U.S. Food and Drug Administration
Protecting and Promoting Public Health

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Prescription Drug User Fee Act (PDUFA) Reauthorization Public Meeting

August 15, 2016

Basic PDUFA Construct

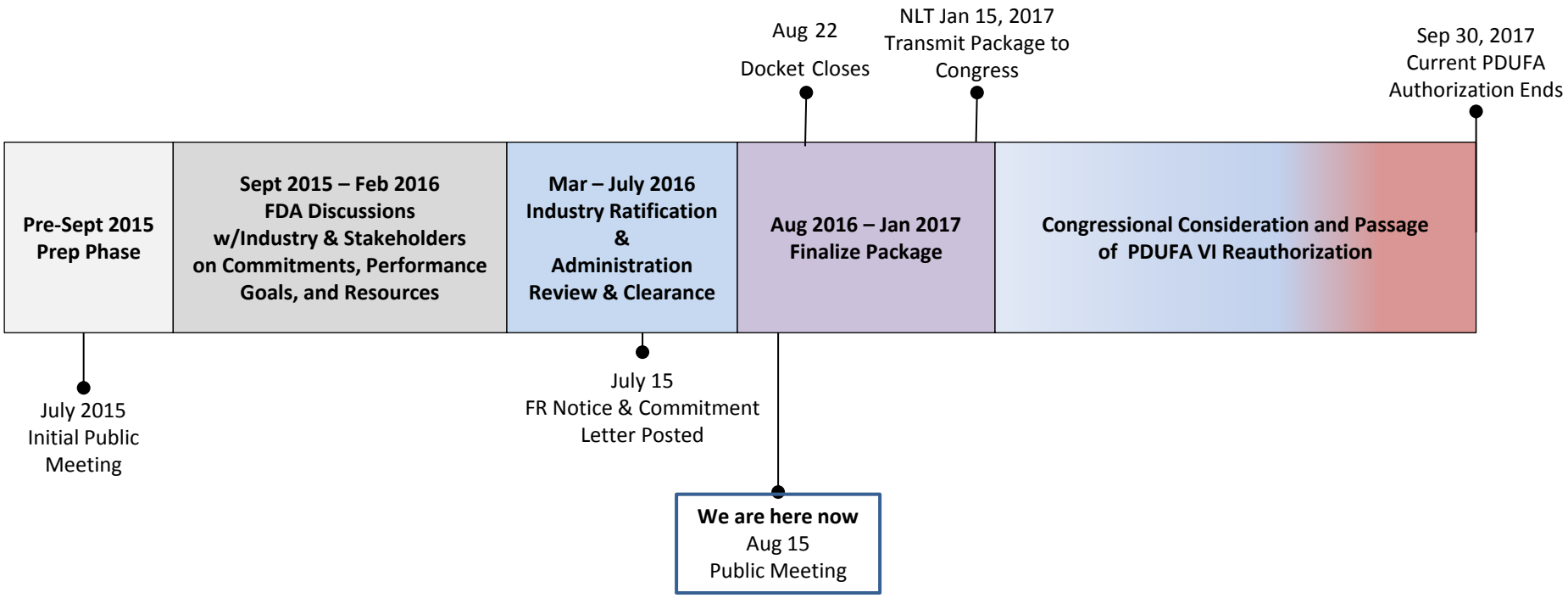
- Fee funds are added to non-fee funds and are intended to increase staffing and other resources to speed and enhance review process
- User fees pay for services that directly benefit fee payers*
- Fee discussions with industry focus on desired enhancements in terms of specific aspects of activities in "process for the review of human drugs"
  - What new or enhanced process will the FDA want or industry seek to include in the next 5 years?
  - What is technically feasible?
  - What resources are required to implement and sustain these enhancements?
  - No discussion of policy.
- Experience: *Devil is in the Details*

* OMB Circular A-25; direct benefit distinguishes user fees from tax

Performance Commitments and Fee Funding Have Evolved Since 1992

- **PDUFA I: 1993-1997**
  - Added funds for pre-market review; reduce backlog and set predictable timelines (goals) for review action
- **PDUFA II (FDAMA): 1998-2002**
  - Shorten review timelines; add review goals; add process and procedure goals; some added funding
- **PDUFA III (BT Preparedness & Response Act): 2003-2007**
  - Significant added funding; increase interaction in first review cycle (GRMPs); allow limited support for post-market safety
- **PDUFA IV (FDAAA): 2008-2012**
  - Increased and stabilized base funding; enhanced pre-market review; modernize post-market safety system
- **PDUFA V (FDASIA): 2013-2017**
  - Small increase to base funding; review enhancements increase communication with sponsors; strengthen regulatory science & post-market safety; electronic data standards

PDUFA VI Reauthorization Timeline



Today's Meeting is to Further the Reauthorization Process

PDUFA REAUTHORIZATION and REPORTING REQUIREMENTS as of PDUFA V.

(d) REAUTHORIZATION.—

(1) CONSULTATION.—In developing recommendations to present to the Congress with respect to the goals, and plans for meeting the goals, for the process for the review of human drug applications for the first 5 fiscal years after fiscal year 2017 and for the reauthorization of this part for such fiscal years, the Secretary shall consult with— **(A) the Committee on Energy and Commerce of the House of Representatives; (B) the Committee on Health, Education, Labor, and Pensions of the Senate; (C) scientific and academic experts; (D) health care professionals; (E) representatives of patient and consumer advocacy groups; and (F) the regulated industry.**

(2) PRIOR PUBLIC INPUT.—Prior to beginning negotiations with the regulated industry on the reauthorization of this part, the Secretary shall—

(A) publish a notice in the Federal Register requesting public input on the reauthorization; (B) **hold a public meeting** at which the public may present its views on the reauthorization, including specific suggestions for changes to the goals referred to in subsection (a); (C) **provide a period of 30 days after the public meeting to obtain written comments** from the public suggesting changes to this part; and (D) **publish the comments on the Food and Drug Administration's Internet Web site.**

(3) PERIODIC CONSULTATION.—Not less frequently than once every month during negotiations with the regulated industry, the Secretary shall **hold discussions with representatives of patient and consumer advocacy groups** to continue discussions of their views on the reauthorization and their suggestions for changes to this part as expressed under paragraph (2).

(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.

(6) MINUTES OF NEGOTIATION MEETINGS.—

(A) PUBLIC AVAILABILITY.—Before presenting the recommendations developed under paragraphs (1) through (5) to the Congress, the Secretary shall **make publicly available, on the public Web site of the Food and Drug Administration, minutes of all negotiation meetings** conducted under this subsection between the Food and Drug Administration and the regulated industry.

(B) CONTENT.—The minutes described under subparagraph (A) shall **summarize any substantive proposal made by any party to the negotiations as well as significant controversies or differences of opinion during the negotiations and their resolution**.

Organization of Today's Meeting

- Panel 1: Pre-Market Review and Post-Market Safety
- Panel 2: Regulatory Decision Tools
- Panel 3: Administrative Enhancements:
  - Electronic submissions and data standards activities
  - Hiring capacity
  - Financial management

PANEL 1
PRE-MARKET REVIEW AND POST-MARKET SAFETY

New Molecular Entity Review Program 2.0

Opportunity:

Reducing the administrative burden and complexity of the new molecular entity (NME) Program while increasing flexibility for some applications would benefit FDA and sponsors

Proposed Approach:

- FDA and sponsor have the option to agree on a Formal Communication Plan during application review that may or may not include Program elements (e.g., late-cycle meetings) and interactions that are not part of the Program (e.g., application orientation meetings).
- Current practices regarding Program flexibility for expedited reviews are codified.
- Applications that are “Filed over Protest” are subject to Program performance goals but do not benefit from Program elements; any subsequent resubmissions do not have performance goals.
- Review activities regarding FDA’s scheduling recommendation (under the Controlled Substances Act) are discussed at Program meetings, if relevant.
- Additional flexibility for scheduling AC meetings is provided; FDA and applicant have the option to agree to hold a follow-up informal teleconference to discuss AC feedback.

Goal Extensions for Missing Manufacturing Facility Information

Opportunity:

Late inspections of previously unidentified manufacturing facilities can impact FDA's ability to meet PDUFA goals.

Proposed Approach:

- Apply to all applications and supplements the current PDUFA V NME Review Program expectation of a comprehensive and readily located list of manufacturing facilities.
  - If FDA identifies the need to inspect a facility that was not included on the list, the Agency may extend the goal date for an original application, efficacy supplement, or manufacturing supplement.

Meeting Management

Opportunity:

- The number of formal meeting requests is rapidly increasing; in FY2015, FDA received over 3,000 formal PDUFA meeting requests from sponsors.
- Meeting background packages can be lengthy (1,000+ pages); current timeframes do not allow enough time for review and internal deliberation before providing advice to companies on complex drug development questions.

Proposed Approach:

- Create Type B(EOP) meetings for certain EOP1 and EOP2/pre-phase 3 meetings and changes to timeframes for Type C meetings.
  - Modify timing for FDA's response to meeting requests, submission of meeting packages to FDA, and FDA's issuance of preliminary responses for Type B(EOP) and C meetings to give FDA more time to review package.
  - Sponsors may request a Written-Response-Only (WRO) for any meeting type, with FDA deciding if that is appropriate; as in PDUFA V, FDA may issue WROs for pre-IND and Type C meetings.

FDA-Sponsor Communication During Drug Development

Opportunity:

FDA and industry believe that a more systematic understanding of best practices and behavior during drug development could be useful to ensure efficient and effective drug development.

Proposed Approach:

- Conduct third-party evaluation of current communication practices of FDA and sponsors during drug development.
- Convene public workshop to discuss evaluation results.
- Update draft or final guidance on “Best Practices for Communication Between IND Sponsors and FDA During Drug Development,” if necessary.

Early Consultations on New Surrogate Endpoints

Opportunity:

Early consultation can be important when a sponsor intends to use a biomarker as a new surrogate endpoint as the primary basis for product approval. Such engagement allows FDA to provide early advice to the sponsor on a critical aspect of their development program.

Proposed Approach:

- Requests for early consultation in PDUFA VI will be considered a Type C meeting request.
- Meeting purpose is to discuss feasibility of the surrogate as a primary endpoint, any knowledge gaps, and how these gaps should be addressed before surrogate could be used as primary basis for approval.
  - Meeting background package is due at the time of the meeting request and must include preliminary human data indicating impact of drug on biomarker.

PDUFA–led Combination Product Review

Opportunity:

FDA and industry agreed that FDA's inter-center and intra-center PDUFA-led combination product review coordination (among CDER, CBER, and CDRH) and transparency could be improved.

Proposed Approach:

- Develop staff capacity across centers and Office of Combination Products (OCP) to more efficiently review submissions that include combination products.
- Streamline combination product review and improve FDA's ability to assess combination product workload.
- Establish MAPPs to describe review processes and procedures for combination products, including consultation of internal experts across centers.
- Establish submission procedures and performance goals for review of protocols for human factors studies.
- Conduct third-party evaluation of combination product review, engaging FDA review teams and sponsors. Use findings to update Manuals of Policies and Procedures (MAPPs) and submission procedures, as necessary.
- Publish/update guidance on bridging studies and patient-oriented labeling.

Breakthrough Therapies

Opportunity:

- FDA's workload for the breakthrough therapy program has been higher than anticipated in terms of the number of products requesting and receiving breakthrough status.
- Breakthrough products represent a significant and concentrated effort for FDA staff at all levels.

Proposed Approach:

- Provide additional staffing to FDA to allow agency to continue to work closely with sponsors of breakthrough products throughout designation, development, and review processes.

Rare Disease Drug Development

Opportunity:

The PDUFA V activities of the Rare Disease Program (RDP) have been successful and should be continued.

Proposed Approach:

- Integrate RDP staff into review teams for rare disease development programs and application review.
- Continue current and ongoing activities of RDP, including staff training, promoting best practices for review and regulation of rare disease products, and conducting outreach to sponsors, patient groups, etc.

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

Opportunity:

FDA has process improvement efforts already underway to address the management and oversight of postmarketing safety issues. Industry raised specific concerns about inconsistencies in FDA's process for communicating safety issues to Sponsors.

Proposed Approach:

- Improve processes and IT systems that capture and track information in order to support the management, oversight, and communication of postmarketing drug safety issues
- Update policies and procedures to include consistent and timely notification of sponsors:
  - When a serious safety signal is identified, and
  - Not less than 72 hours before public posting of a quarterly FDAAA 921 safety notice (to the extent practicable)
- Conduct an assessment of the data systems and processes that support review, oversight, and communication of postmarketing drug safety issues

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

Opportunity:

- Recently, FDA successfully transitioned from the Mini-Sentinel pilot to the Sentinel System, but full utilization of the System remains a work in progress.
- Continued development and integration of the Sentinel System is needed to realize the System's full value to the postmarketing safety review process.

Proposed Approach:

- Continue to expand Sentinel's sources of data and core capabilities
- Systematically integrate the System into postmarketing review activities
- Development of a comprehensive training program for review staff to ensure that staff:
  - Have a working knowledge of Sentinel
  - Can identify when Sentinel can inform important regulatory questions
  - Are able to consistently participate in use of Sentinel to evaluate safety issues
- Enhancement of Sentinel communication practices with sponsors and the public
- Analysis of the impact of Sentinel expansion and integration on FDA's use of Sentinel for regulatory purposes

PANEL 2
REGULATORY DECISION TOOLS

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

Opportunity:

Develop systematic approaches to bridge from patient-focused drug development meetings to fit-for-purpose tools to collect meaningful patient input that can be incorporated into regulatory review.

Proposed Approach:

- Conduct public workshops and develop series of guidance documents on:
  - collecting comprehensive patient-community input on burden of disease and current therapy
  - development of holistic set of disease or treatment impacts most important to patients
  - development of measures for an identified set of impacts
  - clinical outcome assessments (COAs) and better ways to incorporate COAs into endpoints
- Revise MAPPs and standard operating procedures and policies (SOPPs) as needed to incorporate increased patient focus
- Repository of info on publicly available tools and ongoing efforts
- Enhance staff capacity to facilitate development and use of patient-focused methods to inform drug development and regulatory decisions

Enhancing Benefit-Risk Assessment in Regulatory Decision-Making

Opportunity:

Strengthen sponsors' and the public's understanding of FDA's approach to B-R assessment throughout the new drug lifecycle

Proposed Approach:

- Publish an update to the FDA's PDUFA V Benefit-Risk Implementation plan titled "Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making"
- Develop guidance on benefit-risk assessments for new drugs and biologics
- Conduct evaluation of the implementation of the Benefit-Risk Framework in the human drug review process
- As appropriate, revise relevant MAPPs and SOPPs

Enhancing Capacity to Review Complex Innovative Designs

Opportunity:

Advance simulation approaches that can support innovation and regulatory evaluation of novel complex clinical trial designs and clarify for sponsors FDA expectations for simulations needed to adequately characterize the performance of these complex trials.

Proposed Approach:

- Enhance staff capacity to facilitate appropriate use of complex adaptive, Bayesian, and other novel clinical trial designs.
- Conduct pilot program for highly innovative trial designs for which simulations are necessary to determine trial operating characteristics.
  - Include a limited number of investigational new drug (IND) applications
  - Conduct pair of dedicated meetings with sponsor to discuss FDA expectations and review of simulations
- Convene a public workshop to discuss various complex adaptive, Bayesian, and other novel clinical trial designs.
- Develop guidance on complex adaptive (including Bayesian adaptive) trial designs.
- As appropriate, develop or revise relevant MAPPs and SOPPs.

Enhancing Capacity to Support Analysis Data Standards for Product Development and Review

Opportunity:

As NDAs/BLAs are increasingly submitted in fully-standardized electronic form, ensuring that sponsor analysis data sets included in the application can be readily opened and analyzed is critical for timely statistical review.

Proposed Approach:

- Enhance staff capacity to efficiently review and provide feedback to sponsors on the readiness of submitted analysis data sets and programs for statistical review.
- Improve staff capacity to assist with FDA development and updating of info and standards in therapeutic area user guides.
- Convene a public workshop to advance the development and application of analysis data standards.
- As appropriate, develop or revise relevant MAPPs and SOPPs.

Advancing Model-Informed Drug Development

Opportunity:

Advance the development and application of exposure-based, biological, and statistical models derived from preclinical and clinical data sources, referred to as “model-informed drug development” (MIDD) approaches

Proposed Approach:

- Convene a series of workshops to identify best practices for MIDD
- Conduct a pilot program for MIDD approaches.
  - Including dedicated meetings with the sponsor to discuss the development and application of models and simulations (e.g., for disease progression, concentration-response)
- Develop guidance, or revise relevant existing guidance, on model-informed drug development
- Revise relevant MAPPs and SOPPs as appropriate,
- Strengthen staff capacity to support MIDD strategies

Enhancing Drug Development Tools (DDT) Qualification Pathway for Biomarkers

Opportunity:

To handle growing number of qualification programs, improve capacity to review and the predictability of the biomarker qualification process by clarifying evidentiary standards for biomarkers and refining processes related to review of qualification submissions and communication among FDA and other stakeholders.

Proposed Approach:

- Develop staff capacity to enhance biomarker qualification review by increasing base capacity.
- Convene public meeting to discuss DDT qualification for biomarkers.
- Develop guidances for internal staff and industry on biomarker taxonomy, contexts of use, and general evidentiary standards.
- As appropriate, develop or revise relevant MAPPs and SOPPs.
- Maintain public website to communicate a list of biomarker qualification submissions in the qualification process.

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

Opportunity:

As the ability to generate and use "real-world evidence" (RWE) continues to evolve and grow, it is important that FDA explore the possibilities of using this data to evaluate safety and effectiveness.

Proposed Approach:

- Conduct a public workshop to gather input into topics related to the use of RWE for regulatory decision-making.
- Initiate appropriate activities (e.g. pilot studies or methodology development projects) to address key issues in the use of RWE for regulatory decision-making purposes.
- Publish draft guidance on how RWE can contribute to the assessment of safety and effectiveness in regulatory submissions (e.g. supplemental applications, postmarketing requirements).

PANEL 3
ADMINISTRATIVE ENHANCEMENTS

ELECTRONIC SUBMISSIONS AND DATA STANDARDS ACTIVITIES

HIRING CAPACITY

FINANCIAL MANAGEMENT

Electronic Submission Process

Opportunity:

The predictability and transparency of PDUFA electronic submission processes could be improved.

Proposed Approach:

- Publish and maintain up-to-date electronic submission documentation to include a description of the process, milestones, and notifications; rejection process; and validation criteria.
- Publish targets for and measure Electronic System Gateway (ESG) availability overall (including scheduled downtime) and during business hours.
- Publish target time frames for the 1) expected submission upload duration(s) and 2) timeframe between key milestones and notifications.
- Implement the ability to communicate electronic submission milestone notifications, including final submission upload status (e.g., successfully processed or rejected), to sender/designated contact.
- Document and implement a process to provide ample advance notification on systems and process changes commensurate with the complexity of the change and the impact to sponsors.

Electronic Submissions and Data Standards Activities

Opportunity:

The transparency and communication of FDA electronic submission and Data Standards activities could be enhanced.

Proposed Approach:

- Plan and hold quarterly meetings to share performance updates between FDA and Industry.
- Hold annual public meetings to seek stakeholder input related to electronic submission system past performance, future targets, emerging industry needs and technology initiatives to inform the FDA IT Strategic Plan and published targets.
- Post, at least annually, historic and current metrics on ESG performance in relation to published targets, characterizations and volume of submissions, and standards adoption and conformance.
- Incorporate strategic initiatives in support of PDUFA goals into the FDA IT Strategic Plan.
- Collaborate with Standards Development Organizations and stakeholders to ensure long-term sustainability of supported data standards.

Hiring Capacity Enhancements

Opportunity:

The ability to hire and retain qualified staff is critical to ensuring the availability of new safe and effective drugs.

Proposed Approach:

- Modernize the hiring system and infrastructure.
- Augment human resources capacity through the use of dedicated expert contractors.
- Establish a dedicated function for the recruitment and retention of scientific staffing.
- Set clear goals for hiring.
- Conduct a comprehensive and continuous assessment of hiring and retention practices.

Enhance Management of PDUFA Resources

Opportunity:

Enhance management of PDUFA resources and ensure PDUFA user fee resources are administered, allocated, and reported in an efficient and transparent manner.

Proposed Approach

- Establish a capacity planning function utilizing modernized time reporting.
- Enhance financial transparency and efficiency:
  - 3rd party assessment to evaluate the financial administration of the PDUFA program to identify recommendations for improvement.
  - Publish a PDUFA 5-year financial plan in FY 2018 and publish updates to the 5-year plan each subsequent fiscal year.
  - Convene a public meeting each fiscal year starting in FY 2019 to discuss the PDUFA 5-year financial plan, and the Agency's progress in implementing modernized time reporting and the capacity planning function.

Enhance Financial Predictability, Stability, and Efficiency

Opportunity:

The current fee structure, target revenue allocations, and fee adjustment methodology creates unpredictability in FDA funding levels and sponsor invoices; introduces inefficiency for FDA and industry in fee administration/payment; and hinders FDA's ability to engage in long-term financial planning.

Proposed Approach:

- Modifications to the user fee structure and target revenue allocation:
  - Shift greater portion of target revenue allocation to predictable fee paying types.
    - Modify target revenue allocation from applications from 33% to 20%
    - Modify target revenue allocation for PDUFA Program Fee ("prescription drug fee" in PDUFA V) to 80%
  - Discontinue establishment fee.
  - Discontinue supplement fee.
  - Modify Program fee billing date to avoid multiple billing cycles.
  - Add a limitation of no more than 5 Program fees for products identified in each distinct approved application.
  - Discontinue the Fees-Exceed-the Costs waiver.

Enhance Financial Predictability, Stability, and Efficiency

Proposed Approach (continued):

- Modifications to PDUFA VI revenue amounts and fee adjustments.
  - Make feasible short-term improvements to the current workload adjuster (now called the “Capacity Planning Adjustment”) and implement a robust new methodology for adjusting fees based on workload following operationalization of a modernized time reporting and capacity planning function.
  - Replace the 5th-year offset and final year adjustment provisions with an annual “operating reserve adjustment.”