to address drug safety issues (an added \$50 million to support this capability). FDA also notes that enhancements in regulatory science and decision tools to further enhance approaches for developing information on safety and effectiveness during drug development, increased development-phase consultations to ensure appropriate measurement and assessment of benefit versus risk, and premarket review of these considerations—also addressed in the commitment letter—are all directly concerned with the critical consideration of drug safety. Some consumer groups and individual commenters also expressed concern about a focus on “speed” rather than on improving the safety of drugs. FDA appreciates the sharing of such a concern, and would like to point out that PDUFA VI does not include proposals to shorten review timeframes; and instead proposes to retain the longer timeframes for new molecular entity new drug applications (NDAs) and original biological license applications (BLAs) that were extended by two months in PDUFA V. In addition PDUFA VI proposes to lengthen the time for scheduling a Type B(EOP) meeting, and to lengthen the time that FDA will have available to review meeting packages for Type B(EOP) and Type C milestone meetings.

Many commenters provided their views on specific proposed enhancements under PDUFA VI. These include comments of support, advice, and implementation considerations, as well as specific suggestions for enhancement proposals. FDA will further consider this input as it develops its implementation plans.

The discussion that follows provides a summary of comments organized by proposed enhancements included in the PDUFA VI package.

Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs

The program for enhanced review transparency and communication for NME NDAs and original BLAs (the Program), first established in PDUFA V, provides for additional communication between FDA review teams and the applicants of NME NDAs or original BLAs in the form of pre-submission meetings, mid-cycle communications, and late-cycle meetings, while also adding 60 days to the review timeframe to accommodate this additional interaction. PDUFA VI proposes to maintain the Program with minor modifications to reduce administrative burden and increase flexibility to the benefit of FDA review teams and applicants. One industry group commented that PDUFA VI will build on the successes of the Program review model in PDUFA V.

FDA-Sponsor Communication During Drug Development

PDUFA VI builds on improvements to communication with sponsors by conducting an evaluation of communication practices, convening a public workshop, and updating guidance, if necessary. Six patient groups, two industry groups, one consumer group and one healthcare group expressed support for this provision. One regulated company recommended that a stratified sampling method be employed for the communication study to ensure equivalent representation across review divisions. One consumer group, while supporting the communication provision, urged FDA to ensure that required communications do not become too burdensome for review staff. Two patient groups suggested extending the evaluation of communication practices to include communication between the FDA and patient groups. FDA notes that the intent of this study is targeted to a specific area of communication practices during drug development between sponsors and review teams; approaches to developing appropriate methodologies for the incorporation of patient views are addressed under the enhancement related to the incorporation of the patient's voice in drug development and decision-making.

Breakthrough Therapies

PDUFA VI provides resources to support continued success of the breakthrough therapy program. Nine patient groups, one consumer group, and two industry groups expressed support for this provision. Two of the supportive patient groups recommended that the FDA ensure that resources for breakthrough therapies do not adversely affect other review efforts. FDA notes that the resources provided for breakthrough therapies under PDUFA VI are additive to the review program to account for the breakthrough therapy workload, and will therefore strengthen the overall review program rather than direct resources away from any other priorities.

Early Consultation on New Surrogate Endpoints

PDUFA VI clarifies procedures to provide early consultations on the use of a biomarker as a new surrogate endpoint as the primary basis for product approval. Eight patient groups and two industry groups expressed support for this provision.

Rare Disease Drug Development

PDUFA VI proposes to continue the efforts of the Rare Disease Program (RDP), including staff training, promoting best practices for review of rare disease products, conducting outreach, and integrating RDP staff into review teams for rare disease review and development programs. One industry group and eight patient groups expressed specific support for the RDP provisions. Several commenters provided advice or other input for FDA to consider as it implements the recommendations. One patient group, while expressing support for the provision to integrate RDP members in review teams, cautioned against a possible risk of RDP staff becoming "siloed" rather than providing synergies between teams. One individual commenter suggested tracking metrics to include involvement of RDP staff in reviews. One consumer group recommended ensuring that orphan classification is not being misused by older products being reclassified as orphan products. FDA appreciates the input and will consider these comments as it develops its implementations plans.

Enhancing Use of Real World Evidence for Use in Regulatory Decision-making

In PDUFA VI, FDA proposes to explore the uses and application of real-world evidence in regulatory decision-making and publishing guidance on this topic. Fourteen patient groups, one group of academic commenters, five healthcare professional organizations, two industry organizations, one non-profit policy organization, and one individual commenter expressed support for these provisions.

One supportive healthcare organization recommended including pharmacists in this process. One supportive patient organization recommended FDA include psychosocial and behavioral health experts to ensure that data are capturing values that matter to patients. One academic comment noted that through real-world evidence FDA can realize a massive opportunity to improve our evidence base. One supportive individual commenter recommended FDA accelerate its timetable for its commitments in this area. A number of commenters noted that incorporating real-world evidence into regulatory decision-making needs to be explored in a thoughtful and methodological manner, and applauded the approach as outlined in the commitment letter. FDA will consider these comments as it develops approaches to considering the use of real world evidence, and also notes that this effort will include at least one public workshop that will provide stakeholders with further opportunity to express their views on optimal approaches to implementation of these provisions.

Enhancing the Incorporation of the Patient's Voice in Drug Development and Decision-making

PDUFA VI proposes to build on the patient-focused drug development effort to bridge to developing systematic approaches and publishing guidance to facilitate collection of meaningful patient input that can be incorporated into regulatory review. Sixteen patient groups, four healthcare professional organizations, two industry groups, and one non-profit policy organization expressed specific support for this provision.

Two supportive patient groups voiced concern about possible workload strain on the Agency resulting from this enhancement. FDA believes that the resources proposed under PDUFA VI will be sufficient to meet this workload. One patient group expressed specific support for the commitment to incorporate the new staff for this enhancement as core members of review teams and noted that the guidance topics committed to each explore an important question in this space. A few patient groups encouraged the FDA to advance the timelines committed to for publishing of the guidances. FDA notes that the current shortage of staff in this area presented a key consideration in the proposed timing of the guidances since it requires significant time and effort by the most experienced review staff to develop the guidance. Multiple organizations applauded the commitment to publish a repository of publically available tools on the FDA's website. One patient group encouraged the Agency to ensure all patient populations, including patients with rare diseases, can equitably participate. FDA appreciates the input and will consider these comments as it develops its implementations plans.

Enhancing Benefit-Risk Assessment in Regulatory Decision-making

In PDUFA VI, FDA commits to strengthening sponsors' and the public's understanding of FDA's approach to Benefit-Risk assessment throughout the new drug lifecycle. Nine patient groups, one healthcare professional organization, one non-profit policy group, and two industry groups expressed specific support for this provision.

Multiple groups applauded the effort to integrate the patient perspective into the benefit-risk framework across the product lifecycle. One patient group encouraged FDA to be cautious about any changes to the drug review program that might weaken assurances to patients that approved drugs are safe and effective. FDA notes that the intent of these commitments is to strengthen the structured approach to benefit-risk assessment in the product lifecycle, not to change the approval standard. Another patient group encouraged the FDA to consider the diverse needs of different patient populations, as well as their caregivers, in the benefit-risk framework. FDA appreciates the input and will consider these comments as it develops its implementations plans.

Advancing Model-Informed Drug Development

PDUFA VI proposes to advance the development and application of statistical modeling, "model-informed drug development", in drug development and review. Four patient groups, one healthcare professional organization, and two industry groups expressed specific support for this provision. One supportive patient group encouraged the Agency to ensure that these enhancements are adequately resourced so as not to divert resources from drug review activities. Another patient group noted that model-informed drug development may open the door for rare disease therapeutic development that may not have moved forward otherwise.

Enhancing Capacity to Review Complex Innovative Designs

PDUFA VI proposes to advance simulation approaches that can support utilization of novel complex clinical trial designs in drug development and review. Eight patient groups, one healthcare professional organization, and two industry groups expressed specific support for this provision.

One supportive patient group encouraged the FDA to create incentives for sponsors to include psychosocial measures in clinical trial protocols. Another patient group encouraged the FDA to consider how to incorporate the pilot program into review offices to ensure that the effort is not "siloed". Another patient group encouraged an evaluation of the Oncology Center of Excellence's ability to review complex trial designs. FDA appreciates the input and will consider these comments as it develops its implementations plans.

Enhancing Drug Development Tools Qualification Pathway for Biomarkers

PDUFA VI proposed to improve capacity to enhance the predictability of the biomarker qualification process by clarifying evidentiary standards for biomarkers and refining review processes. Six patient groups and two industry groups expressed specific support for this provision. One supportive patient group encouraged the FDA to consider focusing on training

for investigators in addition to its own staff. Another patient group expressed support for the FDA's commitment to gather stakeholder input on biomarker qualification through a public meeting. Multiple groups noted the importance of biomarkers to development of therapies in their disease areas. FDA appreciates the input and will consider these comments as it develops its implementations plans.

Advancing Postmarketing Drug Safety Evaluation Through Expansion of the Sentinel System and Integration into FDA Pharmacovigilance Activities

PDUFA VI proposes to expand the Sentinel System and systematically integrate it into FDA drug safety activities. Three patient groups, three healthcare professional organizations, two consumer groups and two industry organizations expressed specific support for this provision. The two supportive consumer groups encouraged the FDA to make Sentinel databases available to independent researchers. FDA notes that the Agency does not own these data, but in PDUFA VI it has committed to evaluating ways to facilitate public and sponsor access to Sentinel's distributed data network.

Timely and Effective Evaluation and Communication of Postmarketing Safety Findings Related to New Drugs

In PDUFA VI, FDA proposes to improve its processes and systems that support the review, oversight, tracking, and communication of postmarketing drug safety system. This would include an assessment, to be conducted by FY 2022, of how its data systems and processes support review, oversight and communication of postmarket safety drug issues. Two industry groups expressed specific support for this provision. In addition, one consumer group urged the FDA to conduct the proposed assessment sooner than fiscal year 2022. FDA appreciates the support for conducting this assessment and notes that it has committed to first implementing improvements to its current processes and systems, and that it would be these improved processes and systems that would then be assessed no later than the end of fiscal year 2022. The timeframe for the assessment is intended to allow time for the proposed improvements to have effect.

Electronic Submissions and Data Standards Activities

PDUFA VI proposes to improve the predictability and consistency of PDUFA electronic submission processes. One industry group expressed specific support for this provision.

Improving FDA Hiring and Retention of Review Staff

Under PDUFA VI, FDA proposes to engage in activities to strengthen internal systems and processes to improve hiring and retention of key scientific and technical talent. Twelve patient groups, two healthcare professional organizations, two industry groups, and one consumer group expressed specific support for this provision. Multiple supportive groups noted that this provision was a critical component of the PDUFA VI commitment letter as the Agency needs growth and stability in its workforce to be able to achieve success its commitments in PDUFA

VI. Two supportive patient groups also expressed concern that that the proposed hiring provisions not have adverse impacts on the new Oncology Center of Excellence.

Financial Enhancements

Under PDUFA VI, FDA commits to establishing a resource capacity planning function utilizing modernized time reporting data, updating the fee structure to improve predictability of collections and fee amounts while reducing administrative burden, and implementing mechanisms to increase transparency on the use of fee-resources, including the publishing of a five-year plan and annual public meetings. Two industry groups commented on this and expressed specific support for these provisions.

Other Comments

FDA received a number of comments that are related to broader program operations or regulatory policy issues. The comments included, for example, a recommendation that fees should be used to add staffing to shorten the time for review of orphan designation and recommendations that fees should be used towards monitoring the safety of off-label uses of drugs and to develop informed consent procedures for drugs used off-label. With respect to the latter, FDA notes that its activities to collect, develop, and review safety information on approved drugs, including adverse event reports, are already within the scope of the new drug review program and eligible for support by PDUFA fees. A number of the comments, regardless of their merit, are outside the scope of the PDUFA reauthorization discussions: performance goals and procedures for the review of human drug applications. FDA emphasized this scope consideration during the public meetings and at the other stakeholder consultation and negotiation meetings conducted throughout the process. The comments received in the docket include the following: a recommendation that fees be used to review or pre-approve direct-to-consumer drug advertisements,¹ a recommendation that fees be used to verify the accuracy of data in clinicaltrials.gov vis a vis FDA's data systems; a recommendation that, while FDA does not directly control drug pricing, it should consider pricing as it finalizes this agreement, and creation of a new Office of Patient Affairs.

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. Reflecting the significant and wide-spread support expressed for the recommendations, FDA has not made changes to those recommendations for the reauthorization of PDUFA.

¹ FDA notes that a fee program for review of direct-to-consumer advertisements was authorized as part of the Food and Drug Administration Amendments Act of 2007, however, fee funds were not appropriated by Congress to support this program and the program was not reauthorized in 2012.