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

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Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, submits these comments to the Food and Drug Administration (FDA) regarding the Agency's draft Commitment Letter for the reauthorization of the Prescription Drug User Fee Act (PDUFA) for fiscal years 2023 through 2027.[1] These comments make specific suggestions to revise that proposed Commitment Letter text to strengthen the FDA's ability to optimize its critical role as the nation's regulator of new and existing drugs and biologics. Because of PDUFA, the FDA is clearly too deferential to the drug and biologics industries such that the nation's public health suffers.

The currently proposed performance goals put forth in the draft Commitment Letter contain numerous quota measures intended to please the regulated industry's desire for fast reviews, such as the following:

A. REVIEW PERFORMANCE GOALS

1. NDA [new drug application]/BLA [biologics license application] Submissions and Resubmissions

a. Review and act on 90 percent of standard NME NDA and original BLA submissions within 10 months of the 60-day filing date.[2]

[1] Food and Drug Administration. PDUFA reauthorization performance goals and procedures fiscal years 2023 through 2027. https://www.fda.gov/media/151712/download. Accessed October 22, 2021.
[2] *Ibid.* PDF page 4.

Additional performance measures should be developed to assess the actual short- and long-term public health impacts of the FDA's decisions regarding drugs and biologics. We offer the following five examples of such public health performance measures:

(1) Counts and percentages of those NDAs/BLAs reviewed each year that were rejected because there was a lack of evidence establishing safety or efficacy;
(2) Counts and percentages of those NDAs/BLAs reviewed each year that were the subject of subsequent FDA warnings or withdrawals during the first several years post-approval;
(3) Counts and percentages of those NDAs/BLAs reviewed each year approved with at least two phase 3 randomized, controlled clinical trials demonstrating consistent and robust evidence of safety and efficacy and favorable benefit-risk profiles, and those with one or fewer such clinical trials;
(4) Counts and percentages of those NDAs/BLAs reviewed each year subject to mandated post-marketing studies where those obligations were fulfilled in the prespecified time allotted and that confirmed safety and efficacy; and
(5) Counts and percentages of NDAs/BLAs reviewed each year for which the FDA decision regarding approval was concordant with advisory committee recommendations.

The aim of these additional performance measures is to ensure that the FDA reports sufficient information to the public and to Congress to allow an independent evaluation of the Agency's - accomplishments and failures.

Related to FDA reviewer and advisory committee activities, we recommend that the final Commitment Letter include performance measures based on anonymous surveys of FDA reviewers and advisory committee members about their experiences reviewing NDAs/BLAs**.** Past surveys have been too infrequent and concerning. For example, in 2003, a Department of Health and Human Services Office of Inspector General Report found that among 136 Center for Drug Evaluation and Research (CDER) reviewers surveyed, only 64% were confident in FDA decisions regarding the safety of a drug.[3] In 2018, a former FDA medical team leader told *Propublica*, "you don't survive as a senior official at the FDA unless you're pro-industry."[4]

More recently, Aaron Kesselheim M.D., J.D., M.P.H., Director of the Division of Pharmacoepidemiology and Pharmacoeconomics at Harvard Medical School, resigned from the Peripheral and Central Nervous System Advisory Committee because of the FDA's decision to approve aducanumab (Aduhelm) for treatment of Alzheimer's disease in direct opposition to the nearly unanimous opinion of that expert advisory committee. In his resignation letter to Acting

[3] Department of Health and Human Services, Office of Inspector General. *FDA's Review Process For New Drug Applications*. March 2003. Publication OEI-01-01-00590.
[4] Chen C. FDA repays industry by rushing risky drugs to market. *ProPublica*. June 26, 2018. https://www.propublica.org/article/fda-repays-industry-by-rushing-risky-drugs-to-market. Accessed October 22, 2021.

FDA Commissioner Janet Woodcock, Dr. Kesselheim wrote: "FDA is not presently capable of adequately integrating the Committee's scientific recommendations into its approval decisions."[5]

Candid FDA staff and advisory committee member perspectives on the adequacy of the Agency's review and decision-making processes are certainly germane to Program performance and thus should be measured and presented to the public on a regular basis. Important measures that could be derived from routine surveys include the following:

(1) Counts and percentages of NDA/BLA reviewers or committee members who had concerns about FDA NDA/BLA decisions related to safety or efficacy;
(2) Counts and percentages of NDA/BLA reviewers or committee members who felt they were free from direct or indirect pressure from the regulated industry when reviewing NDAs/BLAs;
(3) Counts and percentages of NDA/BLA reviewers or committee members who felt they had ample time and resources to review the NDAs/BLAs they were assigned; and
(4) Counts and percentages of NDA/BLA reviewers or committee members who felt their concerns about NDAs/BLAs were properly ascertained and respected by FDA decision-makers.

More generally, the Commitment Letter language should be recast to emphasize the FDA's regulatory role and responsibility. Presently, for example, it has prominent language like the following:

> The goal of the Program is to promote the efficiency and effectiveness of the first cycle review process and minimize the number of review cycles necessary for approval, ensuring that patients have timely access to safe, effective, and high-quality new drugs and biologics.[6]

Such language should be modified by adding that a primary program goal is to protect public health by minimizing the probability that unsafe or ineffective drugs or biologics enter the market.

Moreover, the Commitment Letter should state that although the Agency offers technical assistance to NDA/BLA sponsors in the preparation of their applications, ensuring the quality of the NDA/BLA is ultimately the responsibility of the sponsor, not of the FDA.

There are several places in the draft Commitment Letter where "expediting drug development" is the clear goal, including under Section K. "Enhancing regulatory science…" Such language suggests the Agency is responsible for "…ensuring the sustained success of the breakthrough

[5] Kesselheim AS. Letter to Acting Food and Drug Administration Commissioner Janet Woodcock. June 10, 2021. https://pbs.twimg.com/media/E3jKN4GWYAUGj9U.png. Accessed October 26, 2021.
[6] Food and Drug Administration. PDUFA reauthorization performance goals and procedures fiscal years 2023 through 2027. https://www.fda.gov/media/151712/download. Accessed October 22, 2021. PDF page 7.

therapy program, … use of new surrogate endpoints as the primary basis for product approval, …and exploring the use of real-world evidence for use in regulatory decision-making."[7]

Such goals should be revised by adding statements limiting surrogate endpoint use to those that have been scientifically validated and therefore deemed by the majority of the medical community to be predictive of clinically meaningful outcomes. It should further caution that real-world evidence must not supplant well-designed randomized controlled trials (RCTs) to establish safety and efficacy of each product's FDA-approved indications and affirm at least two phase 3 RCTs as the usual standard for demonstrating substantial evidence of effectiveness.

The need for these cautions and standards is supported by research that shows that 81% of NDA approvals in 2018 involved Accelerated Approval, Fast-Track, or Priority Review[8] and that faster approvals under PDUFA correlated with the marketing of products that were less safe than those marketed before the PDUFA was instituted.[9]

The draft Commitment Letter also states the following:

> FDA's philosophy is that timely interactive communication with sponsors during drug development is a core Agency activity to help achieve the Agency's mission to facilitate the conduct of efficient and effective drug development programs…[10]

The FDA's review and approval of the BLA for aducanumab for treatment of Alzheimer's disease revealed that such interactive communications established under PDUFA have resulted in inappropriately close collaborations between the Agency and sponsors that have compromised the integrity for NDA/BLA reviews.

To address this problem, the Commitment Letter should be modified to include provisions that specifically:

(1) Characterize the FDA's primary role as being the gatekeeper, watchdog, and judge of industry products (to assert and further codify the Agency's responsibility to be objective and independent from the firms they regulate);
(2) Establish procedures that separate (with a firewall between) staff involved in pre-NDA/BLA-submission interactions with sponsors from staff who formally review those applications for regulatory decision-making purposes; and

[7] *Ibid*. PDF page 27.
[8] Darrow JJ, Avorn J, Kesselheim AS. FDA approval and regulation of pharmaceuticals, 1983-2018. *JAMA*. 2020;323(2):164-176.
[9] Frank C, Himmelstein DU, Woolhandler S, et al. Era of faster FDA drug approval has also seen increased black-box warnings and market withdrawals. *Health Aff (Millwood).* 2014;33(8):1453-1459.
[10] Food and Drug Administration. PDUFA reauthorization performance goals and procedures fiscal years 2023 through 2027. https://www.fda.gov/media/151712/download. Accessed October 22, 2021. PDF page 27.

(3) Require FDA staff training on how to minimize the risk of regulatory capture of the Agency by sponsors.

Finally, we urge the FDA to pursue the following actions regarding drug and biologic regulatory policy as it finalizes the PDUFA Commitment Letter to Congress:

(1) Seek considerably more direct appropriations from Congress to decrease the Agency's financial dependence on the regulated industry. Presently, CDER and the Center for Biologics Evaluation and Research are too dependent on the financial support of regulated industries.
(2) Revise the PDUFA reauthorization negotiation process to make all meetings between industry and the FDA fully open to the public. At present the regulated industry and the FDA hold closed meetings in which they hammer out specifics regarding the program's budgeting, personnel, and overall operation goals. This asymmetry of influence for industry versus patients and the broader American public is completely inappropriate and unacceptable.
(3) Implement the National Academies of Science, Engineering, and Medicine's public health framework for regulatory oversight of opioids. This framework will enhance the Agency's stated goal to ensure that the review of drugs and biologics appropriately considers the benefits and risks associated with such products before they are approved for marketing.
(4) Maintain in-person, on-site inspections of pharmaceutical manufacturing facilities rather than allowing remote, paper-based inspections.
(5) Commission objective studies that quantify the avoided or realized harms resulting from NDA/BLA approval decisions. This suggestion follows directly from the suggestion made at the outset of this comment which calls for public health performance measures. Third-party researchers should be regularly commissioned to conduct independent reviews of public health performance indicators tied directly to the FDA's decisions.
(6) Minimize reliance on Risk Evaluation and Mitigation Strategies mandated in lieu of premarket resolution of safety concerns. Industry is too often allowed to delay safety studies while it reaps tremendous profits on prematurely approved drugs and biologics.
(7) Add performance indicators that specifically report each year on the number of novel BLAs/NDAs that specifically address illnesses that impact minority and other neglected populations (e.g., sickle cell disease therapies or treatments for ovarian cancer) and that report how often pivotal RCTs enroll representative proportions of minorities. These performance measures will help the Agency ensure that results of clinical trials supporting approval of new drugs are generalizable to minority populations.

Thank you for the opportunity to comment on these important public health matters.