Public Meeting on the Recommendations for Prescription Drug User Fee Act (PDUFA) Reauthorization: Commitment Letter Draft Review

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(I have no financial conflicts of interests)

Annual performance measures

Quota and timeline based, focused mostly on pleasing industry with fast reviews

Example: % of NDAs/BLAs acted upon within 10 months of the completed application

❖ **Public health indicators should be added and emphasized**

Examples:

1. % of NDAs/BLAs which were rejected because there was a lack of evidence establishing safety or efficacy
2. % of previously approved NDAs/BLAs that were the subject of subsequent FDA warnings or withdrawals during the first several years post approval
3. % of NDAs/BLAs approved with at least two phase 3 randomized, controlled trials demonstrating consistent and robust evidence of safety and efficacy and favorable benefit-risk profiles
4. % of NDAs/BLAs subject to mandated post-marketing studies where those obligations were fulfilled and confirmed safety and efficacy
5. % of NDAs/BLAs for which the FDA decision regarding approval was concordant with advisory committee recommendations

Formally survey content experts…

- FDA clinical, statistical and other review staff; advisory committee members

❖ **Use the data to derive the following types of performance measures**

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

Recast commitment language

❖ **Emphasize FDA's regulatory role and responsibilities**

Example

Commitment letter states: "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."

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.

Further modifications to the language should be made stating that ensuring the quality of the NDA/BLA is ultimately the responsibility of the sponsor, not of the FDA.

Reaffirm the commitment to substantial evidence

The draft commitment letter encourages fast approval at the expense of careful approval

For example:

- Under a section "K. Enhancing regulatory science and expediting drug development" it is suggested that the Agency is responsible for:

  "…ensuring the sustained success of the breakthrough therapy program, continuing early consultations between FDA and sponsors on the 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."

❖ **Such pronouncements and goals should be clarified by explicit language which:**

1. Limits surrogate endpoint use to those that have been scientifically validated and deemed by the majority of the medical community to be predictive of clinically meaningful outcomes.
2. States that RWE should not substitute for well-designed, randomized controlled trials (RCTs).
3. Affirms at least two phase 3 RCTs as the usual standard for demonstrating substantial evidence of effectiveness.

Regulatory capture of the Agency

The draft commitment letter states: “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.”

- **Because such interactive communications established under PDUFA have resulted in collaborations between the Agency and sponsors that have compromised the integrity of NDA/BLA reviews — evident during the review for aducanumab — the commitment letter should be modified to include provisions that:**

1. Characterize the FDA’s primary role as being a gate-keeper, watchdog, and judge of industry products (to assert and codify its objectivity and independence)

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

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

Using the commitment letter, the FDA should also aim to…

1. Request an increase in their discretionary drug/biologic regulatory budget
2. Eliminate closed meetings with industry during reauthorization negotiations
3. Implement the National Academies' public health framework for regulatory oversight of opioids
4. Maintain in-person manufacturing facility inspections as the standard
5. Commission objective studies that quantify the avoided or realized harms resulting from NDA/BLA approval decisions
6. Minimize reliance on REMS mandates in lieu of premarket resolution of safety concerns

Thank you. For more information:

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