**Prescription Drug User Fee Act**
PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017.


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PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2013 THROUGH 2017

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PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FOR FISCAL YEARS 2013 THROUGH 2017

The performance goals and procedures of the FDA Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), as agreed to under the fifth authorization of the prescription drug user fee program, are summarized below.

Unless otherwise stated, goals apply to cohorts of each fiscal year (FY).

I. REVIEW PERFORMANCE GOALS

A. NDA/BLA Submissions and Resubmissions¹

1. Review and act on 90 percent of standard NME NDA and original BLA submissions within 10 months of the 60 day filing date.

2. Review and act on 90 percent of priority NME NDA and original BLA submissions within 6 months of the 60 day filing date.

3. Review and act on 90 percent of standard non-NME original NDA submissions within 10 months of receipt.

4. Review and act on 90 percent of priority non-NME original NDA submissions within 6 months of receipt.

5. Review and act on 90 percent of Class 1 resubmitted original applications within 2 months of receipt.

6. Review and act on 90 percent of Class 2 resubmitted original applications within 6 months of receipt.

B. Original Efficacy Supplements

1. Review and act on 90 percent of standard efficacy supplements within 10 months of receipt.

2. Review and act on 90 percent of priority efficacy supplement within 6 months of receipt.

C. Resubmitted Efficacy Supplements

1. Review and act on 90 percent of Class 1 resubmitted efficacy supplements within 2 months of receipt.

¹ Refer to Section II.A.4 for a description of the review program for NME NDAs and original BLAs.
2. Review and act on 90 percent of Class 2 resubmitted efficacy supplements within 6 months of receipt.

D. Original Manufacturing Supplements

1. Review and act on 90 percent of manufacturing supplements requiring prior approval within 4 months of receipt, and review and act on 90 percent of all other manufacturing supplements within 6 months of receipt.

E. These review goals are summarized in the following tables:

Original and Resubmitted Applications and Supplements:

<table>
<thead>
<tr>
<th>SUBMISSION COHORT</th>
<th>STANDARD</th>
<th>PRIORITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>NME NDAs and original BLAs</td>
<td>90% in 10 months of the receipt date</td>
<td>90% in 6 months of the receipt date</td>
</tr>
<tr>
<td>Non NME NDAs</td>
<td>90% in 10 months of the filing date</td>
<td>90% in 6 months of the receipt date</td>
</tr>
<tr>
<td>Class 1 Resubmissions</td>
<td>90% in 2 months of the receipt date</td>
<td>90% in 2 months of the receipt date</td>
</tr>
<tr>
<td>Class 2 Resubmissions</td>
<td>90% in 6 months of the receipt date</td>
<td>90% in 6 months of the receipt date</td>
</tr>
<tr>
<td>Original Efficacy Supplements</td>
<td>90% in 10 months of the receipt date</td>
<td>90% in 6 months of the receipt date</td>
</tr>
<tr>
<td>Class 1 Resubmitted Efficacy Supplements</td>
<td>90% in 2 months of the receipt date</td>
<td>90% in 2 months of the receipt date</td>
</tr>
<tr>
<td>Class 2 Resubmitted Efficacy Supplements</td>
<td>90% in 6 months of the receipt date</td>
<td>90% in 6 months of the receipt date</td>
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</tbody>
</table>

II. NEW MOLECULAR ENTITY NDA AND ORIGINAL BLA PERFORMANCE GOALS

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

To promote greater transparency and improve communication between the FDA review team and the applicant, FDA will establish a review model (hereafter referred to as “the Program”) that will apply to all New Molecular Entity New Drug Applications (NME NDAs) and original Biologics License Applications (BLAs), including applications that are resubmitted following a Refuse-to-File action,
received from October 1, 2012, through September 30, 2017. The goal of the Program is to improve the efficiency and effectiveness of the first cycle review process and decrease the number of review cycles necessary for approval, ensuring that patients have timely access to safe, effective, and high quality new drugs and biologics. The Program shall be evaluated by an independent contractor with expertise in assessing the quality and efficiency of biopharmaceutical development and regulatory review programs. The parameters of the Program are as follows:

1. **Pre-submission meeting:** The applicant is strongly encouraged to discuss the planned content of the application with the appropriate FDA review division at a pre-NDA/BLA meeting

   a) The pre-NDA/BLA meeting should be held sufficiently in advance of the planned submission of the application to allow for meaningful response to FDA feedback and should generally occur not less than 2 months prior to the planned submission of the application.

   b) At the pre-NDA/BLA meeting, the FDA and the applicant will agree on the content of a complete application for the proposed indication(s), including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. This meeting will be attended by the FDA review team including appropriate senior FDA staff. The agreement and discussions will be summarized at the conclusion of the meeting and reflected in the FDA meeting minutes.

   c) At the meeting, the FDA and the applicant may also reach agreement on submission of a limited number of application components not later than 30 calendar days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. Any such agreement that is reached on delayed submission of application components will be summarized at the conclusion of the meeting and reflected in the FDA meeting minutes.

      (1) Examples of application components that may be appropriate for delayed submission include updated stability data (e.g., 15-month data to update 12-month data submitted with the original submission) or the final audited report of a preclinical study (e.g., carcinogenicity) where the final draft report is submitted with the original application.

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2 The decision as to whether the application is included or excluded from the Program is distinct from FDA's determination as to whether the drug product contains a "new chemical entity," as defined under 21 CFR 314.108(a). Determinations regarding new chemical entity exclusivity are made at the time of approval of an application.
d) Major components of the application (e.g., the complete study report of a Phase 3 clinical trial or the full study report of required long-term safety data) are expected to be submitted with the original application and are not subject to agreement for late submission.

2. **Original application submission:** Applications are expected to be complete, as agreed between the FDA review team and the applicant at the pre-NDA/BLA meeting, at the time of original submission of the application. If the applicant does not have a pre-NDA/BLA meeting with FDA, and no agreement exists between FDA and the applicant on the contents of a complete application or delayed submission of certain components of the application, the applicant’s submission is expected to be complete at the time of original submission.

   a) All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

   b) Any components of the application that FDA agreed at the pre-submission meeting could be submitted after the original application are expected to be received not later than 30 calendar days after receipt of the original application.

   c) Incomplete applications, including applications with components that are not received within 30 calendar days after receipt of the original submission, will be subject to a Refuse-to-File decision.

      (1) Applications that are subject to a Refuse-to-File action, and are subsequently filed over protest, will not be subject to the procedures of the Program, but will instead be subject to the 6 and 10 month review performance goals for priority and standard applications, respectively, as described in Section I.

   d) Since applications are expected to be complete at the time of submission, unsolicited amendments are expected to be rare and not to contain major new information or analyses.

      (1) Review of unsolicited amendments, including those submitted in response to an FDA communication of deficiencies, will be handled in accordance with the guidance “Good Review Management Principles and Practices (GRMPs) for PDUFA Products.” This guidance includes the underlying principle that FDA will consider the most efficient path toward completion of a comprehensive review that addresses application deficiencies and leads toward a first cycle approval when possible.

3. **Day 74 Letter:** FDA will follow existing procedures and performance goals (see Section III) regarding identification and communication of filing review
issues in the “Day 74 letter.” For applications subject to the Program, the timeline for this communication will be within 74 calendar days from the date of FDA receipt of the original submission. The planned review timeline included in the Day 74 letter for applications in the Program will include the planned date for the internal mid-cycle review meeting. The letter will also include preliminary plans on whether to hold an Advisory Committee (AC) meeting to discuss the application.

4. **Review performance goals:** For NME NDA and original BLA submissions that are filed by FDA under the Program, the PDUFA review clock will begin at the conclusion of the 60 calendar day filing review period that begins on the date of FDA receipt of the original submission. The review performance goals for these applications are as follows:

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

   b) Review and act on 90 percent of priority NME NDA and original BLA submissions within 6 months of the 60 day filing date.

5. **Mid-Cycle communication:** The FDA Regulatory Project Manager (RPM), and other appropriate members of the FDA review team (e.g., Cross Discipline Team Leader (CDTL)), will call the applicant, generally within 2 weeks following the Agency’s internal mid-cycle review meeting, to provide the applicant with an update on the status of the review of their application. Scheduling of the internal mid-cycle review meeting will be handled in accordance with the GRMP guidance. The RPM will coordinate the specific date and time of the telephone call with the applicant

   a) The update should include any significant issues identified by the review team to date, any information requests, information regarding major safety concerns and preliminary review team thinking regarding risk management, proposed date(s) for the late-cycle meeting, updates regarding plans for the AC meeting (if an AC meeting is anticipated), and other projected milestones dates for the remainder of the review cycle.

6. **Discipline Review (DR) Letters:** The FDA review team will follow existing guidance on issuance of DR Letters.

   a) Since the application is expected to be complete at time of submission, FDA intends to complete primary and secondary discipline reviews of the application and issue DR letters in advance of the planned late-cycle meeting. In cases where a DR letter is not issued in advance of the planned late-cycle meeting, substantive issues identified to date from that discipline will be communicated in the brief memorandum described in 7(b)(1).
7. **Late-Cycle meeting:** For all applications included in the review Program, a meeting will be held between the FDA review team and the applicant to discuss the status of the review of the application late in the review cycle.

   a) FDA representatives at the late-cycle meeting are expected to include the signatory authority for the application, review team members from appropriate disciplines, and appropriate team leaders and/or supervisors from disciplines for which substantive issues have been identified in the review to date.

   b) For applications that will be discussed at an Advisory Committee (AC) meeting, the late-cycle meeting will occur not less than 12 calendar days before the date of the AC meeting. FDA intends to convene AC meetings no later than 3 months (standard review) or no later than 2 months (priority review) prior to the PDUFA goal date.

      (1) The Agency briefing package for the late-cycle meeting will consist of the Agency’s background package for the AC meeting, which will be sent to the applicant not less than 20 calendar days before the AC meeting, any discipline review letters issued to date, current assessment of the need for REMS or other risk management actions, and a brief memorandum from the review team outlining substantive application issues including potential questions and/or points for discussion for the AC meeting. FDA intends to provide final questions for the AC to the sponsor and the AC 2 calendar days in advance of the AC meeting.

   c) For applications that will not be discussed at an AC meeting, the late-cycle meeting will generally occur not later than 3 months (standard review) or two months (priority review) prior to the PDUFA goal date.

      (1) The Agency background package for the late-cycle meeting, which will be sent to the applicant not less than 12 calendar days before the meeting, will consist of any discipline review letters issued to date, current assessment of the need for REMS or other risk management actions, and a brief memorandum from the review team outlining substantive application issues.

   d) Potential topics for discussion at the late-cycle meeting include major deficiencies identified to date; issues to be discussed at the AC meeting (if planned); current assessment of the need for REMS or other risk management actions; information requests from the review team to the applicant; and additional data or analyses the applicant may wish to submit.

      (1) With regard to submission of additional data or analyses, the FDA review team and the applicant will discuss whether such data
will be reviewed by the Agency in the current review cycle and, if so, whether the submission will be considered a major amendment and trigger an extension of the PDUFA goal date.

8. **Inspections:** FDA’s goal is to complete all GCP, GLP, and GMP inspections for applications in the Program within 6 months of the date of original receipt for priority applications and within 10 months of the date of original receipt for standard applications. This will allow 2 months at the end of the review cycle to attempt to address any deficiencies identified by the inspections.

9. **Quality System:** As part of a quality system approach to managing review in the Program, FDA will implement a tracking system that will document review team performance of the key milestones for each of the applications reviewed under the Program.

   a) These milestones include: conduct of pre-NDA/BLA meeting and agreement on content of complete application; submission of any components of the application within 30 calendar days of original application submission (as per pre-NDA/BLA meeting agreement); issuance of the 74-day letter; completion of mid-cycle communication with sponsor; completion of primary and secondary reviews; DR letters issued; exchange of late cycle meeting package; and conduct of late-cycle meeting.

   b) The process tracking information will support review management, and inform the subsequent analysis to be conducted by an independent third party (see below). The performance information generated by the tracking system will also be summarized and reported in the PDUFA annual performance report.

**B. Assessment of the Program**

The Program described in Section IIA shall be evaluated by an independent contractor with expertise in assessing the quality and efficiency of biopharmaceutical development and regulatory review programs. The statement of work for this effort will be published for public comment prior to beginning the assessment. The assessments will occur continuously throughout the course of the Program. Metrics for the assessments will include adherence by the applicant and FDA to the current GRMP guidance, submission of a complete application at the time of original submission, number of unsolicited amendments submitted by the applicant, timing and adequacy of Day 74 letters, mid-cycle communications, provision of late-cycle meeting memorandum outlining potential issues and questions for AC meeting consideration and discipline review letters; specific milestones of the Program as described in Section IIA; time to approval; percentage of applications approved on the first review cycle; and the percentage of application reviews extended due to major amendments. Following issuance of an FDA regulatory action at the completion of the first review cycle, the independent contractor will assess the
completeness and thoroughness of the submitted application, Day 74 letter, mid-cycle communication, discipline review letters and late-cycle meeting. This assessment will include interviews of the sponsor and members of the review team, as appropriate.

1. **Interim Assessment**: An interim assessment of the Program will be published by March 31, 2015, for public comment. By June 30, 2015, FDA will hold a public meeting during which public stakeholders may present their views on the success of the Program to date including: improving the efficiency and effectiveness of the first cycle review process; decreasing the number of review cycles ultimately necessary for new drugs and biologics that are approved; and helping to ensure that patients have timely access to safe, effective, and high quality new drugs and biologics. During the public meeting, FDA will discuss the findings of the interim assessment, including anonymized aggregated feedback from sponsors and FDA review teams resulting from independent contractor interviews. FDA will also address any issues identified to date including actions proposed to improve likelihood of success for the program.

2. **Final Assessment**: A final assessment of the Program will be published by December 31, 2016, for public comment. FDA will hold a public meeting by no later than March 30, 2017, during which public stakeholders may present their views on the success of the Program, including improving the efficiency and effectiveness of the first cycle review process and decreasing the number of review cycles ultimately necessary for new drugs and biologics that are approved. During the public meeting, FDA will discuss the findings of the final assessment, including anonymized aggregated feedback from sponsors and FDA review teams resulting from independent contractor interviews and discuss any issues identified and plans for addressing these issues.

### III. FIRST CYCLE REVIEW PERFORMANCE

#### A. Notification of Issues Identified during the Filing Review

1. **Performance Goal**: For original NDA/BLA applications and efficacy supplements, FDA will report substantive review issues identified during the initial filing review to the applicant by letter, teleconference, facsimile, secure e-mail, or other expedient means.

2. The timeline for such communication will be within 74 calendar days from the date of FDA receipt of the original submission.

3. If no substantive review issues were identified during the filing review, FDA will so notify the applicant.

4. FDA's filing review represents a preliminary review of the application and is not indicative of deficiencies that may be identified later in the review cycle.
5. FDA will notify the applicant of substantive review issues prior to the goal date for 90% of applications.

B. Notification of Planned Review Timelines

1. Performance Goal: For original NDA/BLA applications and efficacy supplements, FDA will inform the applicant of the planned timeline for review of the application. The information conveyed will include a target date for communication of feedback from the review division to the applicant regarding proposed labeling, postmarketing requirements, and postmarketing commitments the Agency will be requesting.

2. The planned review timeline will be included with the notification of issues identified during the filing review, within 74 calendar days from the date of FDA receipt of the original submission.

3. The planned review timelines will be consistent with the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products (GRMPs), taking into consideration the specific circumstances surrounding the individual application.

4. The planned review timeline will be based on the application as submitted.

5. FDA will inform the applicant of the planned review timeline for 90% of all applications and efficacy supplements.

6. In the event FDA determines that significant deficiencies in the application preclude discussion of labeling, postmarketing requirements, or postmarketing commitments by the target date identified in the planned review timeline (e.g., failure to demonstrate efficacy, significant safety concern(s), need for a new study(ies) or extensive re-analyses of existing data before approval), FDA will communicate this determination to the applicant in accordance with GRMPs and no later than the target date. In such cases the planned review timeline will be considered to have been met. Communication of FDA’s determination may occur by letter, teleconference, facsimile, secure e-mail, or other expedient means.

7. To help expedite the development of drug and biologic products, communication of the deficiencies identified in the application will generally occur through issuance of a DR letter(s) in advance of the planned target date for initiation of discussions regarding labeling, postmarketing requirements, and postmarketing commitments the Agency may request.

8. If the applicant submits a major amendment(s) (refer to Section XVI.B for additional information on major amendments) and the review division chooses to review such amendment(s) during that review cycle, the planned review timeline initially communicated will generally no longer be applicable. Consistent with the underlying principles articulated in the GRMP guidance,
FDA’s decision to extend the review clock should, except in rare circumstances, be limited to occasions where review of the new information could address outstanding deficiencies in the application and lead to approval in the current review cycle.

- If the review division determines that the major amendment will result in an extension of the PDUFA review clock, the review division will communicate to the applicant at the time of the clock extension a new planned review timeline, including a new review timeline for communication of feedback on proposed labeling, postmarketing requirements, and any postmarketing commitments the Agency may request.

- In the rare case where the review division determines that the major amendment will not result in an extension of the PDUFA review clock, the review division may choose to retain the previously communicated planned review timeline or may communicate a new planned review timeline to the applicant.

- The division will notify the applicant promptly of its decision regarding review of the major amendment(s) and whether the planned review timeline is still applicable.

- For original NME NDA and original BLA applications, the new planned review timeline will include a new planned date for the internal mid-cycle review meeting if appropriate depending on when during the course of review the major amendment(s) is accepted for review.

C. Report on Review Timeline Performance

1. FDA will report its performance in meeting the goals for inclusion of a planned review timeline with the notification of issues identified during the filing review in the annual PDUFA performance report.

2. FDA will report its performance in meeting the planned review timeline for communication of labeling comments, postmarketing requirements, and postmarketing commitment requests in the annual PDUFA performance report. The report will include the percentage of applications for which the planned target dates for communication of labeling comments, postmarketing requirements, and postmarketing commitment requests were met. The report will also note how often the planned review timeline was met based on communication of labeling comments, postmarketing requirements, and postmarketing commitment requests by the target date, and how often such communication did not occur due to FDA’s determination that significant deficiencies in the application precluded communication of labeling comments, postmarketing requirements, and postmarketing commitment...
requests at the time initially projected. Communication of labeling comments, postmarketing requirements, and postmarketing commitment requests, or communication of FDA’s determination that significant deficiencies preclude initiation of such discussions that occurs within 7 calendar days of the target date stated in the planned review timeline will be considered to have met the target date. FDA will also report the number of times that the review timelines were inapplicable due to the Agency’s decision to review an unsolicited major amendment or a solicited major amendment that did not result in an extension of the review clock (unless the review division chose to retain the previously communicated planned review timeline).

IV. REVIEW OF PROPRIETARY NAMES TO REDUCE MEDICATION ERRORS

To enhance patient safety, FDA will utilize user fees to implement various measures to reduce medication errors related to look-alike and sound-alike proprietary names and such factors as unclear label abbreviations, acronyms, dose designations, and error prone label and packaging design.

A. Review Performance Goals – Drug/Biological Product Proprietary Names

1. Proprietary names submitted during IND phase (as early as end-of-phase 2)
   a) Review 90% of proprietary name submissions filed within 180 days of receipt. Notify sponsor of tentative acceptance or non-acceptance.
   b) If the proprietary name is found to be unacceptable, the sponsor can request reconsideration by submitting a written rebuttal with supporting data or request a meeting within 60 days to discuss the initial decision (meeting package required).
   c) If the proprietary name is found to be unacceptable, the above review performance goals also would apply to the written request for reconsideration with supporting data or the submission of a new proprietary name.
   d) A complete submission is required to begin the review clock.

2. Proprietary names submitted with NDA/BLA
   a) Review 90% of NDA/BLA proprietary name submissions filed within 90 days of receipt. Notify sponsor of tentative acceptance/non-acceptance.
   b) A supplemental review will be done meeting the above review performance goals if the proprietary name has been submitted previously (IND phase after end-of-phase 2) and has received tentative acceptance.
c) If the proprietary name is found to be unacceptable, the sponsor can request reconsideration by submitting a written rebuttal with supporting data or request a meeting within 60 days to discuss the initial decision (meeting package required).

d) If the proprietary name is found to be unacceptable, the above review performance goals apply to the written request for reconsideration with supporting data or the submission of a new proprietary name.

e) A complete submission is required to begin the review clock.

V. MAJOR DISPUTE RESOLUTION

A. Procedure: For procedural or scientific matters involving the review of human drug applications and supplements (as defined in PDUFA) that cannot be resolved at the signatory authority level (including a request for reconsideration by the signatory authority after reviewing any materials that are planned to be forwarded with an appeal to the next level), the response to appeals of decisions will occur within 30 calendar days of the Center’s receipt of the written appeal.

B. Performance goal: 90% of such answers are provided within 30 calendar days of the Center’s receipt of the written appeal.

C. Conditions:

1. Sponsors should first try to resolve the procedural or scientific issue at the signatory authority level. If it cannot be resolved at that level, it should be appealed to the next higher organizational level (with a copy to the signatory authority) and then, if necessary, to the next higher organizational level.

2. Responses should be either verbal (followed by a written confirmation within 14 calendar days of the verbal notification) or written and should ordinarily be to either grant or deny the appeal.

3. If the decision is to deny the appeal, the response should include reasons for the denial and any actions the sponsor might take to persuade the Agency to reverse its decision.

4. In some cases, further data or further input from others might be needed to reach a decision on the appeal. In these cases, the “response” should be the plan for obtaining that information (e.g., requesting further information from the sponsor, scheduling a meeting with the sponsor, scheduling the issue for discussion at the next scheduled available advisory committee).

5. In these cases, once the required information is received by the Agency (including any advice from an advisory committee), the person to whom the appeal was made, again has 30 calendar days from the receipt of the required information in which to either deny or grant the appeal.
6. Again, if the decision is to deny the appeal, the response should include the reasons for the denial and any actions the sponsor might take to persuade the Agency to reverse its decision.

7. N.B. If the Agency decides to present the issue to an advisory committee and there are not 30 days before the next scheduled advisory committee, the issue will be presented at the following scheduled committee meeting to allow conformance with advisory committee administrative procedures.

VI. CLINICAL HOLDS

A. Procedure: The Center should respond to a sponsor’s complete response to a clinical hold within 30 days of the Agency’s receipt of the submission of such sponsor response.

B. Performance goal: 90% of such responses are provided within 30 calendar days of the Agency’s receipt of the sponsor’s response.

VII. SPECIAL PROTOCOL QUESTION ASSESSMENT AND AGREEMENT

A. Procedure: Upon specific request by a sponsor (including specific questions that the sponsor desires to be answered), the Agency will evaluate certain protocols and issues to assess whether the design is adequate to meet scientific and regulatory requirements identified by the sponsor.

1. The sponsor should submit a limited number of specific questions about the protocol design and scientific and regulatory requirements for which the sponsor seeks agreement (e.g., is the dose range in the carcinogenicity study adequate, considering the intended clinical dosage; are the clinical endpoints adequate to support a specific efficacy claim).

2. Within 45 days of Agency receipt of the protocol and specific questions, the Agency will provide a written response to the sponsor that includes a succinct assessment of the protocol and answers to the questions posed by the sponsor. If the Agency does not agree that the protocol design, execution plans, and data analyses are adequate to achieve the goals of the sponsor, the reasons for the disagreement will be explained in the response.

3. Protocols that qualify for this program include: carcinogenicity protocols, stability protocols, and Phase 3 protocols for clinical trials that will form the primary basis of an efficacy claim. For such Phase 3 protocols to qualify for this comprehensive protocol assessment, the sponsor must have had an end of Phase 2/pre-Phase 3 meeting with the review division so that the division is aware of the developmental context in which the protocol is being reviewed and the questions being answered.

4. N.B. For products that will be using Subpart E or Subpart H development schemes, the Phase 3 protocols mentioned in this paragraph should be construed to mean those protocols for trials that will form the primary basis of
an efficacy claim no matter what phase of drug development in which they happen to be conducted.

5. If a protocol is reviewed under the process outlined above and agreement with the Agency is reached on design, execution, and analyses and if the results of the trial conducted under the protocol substantiate the hypothesis of the protocol, the Agency agrees that the data from the protocol can be used as part of the primary basis for approval of the product. The fundamental agreement here is that having agreed to the design, execution, and analyses proposed in protocols reviewed under this process, the Agency will not later alter its perspective on the issues of design, execution, or analyses unless public health concerns unrecognized at the time of protocol assessment under this process are evident.

B. Performance goal: 90% of special protocols assessments and agreement requests completed and returned to sponsor within timeframes.

C. Reporting: The Agency will track and report the number of original special protocol assessments and resubmissions per original special protocol assessment.

VIII. MEETING MANAGEMENT GOALS

A. Responses to Meeting Requests

1. Procedure: Within 14 calendar days of the Agency’s receipt of a request from industry for a formal Type A meeting, or within 21 calendar days of the Agency’s receipt of a request from industry for a formal Type B or Type C meeting (i.e., a scheduled face-to-face, teleconference, videoconference, or written response), CBER and CDER should notify the requester in writing (letter or fax) of the date, time, and place for the meeting, as well as expected Center participants. In the case of pre-IND and Type C meeting requests, the sponsor may request a written response to its questions rather than a face-to-face meeting, videoconference or teleconference. In some cases, while the sponsor may request a face-to-face pre-IND or Type C meeting, the Agency may determine that a written response to the sponsor’s questions would be the most appropriate means for responding to the meeting request. When it is determined that the meeting request can be appropriately addressed through a written response to questions, FDA shall notify the requester of the date it intends to send the response.

2. Performance Goal: FDA will provide this notification within 14 days for 90% of Type A meeting requests and within 21 days for 90% of Type B and Type C meeting requests.

B. Scheduling Meetings

1. Procedure: The meeting date should reflect the next available date on which all applicable Center personnel are available to attend, consistent with the
component’s other business; however, the meeting should be scheduled consistent with the type of meeting requested. If the requested date for any of these types of meetings is greater than 30, 60, or 75 calendar days (as appropriate) from the date the request is received by the Agency, the meeting date should be within 14 calendar days of the requested date.

a) Type A Meetings should occur within 30 calendar days of the Agency receipt of the meeting request.

b) Type B Meetings should occur within 60 calendar days of the Agency receipt of the meeting request. In the case of a written response for a pre-IND meeting, the response should be transmitted by FDA within 60 calendar days of the Agency receipt of the meeting request.

c) Type C Meetings should occur within 75 calendar days of the Agency receipt of the meeting request. In the case of a written response, the response should be transmitted by FDA within 75 calendar days of the Agency receipt of the meeting request.

2. **Performance goal:** 90% of meetings are held within the timeframe, and 90% of written responses are sent within the timeframe.

C. Meeting Minutes

1. **Procedure:** The Agency will prepare minutes which will be available to the sponsor 30 calendar days after the meeting. The minutes will clearly outline the important agreements, disagreements, issues for further discussion, and action items from the meeting in bulleted form and need not be in great detail. Meeting minutes are not required if the Agency transmits a written response for pre-IND or Type C meetings.

2. **Performance goal:** 90% of minutes are issued within 30 calendar days of date of meeting.

D. Conditions

For a meeting to qualify for these performance goals:

1. A written request (letter or fax) should be submitted to the review division; and

2. The letter should provide:

   a) A brief statement of the purpose of the meeting, and in the case of pre-IND and Type C meetings, the sponsor’s proposal for either a face-to-face meeting or a written response from the Agency;

   b) A listing of the specific objectives/outcomes the requester expects from the meeting;
c) A proposed agenda, including estimated times needed for each agenda item;

d) A listing of planned external attendees;

e) A listing of requested participants/disciplines representative(s) from the Center; and

f) The approximate time that supporting documentation (i.e., the “backgrounder”) for the meeting will be sent to the Center (i.e., “x” weeks prior to the meeting), but should be received by the Center at the time of the meeting request for Type A meetings and at least 1 month in advance of the scheduled meeting for Type B and Type C meetings (including those for which a written response will be provided)

3. The Agency concurs that the meeting will serve a useful purpose (i.e., it is not premature or clearly unnecessary). However, requests for a “Type B” meeting will be honored except in the most unusual circumstances.

4. In general, meetings regarding REMS or postmarketing requirements that occur outside the context of the review of a marketing application shall be classified as Type B meetings.

5. In general, a post-action meeting requested by the sponsor within three months after an FDA regulatory action other than an approval (i.e., issuance of a complete response letter) shall be classified as a Type A meeting.

6. FDA shall publish revised draft guidance on formal meetings between FDA and sponsors no later than the end of FY 2013.

Sponsors are encouraged to consult available FDA guidance to obtain further information on recommended meeting procedures.

IX. ENHANCING REGULATORY SCIENCE AND EXPEDITING DRUG DEVELOPMENT

To enhance communications between FDA and sponsors during drug development and to meet the challenges of emerging science in the areas of clinical trial endpoint assessment tools, biomarkers and pharmacogenomics, meta-analysis, and development of drugs for rare diseases, FDA will conduct the following activities:

A. Promoting Innovation Through Enhanced Communication Between FDA and Sponsors During Drug Development

1. 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, which can enhance public health by making new safe and effective drugs available to the American public in a timely manner.
2. By the end of FY 2013, FDA will develop a dedicated drug development communication and training staff within the Office of New Drugs in CDER and augment the manufacturers assistance staff in CBER, focused on enhancing communication between FDA and sponsors during drug development.

3. Within CDER, the drug development communication and training staff will include (1) a dedicated liaison staff to facilitate general and, in some cases, specific interactions with sponsors and (2) a training staff for CDER staff training and for communication of best practices to the sponsor community.

4. The liaison staff will be composed of individuals who are experienced and knowledgeable about the drug review process (and in some cases may be on detail from the review divisions), interact regularly with the staff in review divisions, and are skilled in facilitating communications between applicants and FDA staff.

5. The liaison staff will conduct a range of tasks associated with enhancing communication between the review team and sponsors including identification and dissemination of best practices for enhanced communication, and development of training programs for review staff. In addition, they will work in collaboration with sponsor stakeholders to develop training for sponsors and receive feedback on FDA’s programs regarding best practices for communication during drug development (e.g., participation in workshops and other meetings to communicate CDER’s policy and practice to the sponsor community and to receive feedback on recommended improvements).

6. The liaison staff will serve as a point of contact for sponsors who have general questions about drug development or who need clarification on which review division to contact with their questions. The staff will also serve as a secondary point of communication within CDER for sponsors who are encountering problems in communication with the review team for their IND (e.g., in instances when they have not received a response from the review team to a simple or clarifying question or referral to the formal meeting process within 30 days of the sponsor’s initial request). In such cases the liaison staff will assist in evaluating the issues and working with the review team and the sponsor to facilitate resolution of the problem.

7. By the end of FY 2014, the OND drug development and communication staff will provide training to all CDER staff involved in review of INDs. The training will include:

a) CDER’s philosophy that timely interactive communication with sponsors during drug development is a core activity to help achieve our mission to facilitate the conduct of efficient and effective drug development programs, which can enhance public health by making new safe and effective drugs available to the American public in a timely manner.

b) Best practices for triage of sponsor requests for advice from the review team and timely communication of responses to simple and clarifying
questions or referral of more complex questions to the formal meeting process.

c) Best practices for communication between the review team and the sponsor including establishing clear expectations and agreement on appropriate mechanisms (e.g., when teleconferencing or secure email may be the most appropriate means of communication) and frequency of such communications.

d) The role of the OND liaison staff in facilitating overall enhanced drug development communication between CDER and the drug development sponsor community and the staff’s role in facilitating resolution of individual communication requests that have not been handled successfully in a timely manner by the review team, which is the primary interface with the sponsor regarding the drug under development.

8. By the end of the second quarter of FY 2015, FDA will publish draft guidance for review staff and industry describing best practices for communication between FDA and IND sponsors during drug development. The guidance will describe FDA’s philosophy regarding timely interactive communication with sponsors as a core activity, the scope of appropriate interactions between the review team and the sponsor, outline the types of advice that are appropriate for sponsors to seek from FDA in pursuing their drug development program, describe the general expectations for the timing of FDA response to sponsor inquiries of simple and clarifying questions or referral of more complex questions to the formal meeting process, and describe best practices and communication methods (including the value of person-to-person scientific dialogue) to facilitate interactions between the FDA review team and the sponsor during drug development. FDA will publish final guidance within 18 months of the close of the comment period for the draft guidance.

B. Advancing the Science of Meta-Analysis Methodologies

1. Develop a dedicated review team with appropriate expertise to evaluate different scientific methods and to explore the practical application of scientific approaches and best practices, including methodological limitations, for the conduct of meta-analyses in the context of FDA’s regulatory review process.

2. By the end of FY 2013, hold a public meeting engaging stakeholders in discussing current and emerging scientific approaches and methods for the conduct of meta-analyses, and to facilitate stakeholder feedback and input regarding the use of meta-analyses in the FDA’s regulatory review process.

3. Considering feedback and input received through the public meeting, publish a draft guidance document for comment describing FDA’s intended approach to the use of meta-analyses in the FDA’s regulatory review process by the end of FY 2015. This guidance will promote a better understanding and more consistency among Agency, industry, and other stakeholders regarding meta-analyses and their role in regulatory decision-making.
4. Complete the final guidance describing FDA’s intended approach to the use of meta-analyses in the FDA’s regulatory review process (or revised draft guidance, if appropriate) within 1.5 years of the close of the public comment period.

C. Advancing the Use of Biomarkers and Pharmacogenomics

1. Develop staff capacity to review submissions that contain complex issues involving pharmacogenomics and biomarkers. This additional staff capacity will be integrated into the clinical review divisions and the clinical pharmacology and statistical review disciplines to ensure greater understanding of biomarker use in application review and efficient incorporation of qualified biomarkers in the review process.

2. Provide training for FDA staff on approaches to conducting a pharmacogenomics review of a new product application. This training will focus on the following: facilitation of a greater understanding of the challenges that arise when using pharmacogenomic markers and other biomarkers in a development program (including programs involving companion diagnostics), development of approaches to address these challenges, and promotion of consistency in regulatory review through an understanding of best practices in assessment of applications that use biomarkers in the drug development program.

3. By the end of FY 2013, hold a public meeting to discuss the current status of biomarkers and pharmacogenomics and potential strategies to facilitate scientific exchanges in regulatory and non-regulatory contexts.

D. Advancing Development of Patient-Reported Outcomes (PROs) and Other Endpoint Assessment Tools

1. Develop clinical and statistical staff capacity to more efficiently and effectively respond to submissions that involve PROs and other outcomes assessment tools. These staff will advance the development of these tools by providing IND and qualification consultations and through promoting best practices for review and qualification of outcomes assessment tools. The additional capacity includes staff who will focus on review and qualification of endpoint assessment tools, including IND consultations with sponsors, as well as staff who will be integrated into the review divisions to facilitate evaluation of these tools and improve familiarity and understanding of assessment tools among review staff. These activities will allow for greater understanding of challenges that arise during development of outcomes assessment tools, potential strategies to overcome these challenges, and greater consistency in FDA’s approach to review, qualification, and usage of these tools as part of the drug development process.

2. By the end of FY 2014, hold a public meeting to discuss FDA’s qualification standards for drug development tools, new measurement theory, and implications for multi-national trials.
E. Advancing Development of Drugs for Rare Diseases

1. By the end of FY 2013, FDA will complete a staffing and implementation plan for the CDER Rare Disease Program within the Office of New Drugs and a CBER Rare Disease liaison within the Office of Center Director.

2. FDA will increase by five the staff of the CDER Rare Disease Program and establish and fill the CBER Rare Disease liaison position.

3. On an ongoing basis, the staff in the Rare Disease Programs of the two Centers will develop and disseminate guidance and policy related to advancing and facilitating the development of drugs and biologics for rare diseases, including improving understanding among FDA reviewers of approaches to studying such drugs; considering non-traditional clinical development programs, study design, endpoints, and statistical analysis; recognizing particular challenges with post-market studies; and encouraging flexibility and scientific judgment, as appropriate, on the part of reviewers when evaluating investigational studies and marketing applications for drugs for rare diseases. Rare Disease Program staff will also engage in increased outreach to industry regarding development of such drugs and to patient representatives and organizations.

4. By mid-FY 2014, FDA, through the Rare Disease Program, will conduct a public meeting to discuss complex issues in clinical trials for studying drugs for rare diseases, including such questions as endpoint selection, use of surrogate endpoints/Accelerated Approval, and clinical significance of primary endpoints; reasonable safety exposures; assessment of dose selection; and development of patient-reported outcome instruments. Participants in the discussion will include FDA staff, academic and clinical experts, and industry experts. A summary from the meeting will be made available publicly through the FDA website.

5. By the end of FY 2015, FDA will develop and implement staff training related to development, review, and approval of drugs for rare diseases. The training will be provided to all CDER and CBER review staff, and will be part of the reviewer training core curriculum. Among the key purposes of this training are to familiarize review staff with the challenges associated with rare disease applications and strategies to address these challenges; to promote best practices for review and regulation of rare disease applications; and to encourage flexibility and scientific judgment among reviewers in the review and regulation of rare disease applications. The training will also emphasize the role of the Rare Disease Program staff as members of the review team to help ensure consistency of scientific and regulatory approaches across applications and review teams.

6. By the end of FY 2016, FDA, through the Rare Disease Program, will develop an evaluation tool to evaluate the success of the activities of the Rare Disease
Program, including the reviewer training. Among potential measures of success are the development of a system to track rare disease applications from IND submission through the post-marketing period, increased number of reviewers receiving rare disease-specific training, increased number of activities contributing to regulatory and biomedical science for rare disease drug development, and meeting of PDUFA goals for rare disease applications.

X. ENHANCING BENEFIT-RISK ASSESSMENT IN REGULATORY DECISION-MAKING

A. FDA will develop a five-year plan to further develop and implement a structured benefit/risk assessment in the new drug approval process. FDA will publish its draft plan for public comment by the end of the first quarter of FY 2013. FDA will begin execution of the plan to implement the benefit-risk framework across review divisions in the pre- and post-market human drug review process by the end of the fourth quarter of FY 2013, and the Agency will update the plan as needed and post all updates on the FDA website. The plan will include:

1. A description of FDA’s intended approach to build on the Agency’s current efforts to integrate a structured benefit/risk framework throughout the lifecycle of human drug development.

2. A plan to conduct two public workshops on benefit-risk considerations from the regulator’s perspective that will begin by the first quarter of FY 2014. The first workshop will be primarily informational by focusing discussion on the various frameworks and methods available and their application to regulatory decision-making. The second workshop will focus on the results and lessons learned in implementing frameworks at regulatory agencies in the pre- and post-market drug review process.

3. An evaluation plan to ascertain the impact of the benefit-risk framework in the human drug review process. The evaluation will consider the utility of the framework in facilitating decision-making and review team discussions across disciplines, risk management plan decision-making, training of new review staff, and communicating regulatory decisions. In particular, the evaluation will consider the degree to which the framework supports or facilitates balanced consideration of benefits and risks, a more consistent and systematic approach to discussion and decision-making, and communication of benefits and risks.

B. As appropriate, FDA will revise the CDER Clinical Review Template, Office and Division Director Summary Memo Templates, and corresponding Manuals of Policies and Procedures (MaPP) [and equivalent documents in CBER] to incorporate a structured benefit/risk assessment into the human drug review process on a timeframe outlined in the five-year plan described in (A).
C. Over the period of PDUFA V, FDA will initiate a public process to nominate a set of disease areas that could benefit from a more systematic and expansive approach to obtaining the patient perspective on disease severity or unmet medical need. FDA will convene 4 meetings per year (CDER will host 17 meetings and CBER will host 3 meetings throughout PDUFA V) with each meeting focused on a different disease area. These meetings will include participation of FDA review divisions, the relevant patient advocacy community, and other interested stakeholders. After each meeting, FDA will publish the meeting proceedings and a summary analysis of the input received by FDA that is relevant to FDA’s consideration of disease severity and unmet medical need. This knowledge will be used to more fully develop an understanding of the disease severity and an assessment of the current state of the treatment armamentarium which are both critical components of FDA’s current benefit-risk framework in regulatory decision-making and communication. After the first two meetings, FDA will develop a proposal for how FDA will incorporate these perspectives into the Agency’s decision-making.

In addition, FDA will increase its utilization of FDA’s Patient Representatives as Special Government Employee consultants to CDER and CBER to provide patients’ views early in the medical product development process and ensure those perspectives are considered in regulatory discussions.

D. FDA will train review and management staff on the revised templates and MaPPs described in (B) and fully integrate structured benefit/risk assessment into the regulatory review process by a date specified in the five-year plan.

XI. ENHANCEMENT AND MODERNIZATION OF THE FDA DRUG SAFETY SYSTEM

FDA will continue to use user fees to enhance and modernize the current U.S. drug safety system, including adoption of new scientific approaches, improving the utility of existing tools for the detection, evaluation, prevention, and mitigation of adverse events, and enhancing communication and coordination between post-market and pre-market review staff. Enhancements to the drug safety system will improve public health by increasing patient protection while continuing to enable access to needed medical products. User fees will provide support for 1) enhancing risk evaluation and mitigation strategies (REMS) by measuring their effectiveness and evaluating with stakeholder input appropriate ways to better integrate them into the existing and evolving healthcare system, and 2) continued development and implementation of the Sentinel System.

A. Measure the Effectiveness of REMS and Standardize and Better Integrate REMS into the Healthcare System

FDA will use user fee funds to continue to develop techniques to standardize REMS and with stakeholder input seek to integrate them into the existing and evolving (e.g., increasingly electronic) healthcare system.
1. By the end of FY 2013, FDA will develop and issue guidance on how to apply the statutory criteria to determine whether a REMS is necessary to ensure that the benefits of a drug outweigh the risks.

2. By the end of FY 2013, FDA will hold one or more public meetings to include the pharmaceutical industry, other government healthcare providers, patient groups, and partners from other sectors of the healthcare delivery system to explore strategies to standardize REMS, where appropriate, with the goal of reducing the burden of implementing REMS on practitioners, patients, and others in various healthcare settings. To move towards increased integration of REMS into the healthcare delivery system, FDA will issue a report of its findings by the first quarter of FY 2014 that will identify at least one priority project in each of the following areas including a workplan for project completion: pharmacy systems, prescriber education, providing benefit/risk information to patients, and practice settings.

3. By the end of FY 2013, FDA will initiate one or more public workshops on methodologies for assessing whether REMS are mitigating the risks they purport to mitigate and for assessing the effectiveness and impact of REMS, including methods for assessing the effect on patient access, individual practitioners, and the overall burden on the healthcare delivery system. FDA will issue guidance by the end of FY 2014 on methodologies for assessing REMS. This guidance should specifically address methodologies for determining whether a specific REMS with elements to assure safe use (ETASU) is: (i) commensurate with the specific serious risk listed in the labeling of the drug and (ii) considering the observed risk, not unduly burdensome on patient access to the drug.

B. Sentinel as a Tool for Evaluating Drug Safety Issues That May Require Regulatory Action

FDA will use user fee funds to conduct a series of activities to determine the feasibility of using Sentinel to evaluate drug safety issues that may require regulatory action, e.g., labeling changes, PMRs, or PMCs. The activities will be selected and designed to focus on issues that affect classes of drugs or multiple products.

1. By the end of FY 2013, FDA will hold or support public meetings engaging stakeholders to discuss current and emerging Sentinel projects and facilitate stakeholder feedback and input regarding Sentinel projects that would be appropriate to meet the goals stated above.

2. Informed by the feedback and input received through the public meeting, in FY 2013 through FY 2017, FDA will fund 4-6 activities, which will include multiple product or class-specific studies or methodology development. These activities will be specifically designed to further evaluate safety signals that, in previous cases, have served as the basis for regulatory action(s) or designed more broadly to help determine the utility and validity of the
Sentinel System to evaluate other types of signals in population-based databases. The following are examples of potential activities:

a) Expanding the active surveillance mechanisms begun for the H1N1 pandemic to substitute for the information gathered in large ad hoc, manufacturer-conducted studies

b) Evaluating risk for class-wide adverse events (e.g., cardiovascular events, suicidality)

3. By the end of FY 2015, FDA will conduct (or fund by contract) an interim assessment to evaluate the strengths, limitations and the appropriate use of Sentinel for informing regulatory actions (e.g., labeling changes, PMRs and PMCs) to manage safety issues.

4. By the end of FY 2017, FDA will conduct (or fund by contract) an assessment to evaluate the strengths, limitations, and the appropriate use of Sentinel for informing regulatory actions (e.g., labeling changes, PMRs and PMCs) to manage safety issues.

C. Conduct and support activities designed to modernize the process of pharmacovigilance

1. Continued use of expanded database resources: A critical part of the transformation of the drug safety program is maximizing the usefulness of tools used for adverse event signal detection and risk assessment. Use of data other than passive spontaneous reports, including population-based epidemiological data and other types of observational data resources will continue to enhance FDA’s capability to conduct targeted post-marketing surveillance, evaluate class effects of drugs, and potentially conduct signal detection using data resources other than reports from the Adverse Event Reporting System (AERS). FDA will continue training and development of existing staff on the use of these resources, and develop the information technology infrastructure needed to support access and analysis of data from these resources.

D. Information Systems and Infrastructure

FDA will continue the Agency’s efforts on the following standards-based information systems to support how FDA obtains and analyzes post-market drug safety data and manages emerging drug safety information:

1. Enhanced adverse event reporting system and surveillance tools;

2. IT infrastructure to support access and analyses of externally-linked databases; and

3. Workflow tracking system.
XII. IMPROVING THE EFFICIENCY OF HUMAN DRUG REVIEW THROUGH REQUIRED ELECTRONIC SUBMISSIONS AND STANDARDIZATION OF ELECTRONIC DRUG APPLICATION DATA

A. To enhance the quality and efficiency of FDA’s review of NDAs, BLAs, and INDs, FDA shall consult with stakeholders, including pharmaceutical manufacturers and other research sponsors, to issue draft guidance on the standards and format of electronic submission of applications by December 31, 2012.

B. FDA will issue final guidance no later than 12 months from the close of the public comment period on the draft guidance. Such final guidance and any subsequent revisions to the final guidance shall be binding on sponsors, applicants, and manufacturers no earlier than twenty-four months after issuance of the final guidance.

C. Requirements for electronic submission shall be phased in according to the following schedule:

1. Twenty-four (24) months after publication of the final guidance: All new original NDA and BLA submissions, all new NDA and BLA efficacy supplements and amendments, all new NDA and BLA labeling supplements and amendments, all new manufacturing supplements and amendments, and all other new NDA submissions.

2. Thirty-six (36) months after publication of the final guidance: All original commercial INDs and amendments, except for submissions described in section 561 of the Federal Food, Drug, and Cosmetic Act.

D. Because of the significant investments required to change regulatory submission and review software, initial FDA guidance shall specify the format of electronic submission of applications using eCTD version 3.2.2 unless, after notice and an opportunity for stakeholder comment, FDA determines that another version will provide for more efficient and effective applicant submission or FDA review. In general, when FDA revises final guidance requiring submission using a new version of electronic standards or formats, FDA shall also accept submissions using the previous version for no less than twenty-four (24) months.

E. Clinical Terminology Standards: Using a public process that allows for stakeholder input, FDA shall develop standardized clinical data terminology through open standards development organizations (i.e., the Clinical Data Interchange Standards Consortium (CDISC)) with the goal of completing clinical data terminology and detailed implementation guides by FY 2017.

1. FDA shall develop a project plan for distinct therapeutic indications, prioritizing clinical terminology standards development within and across review divisions. FDA shall publish a proposed project plan for stakeholder review and comment by June 30, 2013. FDA shall update and publish its project plan annually.
F. Development of terminology standards for data other than clinical data: To address FDA-identified nonclinical data standards needs, FDA will request public input on the use of relevant already-existing data standards and the involvement of existing standards development organizations to develop new standards or refine existing standards. FDA will obtain this input via publication of a Federal Register notice that specifies a 60-day comment period.

G. FDA shall periodically publish final guidance specifying the completed data standards, formats, and terminologies that sponsors must use to submit data in applications. In the case of standards for study data, new data standards and terminology shall be applicable prospectively and only required for studies that begin 12 months after issuance of FDA's final guidance on the applicable data standards and terminology.

XIII. PROGRESS REPORTING FOR PDUFA V AND CONTINUING PDUFA IV INITIATIVES

On an annual basis, FDA will report on its website the progress in each of the PDUFA V initiatives described in Sections IX, X, XI, and XII. The annual reports will include: (a) descriptions of the hiring and placement of new staff and use of PDUFA resources to support the new initiatives in Sections IX, X, XI.A, XI.B, and XII, and (b) progress reports on achieving metrics described in each of the sections. Each report will be posted on the FDA website no later than 120 days after the end of the fiscal year. The staff resources will support the new initiatives described in Sections IX, X, XI.A, XI.B and XII and the related work associated with these initiatives to ensure their success.

XIV. INFORMATION TECHNOLOGY GOALS

A. Objective

FDA is committed to achieve the long-term goal of improving the exchange, review, and management of human drug and biologic applications throughout the product life cycle through strategic investments in automated, standards-based information technology (IT).

B. Communications and Technical Interactions

1. FDA will periodically update and publish to the FDA website a five-year plan for business process improvement enabled by IT investments.

   a) The plan will frame the strategy for prioritizing IT-enabled business process change, enumerate the business process improvements expected from each IT investment, and convey a consistent series of milestones for each initiative to track pace and progress.

   b) FDA will conduct an annual assessment of progress against the plan and publish on the FDA website a summary of the assessment within 3 months after the close of each fiscal year.

   c) FDA will publish updates to the plan as FDA deems appropriate. FDA will publish on the FDA website draft revisions to the plan; solicit
comments from the public on those draft revisions; and consider the public comments before completing and publishing updates to the plan.

2. The FDA and industry stakeholders will meet on a quarterly basis to discuss prospective implementation of the plan, progress toward the long term goal, potential impacts that future activities may have on FDA or stakeholders, and potential revisions to the plan.

C. Metrics and Measures

On an annual basis, FDA will measure and report progress toward achievement of the objectives defined in Section XIV.A. Measures will include but are not limited to:

1. The number and percentage of IND, NDA, and BLA submissions received in valid electronic format in compliance with FDA standards, categorized by types of submissions. Increasing the number and percentage of IND, NDA, and BLA submissions received in valid electronic format is a goal that is supported by the FDA and industry stakeholders. Achievement of this goal requires the cooperation of regulated industry. To support the assessment of this goal, the following information will be tracked and reported:
   a) Total number of submissions categorized by type of submission
   b) Total number of submissions in valid electronic format in compliance with FDA standards
   c) Total number of submissions received through the secure electronic single point of entry versus other methods
   d) Total number of submissions received substantially on paper or non-standardized electronic format
   e) Total number of standards-based electronic submissions that fail to comply with FDA electronic submission standards, along with a distribution of these submission failures across categories of failure or problem type

2. Number and significance of IT technical specifications or e-submission guidance implemented requiring industry to change submission content that are not forecasted accurately in the five year plan or those whose content has not been available to industry at least twelve months prior to required implementation.

3. Spending on Center IT systems and IT systems that are common across the organizational divisions participating in the process for the review of human drug applications. This includes systems development versus maintenance spending; infrastructure support; a report of total PDUFA fee-funded spending versus appropriations-funded spending; FDA enterprise versus PDUFA-program specific support.

XV. IMPROVING FDA PERFORMANCE MANAGEMENT

A. The studies conducted under this initiative are intended to foster:
1. Development of programs to improve access to internal and external expertise
2. Reviewer development programs, particularly as they relate to drug review processes
3. Advancing science and use of information management tools
4. Improving both inter- and intra-Center consistency, efficiency, and effectiveness
5. Improved reporting of management objectives
6. Increased accountability for use of user fee revenues
7. Focused investments on improvements in the process of drug review
8. Improved communication between the FDA and industry

B. Studies will include:

1. Assessment by an independent contractor of the Program for NME NDAs and original BLAs as described in Section IIB.
2. Assessment of the impact of the benefit-risk framework in the human drug review process as described in Section X.A.3.
3. Development of a tool to evaluate the success of the activities of the Rare Disease Program as described in Section IX.D.6.
5. Assessments by an independent accounting firm of the review activity adjustment methodology, as described in section 736(c)(2), by the end of the second quarter of FY 2013 and by the end of the fourth quarter of FY 2015 with recommendations for changes, if warranted.

XVI. DEFINITIONS AND EXPLANATION OF TERMS

A. The term “review and act on” means the issuance of a complete action letter after the complete review of a filed complete application. The action letter, if it is not an approval, will set forth in detail the specific deficiencies and, where appropriate, the actions necessary to place the application in condition for approval.

B. Goal Date Extensions for Major Amendments
1. A major amendment to an original application, efficacy supplement, or resubmission of any of these applications, submitted at any time during the review cycle, may extend the goal date by three months.

2. A major amendment may include, for example, a major new clinical safety/efficacy study report; major re-analysis of previously submitted study(ies); submission of a REMS with ETASU not included in the original application; or significant amendment to a previously submitted REMS with ETASU. Generally, changes to REMS that do not include ETASU and minor changes to REMS with ETASU will not be considered major amendments.

3. A major amendment to a manufacturing supplement submitted at any time during the review cycle may extend the goal date by two months.

4. Only one extension can be given per review cycle.

5. Consistent with the underlying principles articulated in the GRMP guidance, FDA’s decision to extend the review clock should, except in rare circumstances, be limited to occasions where review of the new information could address outstanding deficiencies in the application and lead to approval in the current review cycle.

C. A resubmitted original application is a complete response to an action letter addressing all identified deficiencies.

D. Class 1 resubmitted applications are applications resubmitted after a complete response letter (or a not approvable or approvable letter) that include the following items only (or combinations of these items):

1. Final printed labeling
2. Draft labeling
3. Safety updates submitted in the same format, including tabulations, as the original safety submission with new data and changes highlighted (except when large amounts of new information including important new adverse experiences not previously reported with the product are presented in the resubmission)
4. Stability updates to support provisional or final dating periods
5. Commitments to perform Phase 4 studies, including proposals for such studies
6. Assay validation data
7. Final release testing on the last 1-2 lots used to support approval
8. A minor reanalysis of data previously submitted to the application
9. Other minor clarifying information (determined by the Agency as fitting the Class 1 category)

10. Other specific items may be added later as the Agency gains experience with the scheme and will be communicated via guidance documents to industry

E. Class 2 resubmissions are resubmissions that include any other items, including any items that would require presentation to an advisory committee.

F. A Type A meeting is a meeting which is necessary for an otherwise stalled drug development program to proceed (a “critical path” meeting) or to address an important safety issue.

G. A Type B Meeting is a 1) pre-IND, 2) end of Phase 1 (for Subpart E or Subpart H or similar products) or end of Phase 2/pre-Phase 3, or 3) a pre-NDA/BLA meeting. Each requestor should usually only request 1 each of these Type B meetings for each potential application (NDA/BLA) (or combination of closely related products, i.e., same active ingredient but different dosage forms being developed concurrently).

H. A Type C meeting is any other type of meeting.

I. The performance goals and procedures also apply to original applications and supplements for human drugs initially marketed on an over-the-counter (OTC) basis through an NDA or switched from prescription to OTC status through an NDA or supplement.

J. IT-specific definitions (refer also to Section XIV)

1. “Program” refers to the organizational resources, procedures, and activities assigned to conduct “the process for the review of human drug applications,” as defined in the Prescription Drug User Fee Act.

2. “Standards-based” means compliant with published specifications that address terminology or information exchange between the FDA and regulated parties or external stakeholders, as adopted by the FDA or other agencies of the federal government, and often based on the publications of national or international Standards Development Organizations.

3. “FDA Standards” means technical specifications that have been adopted and published by the FDA through the appropriate governance process. FDA standards may apply to terminology, information exchange, engineering or technology specifications, or other technical matters related to information systems. FDA standards often are based on the publications of other federal agencies, or the publications of national or international Standards Development Organizations.

4. “Product life cycle” means the sequential stages of human drug development, regulatory review and approval, post-market surveillance and risk
management, and where applicable, withdrawal of an approved drug from the market. In the context of the process for the review of human drug applications, the product life cycle begins with the earliest regulatory submissions in the Investigational New Drug (IND) phase, continues through the New Drug Application (NDA) or Biological Licensing Application (BLA) review phase, and includes post-market surveillance and risk management activities as covered under the process for the review of human drug applications.
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2010–N–0128]

Prescription Drug User Fee Act; Public Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of public meeting; request for comments.

SUMMARY: The Food and Drug Administration (FDA) is announcing a public meeting to discuss proposed recommendations for the reauthorization of the Prescription Drug User Fee Act (PDUFA), which authorizes FDA to collect user fees and use them for the process for the review of human drug applications for fiscal years (FYS) 2013 through 2017. The legislative authority for PDUFA expires in September 2012. At that time, new legislation will be required for FDA to collect prescription drug user fees for future fiscal years. Following discussions with the regulated industry and periodic consultations with public stakeholders, the Federal Food, Drug, and Cosmetic Act (FD&C Act) directs FDA to publish the recommendations for the reauthorized program in the Federal Register, hold a meeting at which the public may present its views on such recommendations, and provide for a period of 30 days for the public to provide written comments on such recommendations. FDA will then consider such public views and comments and revise such recommendations as necessary.

DATES: The public meeting will be held on October 24, 2011, from 9 a.m. to 5 p.m. Registration to attend the meeting must be received by October 10, 2011. See section IV.B of this document for information on how to register for the meeting. Submit either electronic or written comments by October 24, 2011.

ADDRESSES: The meeting will be held at FDA’s White Oak Campus, 10903 New Hampshire Ave., Bldg. 31, Rm. 1503, Silver Spring, MD 20993.

Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number found in brackets in the heading of this document.

Transcripts of the meeting will be available for review at the Division of Dockets Management and on the Internet at http://www.regulations.gov approximately 30 days after the public meeting (see section IV.C of this document).

FOR FURTHER INFORMATION CONTACT: Sunanda Bahl, Food and Drug Administration, Center for Drug Evaluation and Research, 10903 New Hampshire Ave., Bldg. 51, Rm. 1168, Silver Spring, MD 20993, 301–796–3584, fax: 301–847–8443, PDUFAReauthorization@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Introduction

FDA is announcing a public meeting to discuss proposed recommendations for the reauthorization of the Prescription Drug User Fee Act (PDUFA), which authorizes FDA to collect user fees and use them for the process of the review of human drug applications for FYS 2013 through 2017. Without new legislation, FDA will no longer be able to collect user fees for future fiscal years to fund the human drug review process. Section 736B(d)(4) (21 U.S.C. 379h–2(d)(4)) of the FD&C Act requires that after FDA holds negotiations with regulated industry and periodic consultations with stakeholders, we do the following: (1) Present recommendations to congressional committees, (2) publish recommendations in the Federal Register, (3) provide a period of 30 days for the public to provide written comments on the recommendations, (4) hold a meeting at which the public may present its views, and (5) after consideration of public views and comments, revise the recommendations as necessary.

This notice, the 30-day comment period, and the public meeting will satisfy some of these requirements. After the public meeting, we will revise the recommendations as necessary and present our proposed recommendations to the congressional committees.

The purpose of the meeting is to hear the public’s views on the proposed recommendations for the reauthorized program (PDUFA V). The following information is provided to help potential meeting participants better understand the history and evolution of the PDUFA program and the current status of the proposed PDUFA V recommendations.

II. The PDUFA Program

A. What is PDUFA? What does it do?

FDA considers the timely review of the safety and effectiveness of new drug applications (NDAs) and biologics license applications (BLAs) to be central to the Agency’s mission to protect and promote the public health. Prior to enactment of PDUFA in 1992, FDA’s drug review process was not very predictable and was relatively slow compared to other countries. As a result of concerns expressed by both industry and patients, Congress enacted PDUFA, which provided the added funds through user fees that enabled FDA to hire additional reviewers and support staff and upgrade its information technology systems. At the same time, FDA committed to complete reviews in a predictable timeframe. These changes revolutionized the drug approval process in the United States and enabled FDA to speed the application review process for new drugs and biologics without compromising the Agency’s high standards for demonstration of safety, efficacy, and quality of new drugs prior to approval.

B. PDUFA Achievements

PDUFA has produced significant benefits for public health, providing patients faster access to over 1,500 new drugs and biologics since enactment in 1992, including treatments for cancer, infectious diseases, neurological and psychiatric disorders, and cardiovascular diseases. The United States now leads the world in the first introduction of new active drug substances. Since PDUFA was enacted, the median approval time of original NDAs and BLAs has been reduced by about 50 percent for standard applications (25.6 months in FY 1992 versus 13 months in FY 2009) and 55 percent for priority applications (19.9 months in FY 1992 versus 9 months in 2009).

Increased resources provided by user fees have also enabled FDA to provide a large body of technical guidance to industry that has clarified the drug development pathway for many diseases. These resources have also enhanced FDA’s ability to meet with companies during drug development to...
provide critical advice on specific development programs. In the past 5 years alone, FDA has held over 7,000 meetings within a short time after a sponsor’s request. Innovations in drug development are being advanced by many new companies as well as more established ones, and new sponsors may need, and often seek, more regulatory guidance during development. In FY 2009, more than half of the meetings FDA held with companies at the early investigational stage and midway through the clinical trial process were with companies that had no approved product on the U.S. market.

1. Application Review

PDUFA provides FDA with a source of stable, consistent funding that has made possible our efforts to focus on promoting innovative therapies and help bring to market critical products for patients. As part of the PDUFA agreement, FDA agrees to certain review performance goals, such as reviewing and acting on standard applications within 10 months and on priority applications within 6 months. Priority application reviews are for drugs that generally represent advances in public health, often targeted at severe illnesses where few or no therapeutic options exist.

PDUFA funds help support the use of existing mechanisms in place to expedite the approval of certain promising investigational drugs and also to make them available to the very ill as early in the development process as possible, without unduly jeopardizing the patients’ safety.

One such program is the accelerated approval process, instituted by FDA in 1992. Accelerated approval allows earlier approval of drugs that treat serious diseases and that fill an unmet medical need. One pathway for accelerated approval is based on a surrogate endpoint—a marker used as substitute measurement to represent a clinically meaningful outcome, such as survival or symptom improvement—that is reasonably likely to predict clinical benefit; the other pathway bases approval on a clinical endpoint other than survival or irreversible morbidity. This program allows drugs to be approved before measures of effectiveness that would normally be required for approval are available. In these cases, approval is given on the condition that postmarketing clinical trials verify the anticipated clinical benefit. Over 100 critical products, including most HIV therapies and many cancer treatments, have been approved under accelerated approval since the program was established.

2. Drug Safety

In parallel with improvements in the drug review process, PDUFA funds have enabled FDA to increase its focus on drug safety, including implementing the Food and Drug Administration Amendments Act of 2007 (FDAAA). In FDAAA, Congress authorized additional user fees totaling $225 million for the 5 years of PDUFA IV reauthorization to enhance drug safety activities. FDAAA also provided FDA with important postmarket safety authorities. Under FDAAA, FDA was given the authority to require postmarketing studies and clinical trials to address important drug safety questions. Between the enactment of FDAAA on September 27, 2007, and June 1, 2011, FDA has required applicants to conduct approximately 375 postmarketing studies or trials to address important drug safety questions that could not be addressed before the drug was approved. FDAAA also gave FDA the authority to require safety labeling changes based on new safety information identified after a drug is on the market. FDA has used its new authority to require applicants to place important new safety information onto their drug labels quickly, in some cases using this authority to require changes to the labeling of all members of a class of drugs. FDAAA also provided FDA with authority to manage risks associated with marketed drug products through required risk evaluation and mitigation strategies (REMS). FDA has been using this new authority judiciously to ensure that drugs that could not otherwise be approved because the risks without a REMS would outweigh the benefits, are available to patients.

FDA has implemented other important drug safety initiatives under FDAAA including, for example, initiating systematic reviews of the safety of marketed drugs 18 months after approval; conducting regular screening of the adverse event reporting system database and posting quarterly reports of new safety information or potential signals of serious risks identified from that screening; and developing an active post-market drug safety surveillance capability under the “Sentinel” initiative (http://www.fda.gov/Safety/ FDAsSentinelInitiative/ucm2007250.htm).

III. Proposed PDUFA V Recommendations

In preparing the proposed recommendations to Congress for PDUFA reauthorization, we have conducted discussions with the regulated industry, and we have consulted with stakeholders as required by the law. We began the PDUFA reauthorization process with a public meeting held on April 12, 2010 (75 FR 12555, March 16, 2010). The meeting included presentations by FDA and a series of panels representing different stakeholder groups, including patient advocates, consumer groups, regulated industry, health professionals, and academic researchers. The stakeholders were asked to respond to the following questions:

1. What is your assessment of the overall performance of the PDUFA IV program thus far?
2. What aspects of PDUFA should be retained, changed, or discontinued to further strengthen and improve the program?

Following the April 2010 public meeting, FDA conducted negotiations with regulated industry and continued monthly consultations with public stakeholders from July 2010 through May 2011. As directed by Congress, FDA posted minutes of these discussions on its Web site at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm117890.htm. The proposed enhancements for PDUFA V address many of the top priorities identified by public stakeholders, the top concerns identified by regulated industry, and the most important challenges identified within FDA. These include a new review program for new molecular entity NDAs and original BLAs, proposals to enhance regulatory science and expedite drug development, enhanced benefit-risk assessment, modernization of FDA’s drug safety system, requirements for electronic submissions with standardized application data, a technical correction related to discontinued products, and modifications to the PDUFA inflation adjuster with continued evaluation of the workload adjuster. The full descriptions of these proposed enhancements can be found in the draft PDUFA V commitment letter (draft commitment letter) posted on FDA’s Web site at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm149212.htm. Each enhancement is briefly described below with reference to the section of the draft commitment letter where more detailed information can be found.

A. A Review Program for New Drug Applications (NDA), New Molecular Entities (NME), and Original Biologies License Applications (BLA)

FDA’s existing review performance goals for priority and standard
applications, 6 and 10 months respectively, were established in 1997. Since that time, additional requirements in the drug review process have made those goals increasingly challenging to meet, particularly for more complex applications like NME NDAs and original BLAs. FDA also recognizes that increasing communication between the Agency and sponsors or applicants during the application review process is critical to increase efficiency in the review process. To address the desire for increased communication and efficiency, FDA proposes a new review program for NME NDAs and original BLAs in PDUFA V that will include presubmission meetings, mid-cycle communications, and late-cycle meetings between FDA and sponsors for these applications. FDA’s review clock will begin after the 60-day administrative filing review period to accommodate this increased interaction during regulatory review. The impact of these modifications on the efficiency of drug review for this subset of applications would be assessed during PDUFA V. 

B. Enhancing Regulatory Science and Expediting Drug Development

The following five enhancements focus on enhancing regulatory science and expediting drug development. Regulatory science is the science of developing and applying new tools, standards, and approaches to assess the safety, effectiveness, quality, and performance of FDA-regulated products. The details of these enhancements can be found in section IX of the draft commitment letter.

1. Promoting Innovation Through Enhanced Communication Between FDA and Sponsors During Drug Development

FDA recognizes that timely interactive communication with sponsors can help foster efficient and effective drug development. In some cases, a sponsor’s questions may be complex enough to require a formal meeting with FDA, but in other instances, a question may be relatively straightforward such that a response can be provided more quickly. However, our review staff’s workload and other competing public health priorities can make it challenging to develop an Agency response to matters outside of the formal meeting process. This enhancement involves a dedicated drug development communication and training staff, focused on improving communication between FDA and sponsors during development. This staff will be responsible for identifying best practices for communication between the Agency and sponsors, training review staff, and disseminating best practices through published guidance.

2. Methods for Meta-Analysis

A meta-analysis typically attempts to combine the data or findings from multiple completed studies to explore drug benefits and risks and, in some cases, uncover what might be a potential safety signal in a premarket or postmarket context. However, there is no consensus on best practices in conducting a meta-analysis. With the growing availability of clinical trial data, an increasing number of meta-analyses are being conducted based on varying sets of data and assumptions. If such studies conducted outside FDA find a potential safety signal, FDA will work to try to confirm—or correct—the information about a potential harm that will create uncertainty for patients and health professionals. To do this, FDA must work quickly to conduct its own meta-analyses of publicly available data and the raw clinical trial data submitted by drug sponsors that would typically not be available to outside researchers. This is resource-intensive work that often exceeds the Agency’s current scientific and computational capacity, causing delays in FDA findings that prolong public uncertainty. This proposed recommendation includes the development of a dedicated staff to evaluate best practices and limitations in meta-analysis methods. Through a rigorous public comment process, FDA will develop guidance on best practices and the Agency’s approach to meta-analysis in regulatory review and decision-making.

3. Biomarkers and Pharmacogenomics

Pharmacogenomics and the application of qualified biomarkers have the potential to decrease drug development time by helping to demonstrate benefits, to recognize unmet medical needs, and to identify patients who are predisposed to adverse events. FDA provides regulatory advice on the use of biomarkers to facilitate the assessment of human safety in early phase clinical studies to support claims of efficacy and to establish the optimal dose selection for pivotal efficacy studies. This is an area of new science for drugs that may have an unmet medical need. FDA is well-trained to help drug developers in this area. In addition, FDA will convene a public meeting to discuss standards for PRO qualification, new theories in endpoint measurement, and the implications for multinational trials.

4. Use of Patient-Reported Outcomes (PRO)

Assessments of study endpoints known as patient-reported outcomes (PROs) are increasingly an important part of successful drug development. PROs measure treatment benefit or risk in medical product clinical trials from the patients’ point of view. PROs are critical in understanding the drug benefits and harm from the patients’ perspective. However, PROs require rigorous evaluation and statistical design and analysis to ensure reliability to support claims of clinical benefit. Early consultation between FDA and drug sponsors can ensure that endpoints are well-defined and reliable. However, the Agency does not have the capacity to meet the current demand for industry.

This initiative will improve FDA’s clinical and statistical capacity to address submissions involving PROs and other endpoint assessment tools, including providing consultation to sponsors during the early stages of drug development. In addition, FDA will convene a meeting to discuss standards for PRO qualification, new theories in endpoint measurement, and the implications for multinational trials.

5. Development of Drugs for Rare Diseases

FDA’s oversight of rare disease drug development is complex and resource intensive. Rare diseases are a highly diverse collection of disorders, their natural histories are often not well-described, only small population sizes are often available for study, and the diseases do not usually have well-defined outcome measures. This makes the design, execution, and interpretation of clinical trials for rare diseases difficult and time consuming, requiring frequent interaction between FDA and drug sponsors. If recent trends in orphan designations are any indication, FDA can expect an increase in investigational activity and marketing applications for drug products for rare diseases in the future.

This PDUFA V enhancement includes FDA facilitation of rare disease drug development by issuing relevant guidance, increasing the Agency’s outreach efforts to the rare disease patient community, and providing specialized training in rare disease drug
development for sponsors and FDA staff.

C. Enhancing Benefit-Risk Assessment

FDA has been exploring how to develop an enhanced structured approach to benefit-risk assessments that accurately and concisely describes the benefit and risk considerations in the Agency’s drug regulatory decision-making. Part of FDA’s decision-making lies in thinking about the context of the decision, including gaining a strong understanding of the condition treated and the nature and extent of the unmet medical need. Patients who live with a disease have a direct stake in the outcome of the drug review process. The FDA drug review process could benefit from a more systematic and expansive approach to obtaining the patient perspective on disease severity and the potential gaps or limitations in available treatments in a therapeutic area.

During PDUFA V, FDA will expand its use of a benefit-risk framework in the drug review process including holding public workshops to discuss the application of frameworks for considering benefits and risks that are most appropriate for the regulatory setting. FDA will also conduct a series of public meetings with the relevant patient advocacy communities to review the medical products available for use in specific therapeutic areas. The therapeutic areas to be discussed will be chosen through a public process. This enhancement is discussed in section X of the draft commitment letter.

D. Enhancement and Modernization of the FDA Drug Safety System

The drug safety enhancements in PDUFA V focus on FDA’s use of REMS and the Sentinel Initiative. Additional information on these proposals is found in section XI of the draft commitment letter.

1. Standardizing REMS

FDAAA gave FDA authority to require a REMS when FDA finds that a REMS is necessary to ensure that the benefits of a drug outweigh its risks. Some REMS are more restrictive types of risk management programs that include elements to assure safe use (ETASU). These programs can require such tools as prescriber training or certification, pharmacy training or certification, dispensing only in certain health care settings, documentation of safe use conditions, patient monitoring, and patient registries. ETASU REMS can be challenging to implement and evaluate, involving cooperation of all segments of the health care system. Our experience with REMS to date suggests that the development of multiple individual programs has the potential to create burdens on the health care system and, in some cases, could limit appropriate patient access to important therapies.

FDA will initiate a public process in PDUFA V to explore strategies and initiate projects to standardize REMS programs with the goal of reducing burden on practitioners, patients, and others in the health care setting. In addition, FDA will conduct public workshops and develop guidance on methods for assessing the effectiveness of REMS and the impact on patient access and burden on the health care system.

2. Using the Sentinel Initiative To Evaluate Drug Safety Issues

FDA’s Sentinel Initiative is a long-term program designed to build and implement a national electronic system for monitoring the safety of FDA-approved medical products. FDAAA required FDA to collaborate with Federal, academic, and private entities to develop methods to obtain access to disparate data sources and validated means to link and analyze safety data to monitor the safety of drugs after they reach the market, an activity also known as “active postmarket drug safety surveillance.” FDA will conduct a series of activities during PDUFA V to determine the feasibility of using Sentinel to evaluate drug safety issues that may require regulatory action (e.g., labeling changes, post-marketing requirements, or postmarketing commitments). This may shorten the time it takes to better understand new or emerging drug safety issues. By leveraging public and private health care data sources to quickly evaluate drug safety issues; this proposal may reduce the Agency’s reliance on required postmarketing studies and clinical trials.

E. Required Electronic Submissions and Standardization of Electronic Application Data

The predictability of the FDA review process relies heavily on the quality of sponsor and applicant submissions. The Agency currently receives submissions of original applications and supplements in formats ranging from paper-only to electronic-only, as well as hybrids of the two media. The variability and unpredictability of submitted formats and clinical data layout present major obstacles to conducting a timely, efficient, and rigorous review within current PDUFA goals time frames. Lack of standardized data also limits FDA’s ability to transition to more standardized approaches to benefit-risk assessment and impedes conduct of safety analyses that inform FDA decisions related to REMS and other postmarketing requirements. The PDUFA V enhancements in this area include a phased-in requirement for standardized, fully electronic submissions for all marketing and investigational applications. Through partnership with open standards development organizations, the Agency will also conduct a public process to develop standardized terminology for clinical and nonclinical data submitted in marketing and investigational applications. More information on this initiative can be found in section XII of the draft commitment letter.

F. Technical Change to Section 736(a)(3)(B) of the FD&C Act Related to Discontinued Products

FDA proposes to amend section 736(a)(3)(B) of the FD&C Act, which provides for an exception in assessing a product fee if the same product is approved as an NDA or ANDA. This amendment will clarify FDA’s long-standing policy to use the active portion of the Prescription Drug Product List in the “Approved Drug Products With Therapeutic Equivalence Evaluations” (generally known as the “Orange Book”) to identify fee-eligible prescription drug products. FDA will assess a product fee on a prescription drug product when there are no other products on the Prescription Drug Product List that are the same as that product.

G. PDUFA V Enhancements for a Modified Inflation Adjuster and Additional Evaluations of the Workload Adjuster

In calculating user fees for each new fiscal year, FDA adjusts the base revenue amount by inflation and workload as specified in the statute. PDUFA V financial enhancements include a modification to the inflation adjuster to more accurately account for changes in FDA’s costs related to payroll compensation and benefits as well as changes in non-payroll costs through use of the Consumer Price Index (CPI). This new weighted composite inflation adjuster will help ensure that increases in fees more closely mirror the inflationary pressures that have an impact on FDA’s costs.

FDA will also continue evaluating the workload adjuster that was developed during the PDUFA IV negotiations to ensure that it continues to adequately capture changes in FDA’s workload during PDUFA V. These evaluations will include options to discontinue,
modify, or retain any element of the workload adjuster.

H. Impact of PDUFA V Enhancements on User Fee Revenue

Implementing the proposed enhancements discussed in the previous sections of this document will add $40.4 million to the PDUFA user fee revenue amount in FY 2012. The fee revenue amount for FY 2012 is $652,709,000 as published by notice in the Federal Register of August 1, 2011 (76 FR 45831). This amount includes the additional user fee revenues for drug safety in FY 2012 totaling $65 million as specified in the statute. The additional user fee revenue for the PDUFA V enhancements translates to a 6-percent increase, and a total base of $693.1 million in FY 2013. The following table summarizes the FY 2013 baseline and added resources to support the new PDUFA V enhancements:

<table>
<thead>
<tr>
<th>Financial baseline</th>
<th>Dollars</th>
</tr>
</thead>
<tbody>
<tr>
<td>FY 2012 Baseline</td>
<td>$499,412,000</td>
</tr>
<tr>
<td>Cumulative Inflation Adjustment for FY 2012</td>
<td>104,277,000</td>
</tr>
<tr>
<td>Cumulative Workload Adjustment for FY 2012</td>
<td>49,020,000</td>
</tr>
<tr>
<td>Fee Revenue Amount for FY 2012</td>
<td>652,709,000</td>
</tr>
</tbody>
</table>

PDUFA V Enhancements

| Increased Staff Capacity (129 FTE) | 36,120,000 |
| Other Direct Costs | 4,270,000 |
| Total Statutory Revenue Amount for FY 2013 | 693,099,000 |

1 In determining the fee revenue amount for FY 2012, sections 736(b)(4)(A) and 736(b)(4)(B) of the FD&C Act direct the Secretary of Health and Human Services (Secretary) to base $392,783,000 plus $65,000,000 (for FY 2012) for the amount in paragraph (1)(A). Furthermore, paragraph (1)(B) directs the Secretary to add the amount of the modified workload adjustment for FY 2007 to the amount in paragraph (1)(A) to determine the total revenue amount in FY 2012. This total is $499,412,000.

2 As published in the Federal Register of August 1, 2011 (76 FR 45831).

3 Of this amount, $652,709,000 will be further adjusted according to the new statutory provisions to account for inflation and workload adjustments in determining fees for FY 2013. These adjustments must be captured in calculations of user fee revenue for FYs 2014–2017.

IV. What information should you know about the meeting?

A. When and where will the meeting occur? What format will FDA use?

We will convene a public meeting to hear the public’s views on the proposed recommendations for reauthorization of PDUFA. We will conduct the meeting on October 24, 2011, at FDA’s White Oak Campus (see ADDRESSES). The meeting will include a presentation by FDA and a series of panels representing different stakeholder groups identified in the statute (such as patient advocacy groups, consumer advocacy groups, health professionals, and regulated industry). We will also provide an opportunity for other organizations and individuals to make presentations at the meeting or to submit written comments to the docket before the meeting.

B. How do you register for the meeting or submit comments?

If you wish to attend this meeting, please register by e-mail at: PDUFAReauthorization@fda.hhs.gov by October 10, 2011. Your e-mail should contain complete contact information for each attendee, including: Name, title, affiliation, address, e-mail address, and phone number. Registration is free and will be on a first-come, first-served basis, with the exception below. Early registration is recommended because seating is limited. FDA may limit the number of participants from each organization based on space limitations. Registrants will receive confirmation once they have been accepted. On-site registration on the day of the meeting will be based on space availability. We will try to accommodate all persons who wish to make a presentation. If you need special accommodations because of disability, please contact Sunanda Bahl (see FOR FURTHER INFORMATION CONTACT) at least 7 days before the meeting.

In addition, interested persons may submit to the Division of Dockets Management (see ADDRESSES) either electronic or written comments regarding this document. It is only necessary to send one set of comments. It is no longer necessary to send two copies of mailed comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday. To ensure consideration, all comments must be received by October 31, 2011.

C. Will meeting transcripts be available?

Please be advised that as soon as a transcript is available, it will be accessible at http://www.regulations.gov and http://www.fda.gov. It may be viewed at the Division of Dockets Management (see ADDRESSES). A transcript will also be made available in either hard copy or on CD-ROM, after submission of a Freedom of Information request. Written requests are to be sent to Division of Freedom of Information (ELEM–1029), Food and Drug Administration, 12420 Parklawn Dr., Element Bldg., Rockville, MD 20857.

Dated: September 7, 2011.

Leslie Kux,
Acting Assistant Commissioner for Policy.
[FR Doc. 2011–23251 Filed 9–9–11; 8:45 am]
BILLING CODE 4160–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2011–N–0002]

Request for Notification From Industry Organizations Interested in Participating in the Selection Process for Nonvoting Industry Representatives and Request for Nominations for Nonvoting Industry Representatives on the Tobacco Products Scientific Advisory Committee

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is requesting that industry organizations interested in participating in the selection of nonvoting industry representatives to serve on its Tobacco Products Scientific Advisory Committee, notify FDA in writing. FDA is also requesting nominations for nonvoting industry representatives to serve on the Tobacco Products Scientific Advisory Committee. A nominee may either be self-nominated or nominated by an organization to serve as a nonvoting industry representative. Nominations will be accepted for upcoming vacancies effective with this notice.

DATES: Send letters stating interest in participating in the selection process to FDA by October 12, 2011 (see sections I and II of this document for details). Concurrently, nomination material for prospective candidates should be sent to FDA by October 12, 2011.

ADDRESSES: All letters of interest and nominations should be submitted in writing to TPSAC@fda.hhs.gov, or by mail to Caryn Cohen, Center for Tobacco Products, Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850.

FOR FURTHER INFORMATION CONTACT: Caryn Cohen, Center for Tobacco Products, Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850.
BIO Supports Timely Reauthorization of PDUFA to Promote the Development of Innovative Therapies and Speed New Medicines to Patients

SEPTEMBER 1, 2011

Contact: Stephanie Fischer
Phone: 202-312-9263
Email: sfischer@bio.org

Washington, D.C. (September 1, 2011) – Biotechnology Industry Organization (BIO) President and CEO Jim Greenwood released the following statement on the Prescription Drug User Fee Act (PDUFA) V recommendations as published today* by the U.S. Food and Drug Administration (FDA):

“BIO supports the PDUFA V recommendations as they will enhance the drug development and review process through increased transparency and scientific dialogue, advance regulatory science, and strengthen post-market surveillance. Most importantly, PDUFA V will provide patients and doctors with earlier access to breakthrough therapies.

Since PDUFA was enacted in 1992, it has contributed to the approval of more than 1,200 new medicines and initially reduced review times for the newest, most innovative drugs by more than a year. However, the human drug review program has been under considerable stresses in recent years as new regulatory requirements have been layered on the review process and the scientific complexity of applications has increased. As a result, overall approval times lengthened in the early years of PDUFA IV and patients were forced to wait longer for new therapies.

“Unpredictability in the review process, suboptimal communication with sponsors, and decreased FDA performance not only hinders patient access to new treatments, but also negatively impacts the ability of biotechnology companies to raise funding to support clinical development and ongoing innovation. This undermines economic growth in the biotechnology sector as well as biomedical research into key public health priorities.

“In PDUFA V, industry and FDA have agreed upon a set of enhancements that seek to restore FDA’s review performance and get back-to-basics for patients by strengthening scientific dialogue and transparency between FDA and the sponsor during the review of a novel drug or biologic, with the goal of minimizing review issues that can delay patient access to needed treatments.

“To help advance American innovation and promote the development of the next generation of modern medicines, FDA has also committed to a philosophy that timely, interactive communication with biotechnology and life science companies during drug development is a core Agency activity. Additionally, the agreement makes new resources available to modernize regulatory science, for example, in the areas of personalized medicine and rare disease drug research. It will also enable the FDA to conduct outreach to patients to better understand patient perspectives on disease severity and unmet medical need.

“Under the agreement, industry has reinforced its commitment to a well-funded drug and biologics program that supports sound, science-based regulation consistent with FDA’s public health mission. However, user fees are intended to support limited FDA activities around the drug review process and were never intended to supplant a sound base of appropriations. User fees currently account for nearly two-thirds of the cost of human drug review. We urge Congress to support FDA’s mission and fund the Agency at the Administration’s FY12 requested levels.

“Finally, it is critical for PDUFA to be reauthorized well in advance of PDUFA IV’s expiration in September 2012 in order to avoid a reduction in force at the FDA. Even the threat of a downsizing at the FDA would be devastating to the Agency’s public health mission and its ability to review new drugs and biologics.

“BIO looks forward to working with Congress and FDA to fully implement these enhancements under PDUFA V.”
About BIO
BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products. BIO also produces the BIO International Convention, the world’s largest gathering of the biotechnology industry, along with industry-leading investor and partnering meetings held around the world. BIO produces BIOtechNOW, an online portal and monthly newsletter chronicling “innovations transforming our world.” Subscribe to BIOtechNOW.
PhRMA Statement Regarding User Fee Act Reauthorization

Washington, D.C. (September 1, 2011) — Pharmaceutical Research and Manufacturers of America (PhRMA [1]) Senior Vice President for Scientific and Regulatory Affairs Dr. David E. Wheadon issued the following statement today on reauthorization of the Prescription Drug User Fee Act (PDUFA [2]):

“The PDUFA-V performance goals letter [3] that was published today is the result of lengthy technical negotiations between the biopharmaceutical industry and Food and Drug Administration (FDA [4]), and includes unprecedented input from other stakeholders, including patient and medical provider groups. The agreement represents a shared goal of benefitting patients by facilitating efficient and thorough drug review processes that should allow more timely access to safe and effective new medicines.

[Read Kate Connor's blog piece "One Step Forward In PDUFA Reauthorization [5]."]

“If implemented as published, the PDUFA-V agreement will provide the FDA with much-needed resources and management tools to support patient safety and to promote innovation through increased transparency, predictability, and efficiency in FDA’s science-based human drug review program.

“Our growing and evolving knowledge of science has led to recent breakthroughs in complex areas such as personalized medicine, biomarkers and treatments for rare diseases. The enhancements included in the PDUFA agreement, specifically the advancement of regulatory science at FDA, will more effectively support FDA’s role in promoting innovative approaches to drug development.

“The PDUFA-V agreement will also establish an enhanced review model for novel medicines known as New Molecular Entities (NMEs), providing the FDA with meaningful management tools to support agency review of innovative new medicines. This enhanced review model targets completion of FDA assessments of efficacy and safety within the first review cycle and is intended to reduce the overall time until new medicines become available to patients, while maintaining FDA’s gold standard of
safety and efficacy. One aspect of this proposal which should facilitate this goal is increased scientific communication between FDA and sponsors prior to and throughout the review process.

“FDA’s robust drug safety system would also be strengthened through provisions in the agreement that include greater standardization of and earlier consideration of risk evaluation and mitigation strategies (REMS) in the review process, support for the use of Sentinel as a tool for assessing post-market safety issues, methods for maximizing existing FDA tools for adverse event detection, and adoption of standardized approaches for electronic data submissions.

“Having successfully concluded the technical negotiation phase of the PDUFA-V reauthorization, PhRMA looks forward to continued collaboration with Congress, the Administration, and all other stakeholders as we work toward timely reauthorization of this important program.”

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FDA-Industry PDUFA Agreement Unveiled As Capitol Hill Lobbying Readies

Posted: September 1, 2011

The long-awaited FDA-drug industry agreement on the reauthorization of the Prescription Drug User Fee Act was released Thursday (Sept. 1), finally shedding light on the precise details and tenets of the pact -- which sets fees, metrics and acceptable uses for money paid by drug sponsors when submitting an application. The agreement has been forged after months of negotiations and will be the focal point for FDA lobbying next year, with stakeholders already lining up their legislative ideas as sidecars to the deal. InsideHealthPolicy last week reported that the document would be released on Sept. 1.

The PDUFA agreement's tenets have emerged through minutes of closed-door negotiations, public statements and sources familiar with the conversations, although the actual language of the deal and granular details have not been publicly disseminated. The agreed-upon pact includes language on: standardizing the Risk Evaluation and Mitigation Strategies program; enhanced communication with product sponsors; boosting regulatory science; establishing meta-analysis methods; better incorporation of biomarkers; the consideration of a product’s benefit during the review process; and utilizing the post-market Sentinel system to assess drugs’ impacts on patients (see related stories).

The drug industry immediately issued statements supporting the PDUFA agreement given that the fees help FDA review products more rapidly. Both the Biotechnology Industry Organization and the Pharmaceutical Research and Manufacturers of America have called for the pact to be passed as-is.

"As Congress considers reauthorization next year, a bill that is free of extraneous controversial provisions that would politicize the bill (also known as a 'clean' bill) is vital," said Robert Metcalf, vice president of global regulatory affairs at Eli Lilly and Company, in comments on the firm's website.

The drug industry has also sought reauthorization of the program well before its expiry at the end of fiscal 2012. Some lawmakers have sought passage of PDUFA V by mid summer 2012 to avoid potential political hurdles incurred by the next presidential election.

"[I]t is critical for PDUFA to be reauthorized well in advance of PDUFA IV's expiration in September 2012 in order to avoid a reduction in force at the FDA," said BIO President and CEO Jim Greenwood. "Even the threat of a downsizing at the FDA would be devastating to the Agency’s public health mission and its ability to review new drugs and biologics."

The pharmaceutical industry also called for Congress to fund FDA at the administration’s requested appropriation level, as agency funds are threatened by budget cuts and stakeholders argue that FDA needs at least a 5 percent increase in appropriations each year.

The drug industry vowed to work with Congress and other stakeholders to reauthorize the pharmaceutical user fee program.
"Having successfully concluded the technical negotiation phase of the PDUFA-V reauthorization, PhRMA looks forward to continued collaboration with Congress, the Administration, and all other stakeholders as we work toward timely reauthorization of this important program," said PhRMA Senior Vice President for Scientific and Regulatory Affairs David Wheadon.

Even though the drug industry has advocated that Congress quickly reauthorize PDUFA with no changes to the pact before the fees expire at the end of fiscal 2012, the user fee package is still considered a vehicle for other FDA reforms.

For example, House Democrats and some senators are backing drug safety legislation that would enable FDA to audit foreign facilities more frequently. Similarly, Republicans have eyed measures that could improve consistency and promote innovation, criticizing FDA for employing policies that hinder expert involvement on agency advisory committees.

While FDA negotiated the agreement behind closed-doors with the drug industry, the agency also held meetings with other stakeholders -- such as patient and consumer advocates -- some of whom have complained that their input was not adequately considered and vowed to take their concerns to Capitol Hill.

Alongside PDUFA, FDA is also in the midst of negotiating the reauthorization of medical device user fees, although those discussions have been much more contentious in light of industry's concern that the agency is not consistently reviewing products and could change the core tenets of device review programs.

Further, FDA and the generic drug industry are ironing out the details on creating a user fee program for these lower-cost medicines, with applications piling up at the agency in the meantime. FDA is also negotiating a somewhat controversial fee for the healthcare reform-created biosimilars pathway, with those talks recently overcoming a hurdle on appropriations that slowed the talks.

The user fee agreements are expected to be formally transmitted to Congress in January, with public review held beforehand. Some lawmakers have sought passage of the PDUFA reauthorization by the middle of next year. -- Ben Moscovitch (bmocsovitch@insidehealthpolicy.com)

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Consumer Advocates Say PDUFA V Pact Falls Short On Safety Measures

Posted: September 9, 2011

Consumer and safety advocates are complaining that the user fee agreement negotiated between FDA and industry doesn't commit to scaling-up the post-market safety Sentinel program or using the system to look at effectiveness and non-predictable events, adding that the drug safety monitoring program is not living up to what was envisioned when it was crafted by Congress as part of the FDA Amendments Act in 2007.

The FDA-industry pact to reauthorize the Prescription Drug User Fee Act -- released last week -- states that FDA will spend user fee funds to determine the feasibility of using Sentinel to evaluate drug safety, with the planned activities focused on issues affecting classes of drugs or multiple products.

The agency will hold public meetings to solicit feedback and fund four to six activities to evaluate safety signals that have served as the basis for regulatory action or will help determine the utility and validity of the system in evaluating other types of signals in population-based databases. Examples of these activities include expanding the active surveillance mechanisms begun for the H1N1 pandemic and evaluating risk for class-wide adverse events.

FDA will also conduct an assessment to evaluate the strengths, limitations and appropriate use of Sentinel for informing regulatory actions to manage safety issues.

Diana Zuckerman, president of the National Research Center for Women and Families, said the plan for the Sentinel system outlined in PDUFA "doesn't do anything," essentially protecting industry instead of being equally concerned with helping patients.

"Some things have been singled out to show they care about safety but what they are proposing doesn't add up to much," Zuckerman said. "It is just fluff ... It is adding a little bit of rhetoric without adding any real enforcement."

The language used in the agreement is vague and doesn't commit the agency to any new actions with regard to the Sentinel system, she added.

"Sometimes things are worded vaguely so the agency can do whatever they want and depending on what the agency wants to do, that is fine," Zuckerman said, adding however that the agreement contains little detail on safety or efficacy measures to protect patients. "Maybe this vague wording really means they will continue what they are already doing."

Consumer advocates want user fees to go toward making full use of the system, including looking at non-predictable events, rather than only expected adverse events. Zuckerman said the agency is concerned about using the system in this way because it doesn't want to scare the public with false positives.
"In other words, instead of looking for the predictable problems, we should look for everything," Zuckerman said. "That is what is exciting about Sentinel -- it is an early warning system for something you had no idea was a problem. FDA is too narrowly using Sentinel to look at predictable problems."

The agreement also focuses on using Sentinel to look at safety, not for measuring effectiveness, an idea some consumers have been advocating that the system be used for. FDA officials have said Sentinel is now focused on safety monitoring but it could be used to measure effectiveness, although there is no plan to use the system for that purpose.

Zuckerman said the problems consumers have with the user fee pact and the Sentinel system extend throughout the entire agreement. She said there is a lot of emphasis on meetings between the agency and FDA, and less emphasis on safety and efficacy.

Consumer advocates have appealed to HHS Secretary Kathleen Sebelius to include their proposals in the final PDUFA agreement, circumventing FDA. They said they are focusing first on getting some of their ideas into the final language, but might also push for getting more input into the negotiation process. Stakeholders routinely have meetings with FDA during the negotiations but are not at the table during closed-door meetings between the agency and industry.

George Washington University and the Union of Concerned Scientists are planning a public forum on PDUFA in mid November to discuss possible changes to the agreement.

The Mini-Sentinel pilot project -- the agency's first step toward developing the full Sentinel system -- currently encompasses the data of nearly 100 million patients. The agency says the system allows the scientists to more rapidly evaluate safety questions than through traditional channels. -- Nanci Bompey ( nhibompey@wpmnews.com )

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Drug User Fee Pact Signals Institutionalization Of PRO, Novel Endpoint Use

Posted: September 15, 2011

The FDA-industry agreement to utilize drug user fees to expand the agency's capacity for evaluating patient-reported outcomes (PROs) and other endpoint assessment tools signals that the qualification process for these instruments is becoming institutionalized and could expedite efforts to develop standardized instruments and encourage growth of companies that develop these tools, according to industry sources. A patient advocate said development of PROs could help make the clinical trial process faster and more efficient, leading to better treatments for rare diseases.

The negotiated pact to reauthorize the Prescription Drug User Fee Act -- released last week -- would provide FDA more funds to hire staff for endpoint review and utilize guidance documents previously released by the agency on these instruments.

Raymond Woosley -- president of the Critical Path Institute that organizes the PRO Consortium -- said additional resources could help move along review of both PROs and biomarkers. For example, there are 50 biomarkers under review and only seven have been qualified for use, he said.

"Inclusion of biomarkers and PROs in the user agreement confirms that there is sustained interest in better science driving the methods that drugs are tested by, and that it is an evolving process," Woosley said. "It means that the qualification process is becoming institutionalized."

FDA has issued final guidance on PROs, clarifying how the agency intends to review PRO instruments, and draft guidance on the qualification process for drug development tools, including PROs, which are subjective indications directly from patients that are used to assess a drug's impact.

"Since they came out with draft guidance in 2006 and then the final guidance in 2009, I think everyone in the industry and at the agency has the recognition that there is increased rigor with respect to PROs and that puts a burden with respect to the agency in terms of reviewing submissions and the industry when putting together a package," said Keith Wenzel, senior product director of ePRO at Perceptive Informatics.

In the draft agreement, the agency said user fees will be used to build clinical and statistical staff capacity to more efficiently and effectively respond to submissions that involve PROs and other outcomes assessment tools, including providing drug application and qualification consultations, and promoting best practices for review and qualification of these tools.

As part of the PDUFA pact, dedicated staff will focus on review and qualification of endpoint assessment tools, and staff who will be integrated into review decisions. FDA said this will result in greater consistency in the agency's review, qualification and usage of these endpoint assessment tools.
The agency has also committed to holding a public meeting by the end of fiscal 2014 to discuss FDA’s qualification standards for drug development tools, new measurement theories, and implications for multinational trials.

"I think what we are seeing by these various commitments, both from the agency and the drug industry is 'listen, we need more staffing in order to accomplish this and fulfill our obligations',' Wenzel said. "I think it is a continued example of what the agency has been doing since 2006."

Wenzel said along with the public meetings in the agreement, FDA is also planning a clinical outcome assessment meeting in October, giving companies like Perceptive Informatics, that develop these instruments, at least two opportunities to interact with agency officials.

Wenzel said he would like to hear from the agency how guidance has affected the number of submissions and approval rates, and get feedback from FDA on improving submissions involving PROs and other endpoint assessment tools.

Wenzel would also like to hear the agency’s view on biomarkers and other endpoints, for which FDA has not yet issued final guidance. The PDUFA agreement also includes developing staff capacity and providing training for reviewing submissions that involve pharmacogenomics and biomarkers, and the agency said it will hold a public meeting on using these tools.

Since final guidance on PROs was released in 2009, the number of PRO consulting companies has increased and drug companies are becoming more well-versed on these types of endpoint assessments, Wenzel said. There is now a push toward developing instruments that can be shared among companies for similar types of drugs so that the agency can focus on reviewing products rather than the methods used, a goal of the PRO Consortium.

The consortium is also pushing for development of data standards, which were also part of the agreement. Woosley said rapid "learning" about regulatory science and improved methods for testing new products will be much more efficient, and the review process should be much faster when data standards are in place.

Development of PROs also has implications for developing a qualitative benefit-risk framework, expanding use of biomarkers and development of treatments for rare diseases, three of the top focus areas of the National Health Council, said the group's executive vice president and chief operating officer Marc Boutin.

PROs allow companies to look at what is important to patients, which could mean better medicines in the long run, he said. It is also one way to make the clinical trial process more efficient and faster, important factors when companies are developing drugs for small patient populations, Boutin said.

"It may mean they get better medicines, and a better sense of what is important to the patient community as they go through the process," he said. "It is also an opportunity to make the clinical trial process more efficient and more effective from the beginning." -- Nanci Bompey ( nbompey@ljwnews.com )

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Despite Criticism Of The FDA Review Process, New Cancer Drugs Reach Patients Sooner In The United States Than In Europe

ABSTRACT The US Food and Drug Administration is often criticized as inefficient compared to its European counterpart, the European Medicines Agency. This criticism is especially common in the field of oncology, where severely ill patients have few therapeutic options. We conducted a direct drug-to-drug comparison of the two regulatory agencies’ approvals of new oncology drugs. We found that contrary to public assertions, the median time for approval for new cancer medicines in the United States was just six months—and that these new anticancer medicines are typically available in the United States before they are in Europe. Our findings reinforce the need for strong financial and public support of the Food and Drug Administration, so that such medicines can continue to be made available speedily to patients in need.

In recent years the scientific understanding of the basic biology of cancer has undergone a major transformation. With the advent of bioinformatics, it is now possible to elucidate the molecular pathways involved in cancer development and to design drugs to specifically target these pathways. Examples of such breakthrough drugs include Herceptin (trastuzumab), which blocks the effects of a protein that transmits growth signals to breast cancer cells,1 and Gleevec (imatinib mesylate), which inhibits an enzyme that is active in chronic myelogenous leukemia.2 This new era of scientific discovery has the potential to lead to new anticancer medicines with greater efficacy and reduced toxicity, allowing patients to live longer and healthier lives.

Despite these breakthroughs, some critics argue that given the advances in basic science, we should be able to develop new oncology drugs more quickly than we do.4 One reason cited for the slower-than-desired pace is a regulatory environment that is not sufficiently equipped with the resources and scientific foundation needed to evaluate new approaches to cancer treatment.4 Some critics specifically have characterized the Food and Drug Administration (FDA) as slow and inefficient at reviewing drugs in comparison to its European counterpart, the European Medicines Agency (EMA).3,5 Furthermore, some have claimed that the FDA has become so risk-averse, it is increasingly difficult to obtain approval for effective drugs in the United States.6

To examine these claims as they pertain to new anticancer medicines, we analyzed new oncology drug approvals by the FDA and the EMA. We describe our methods and results below.

Study Data And Methods
We compared review times at the FDA and the EMA for new oncology drugs in the period 2003-10. Our data came from the publicly available drug databases on the FDA and EMA websites; they represent only initial approvals, not supplemental applications. In addition, we investigated only active treatment drugs, not drugs for supportive care, such as pain relievers or antinausea medications.

For each new drug in the United States, we collected the date of the first New Drug Application or Biologics License Application submission...
to the FDA and the date of final approval. Once the FDA approves a drug, it can be marketed in the United States.

In the European Union, two steps are required before a drug can be marketed. First, the EMA Committee for Medicinal Products for Human Use must issue a positive opinion on the marketing authorization. Second, the EMA, in consultation with the European Commission, must adopt that opinion. Thus, for each drug we collected the date of the first Marketing Authorization Application submission to the EMA, as well as the dates of the EMA’s positive opinion and of marketing authorization.

To evaluate the efficiency of the FDA and EMA review processes, we compared the agencies’ review times. To evaluate the delay to market—or the time between a drug’s authorization for sale in the United States and its authorization in Europe—we calculated the number of calendar days between the FDA approval date and the European Commission adoption date.

**Study Limitations**

Our analysis has several limitations. First, as noted above, we considered only initial approvals and not supplemental applications. Therefore, our analysis did not include prominent secondary uses for drugs already on the market. This limitation is addressed in more detail below.

Our analysis also did not compare postapproval decisions in the United States and the European Union. For example, the FDA recently decided to withdraw approval for the use of the drug Avastin in treating breast cancer, when postmarketing trials failed to confirm that it had a clinical benefit for this use. In contrast, the EMA decided to continue to allow Avastin to be marketed in the European Union for the treatment of breast cancer. Such postapproval decisions are rare, however.

Another limitation of our study is that we considered only official review times. This does not take into account difficulties that pharmaceutical companies may encounter in communicating with either agency before submitting their study data, or any difficulties in planning or conducting clinical trials of a drug.

However, the field of oncology is one in which the FDA and the EMA have undertaken several initiatives to coordinate their activities, with the goal of speeding the development and entry onto the market of safe, effective new drugs. For example, they have created a program to provide joint scientific advice to pharmaceutical companies. With the help of these initiatives, manufacturers of oncology products are often able to use the same clinical trials to support approval in both the United States and the European Union. Thus, it seems unlikely that manufacturers experience greater difficulties with the FDA than with the EMA at this stage of oncology drug development.

An additional limitation of our study is that we compared approval data for drugs and biologics only, not devices. Examples of devices relevant to oncology include in vitro diagnostics as well as imaging reagents and equipment. A recent report found that in contrast to our analysis of oncology drugs, the FDA is lagging behind the EMA in review and approval of new and innovative devices. Reforms of the US device review process and new initiatives at the FDA, such as the Medical Device Innovation Initiative, are currently under way.

**Study Results**

We identified thirty-five new oncology drugs that were approved by either the FDA or the EMA in the period 2003–10 (Exhibit 1). All of the drugs that were approved by both regulatory agencies were available to patients in the United States first. There were two reasons for this difference in the timing of approvals. First, we found that pharmaceutical companies typically submit their clinical findings to the FDA prior to submitting them to the EMA. Second, we found that the FDA consistently took less time than the EMA to review a new oncology medicine. We also found that the FDA approved more oncology drugs and biologics in this period than the EMA did.

Of the thirty-five products we investigated, the FDA approved thirty-two. For this subset, the median time between the submission date and the approval date was 182 days, and twenty products were approved within 184 days. Only three of the thirty-two took more than a year to receive approval.

The EMA did not approve nine of the thirty-two products that the FDA approved in this period. Although several of these products were in development in Europe at the time of our study, marketing authorization applications for two—Zolinza, a new drug to treat a type of lymphoma (cutaneous T-cell lymphoma), and Ixempra, for advanced breast cancer—were withdrawn during the EMA review process because of potential safety concerns.

The EMA approved twenty-six of the thirty-five products identified in our analysis. For this subset, the median time between the submission date and the EMA’s issuance of a positive opinion was 350 days. As noted above, three of these products have not been approved by FDA: Ceplene, Mepact, and Yondelis, aimed at acute myeloid leukemia, bone cancer, and advanced soft tissue sarcoma, respectively.
of Ceplene in the European Union was granted only after a secondary review cycle under exceptional circumstances. For both Mepact and Yondelis, the FDA decided against approval after advisory committees voted that these drugs had not demonstrated benefits that would outweigh their probable risks.

Exhibit 2 shows the review times for the twenty-three new oncology drugs that have been approved by both agencies since 2003. Of these, the EMA had a faster review process for only three: Treanda, Tasigna, and Firmagon, which target chronic lymphocytic leukemia, chronic myelogenous leukemia, and prostate cancer, respectively. In the case of Treanda, however, the product was approved in the United States before it was submitted to the EMA. Furthermore, because of the delay between positive EMA opinions and the European Commission’s adoptions of those opinion, Tasigna and Firmagon were still on the market in the United States before they were in Europe. Therefore, all twenty-three of the products approved by both agencies were available to US patients before...
European patients.

Using an unpaired t-test, we determined that this delay in time to market was statistically significant. The median delay was 238 days, and the mean delay was 138 days (95% confidence interval: 89, 187) in favor of the FDA.

Discussion

Cancer is arguably the most feared disease, or set of diseases, facing humanity. The symptoms of cancer can be severe and debilitating, and a cancer diagnosis is often perceived as a death sentence. Although there are some risk factors that predispose people for particular cancers, cancer can strike anyone at any time. Given that the lifetime risk of developing cancer is 30–50 percent, even those without cancer probably have close friends or relatives who have battled or succumbed to the disease.

Many cancers can be cured surgically, and some can be cured with radiation and chemotherapy. However, there is no curative therapy for most metastatic cancers—that is, a cancer that starts in one part of the body and spreads to another—and often not even a therapy that extends the patient’s life. This unmet medical need has made cancer a focus of the public’s evaluation of the process and regulation of drug development. The media frequently use images of dying cancer patients desperately waiting for FDA-approved therapies to invoke public ire at the time-consuming nature of this process, and particularly how long the FDA review takes.

Contrary to repeated public assertions, we found that new oncology medicines are consistently available in the United States before they are in Europe, and they are more likely to be approved by the FDA than by the EMA. Moreover, the median time for approval in the United States was just six months.

INITIAL AND SUPPLEMENTARY APPROVALS Our analysis was specifically limited to initial approvals of drugs. However, supplemental approvals for secondary uses constitute a sizable proportion of oncology drug approvals and are a major route of advancing cancer care.

Although an analysis of supplementary approvals of oncology medicines in Europe and the United States could reveal a trend that differs from what we found with initial approvals, the availability of new anticancer drugs—and hence, initial approvals—are of primary concern. After all, once drugs gain initial approval, they can also be used for off-label indications, as is commonly the case in oncology. The practice of off-label drug use can include using a drug to treat a clinical condition or patient population other than the one for which the drug was approved. The National Comprehensive Cancer Network, an alliance of twenty-one leading cancer centers in the United States, estimated in 2004 that 50–75 percent of all prescriptions for cancer therapies were off-label.22

Because it is not feasible to test every new drug against multiple cancers, particularly rare tumors, Medicare is required to cover off-label cancer therapies that are recommended in approved drug compendiums.23 Therefore, although the rate at which critical new uses are added to labeling is important and will be a focus of future study, the initial approval of new drugs and biologics in the field of oncology serves as a critical market entry point.

EXPEDITED REVIEWS The FDA is often accused of being slow to approve oncology drugs. However, critics have not provided specifics, and our study plainly shows that such assertions are unwarranted. The rapid approval of oncology drugs is not accidental, nor is it surprising. The FDA has long sought to conduct more rapid reviews of drugs with greater therapeutic potential, particularly anticancer drugs.24

Oncology drug development is distinctive in
The rapid approval of oncology drugs is not accidental, nor is it surprising.

that anticancer drugs and biologics are much more likely than drugs in other therapeutic areas to be given priority review ratings or to take advantage of accelerated review mechanisms. For example, Joseph DiMasi and Henry Grabowski found that in the period 1990–2005, 71 percent of oncology drugs received a priority review designation, and 47 percent received accelerated approval, compared to 40 percent and 13 percent, respectively, for all other drug classes. A priority review designation is intended for drugs that are expected to offer major advances in treatment or to provide a treatment for a condition that has no adequate therapy. This designation reduces the expected FDA review time for a drug: The goal for completing a priority review is only six months, as opposed to the ten-month goal for a standard review. Accelerated approval allows the FDA to approve a drug based not on clinical benefits but on surrogate endpoints considered likely to predict those benefits—for example, tumor shrinkage may be considered likely to predict longer survival.

The hope is that these advantages will offset the inherent difficulties of conducting clinical trials in oncology. One challenge is the slow acquisition of patients for trials, a phenomenon with many contributing factors—such as patients’ or physicians’ lack of information about trials, patients’ fear of receiving placebo or a poor treatment, the rarity of some cancers, and confounding factors that may make a patient ineligible for a trial. A second challenge is the particularly long times needed to establish a drug’s efficacy, in part because of the slow acquisition of patients and also the need to measure survival over a period of years. In making these advantages available, the FDA recognizes the serious unmet medical need that continues to exist in the field of cancer. Similar expedited review mechanisms exist in Europe and are frequently used there to designate oncology medicines as a priority.

SPEED VERSUS SAFETY In contrast to those who criticize the FDA for slow drug reviews, others believe that the agency approves applica-

ions too quickly, sacrificing safety for speed and quality for quantity. Indeed, the balance between speeding treatments to critically ill patients and ensuring that those treatments are safe is a delicate one.

Increased review speed has been associated in some studies with increases in serious adverse drug reactions. Other studies have determined that this association disappears when one controls for factors such as the novelty of the mechanism of a new drug and drugs approved with anticipated risks that are expressed in the form of so-called black-box warnings—a warning in the labeling, in which the FDA describes a known serious risk. Although such factors are often applicable to anticancer drugs and biologics, the vast majority of anticancer drugs have good track records for safety.

However, agencies such as the FDA and the EMA recognize the efficiency to be gained by harmonizing drug development around the world. Also, national governments appreciate the need for additional investment in postmarketing safety surveillance and health information technology. As a result of these initiatives to improve both safety and efficiency, drug lags between Europe and the United States will probably decrease.

THE PRESCRIPTION DRUG USER FEE ACT Over the past two decades, the pace at which the FDA reviews drugs has improved considerably, and review times have been shortened. The changes are in large part due to the Prescription Drug User Fee Act of 1992. The law was intended to address a major backlog in new drug applications at the FDA. It gave the agency authority to collect fees from companies that produce certain drugs and biological products, both when the companies submit an application to have a new product approved, and for each drug that they have on the market. This money is added to the budget that Congress appropriates for the FDA; in exchange, the FDA accepts overall performance goals, which emphasize review timeliness as well as other measures. This set of policy initiatives, as well as the establishment of programs such as accelerated approval, has helped alleviate concerns that potentially life-saving therapies were encountering unnecessary delays in the review process, which prevented patients from taking advantage of them.

Subsequent reauthorizations of the Prescription Drug User Fee Act, which occur every five years, have given the FDA new authorities and increased the user fees to meet other needs of the agency. But it is widely agreed by experts in drug regulatory matters—including staff members of the FDA—that the science of developing new tools, standards, and approaches to assess the
safety, efficacy, quality, and performance of FDA-regulated products must advance considerably. For example, as the FDA itself has noted, the vast trove of data stored at the FDA must be transformed into a harmonized format and organized in a common database so that it can be queried by topic and analyzed to address key questions. This, in turn, will require investments in informatics hardware and software and the development of standardized data models for relational databases and scientific computing. With such a common platform in place, scientists could take advantage of existing historical data as well as new data to make better decisions in the context of regulatory review and oversight.

However, user fees are not sufficient to support such regulatory scientific advancement, nor are they an appropriate source of funds for that purpose. Instead, strong public support and additional congressional appropriations are required to move the FDA forward.

As the next reauthorization of the Prescription Drug User Fee Act, scheduled for 2012, draws closer, it is important to examine critically the successes and failures of the current regulatory process. Areas needing improvement must be identified, and appropriate measures devised. Given our findings—that the FDA has approved more new oncology drugs than the EMA has, and that it has approved these drugs more quickly—increasing the speed of drug review times might not be as high a priority as achieving other objectives in advancing regulatory science.

Conclusion

Although our results are applicable only to oncology medicines, they are consistent with FDA Commissioner Margaret Hamburg’s comment in a letter to the editor of the Washington Post that the FDA’s review times of all new drugs are typically shorter than those of the EMA.33 Our results are also consistent with other studies that indicate that the lack of new oncology medicines is due not to slow review processes, but rather to difficulties in carrying out clinical trials in the field of oncology.

Innovative trial designs and development pathways are needed to translate advances in basic science into effective therapeutic options. One example would be permitting adaptive clinical trials—which would allow modifications to be made to an ongoing clinical trial, such as redirecting patients to different trial arms based on accumulating results and therefore increasing the chance of response.

Another example would be creating a regulatory pathway that would allow for simultaneous development of drugs and diagnostics. Such a combined pathway could allow for simultaneous regulatory approval of a diagnostic test to ascertain that a patient had a particular type of cancer with a specific genetic profile, and of a new drug expressly targeted for that type of cancer. These types of drugs and diagnostics already exist, and there could be hundreds if not thousands more of them in the future.

Contrary to the assertions of many critics, then, this article makes clear that the FDA should be congratulated for its swift review of new oncology medicines. However, science at all levels—basic science in the lab and regulatory science at the FDA—must continue to advance for the good of patients. As a result, continued financial support, in the form of user fees and increased appropriations, will be crucial for the agency to keep pace with current scientific discovery—and to maintain and enhance the agency’s critical role of bringing new medicines from the stages of discovery into the clinic and ultimately improving the lives of patients. ■

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11 Makower J, Meir A, Denend L. FDA impact on US medical technology innovation: a survey of over 200 medical technology companies. [place unknown]: Josh Makower; 2010 Nov.


