PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2013 THROUGH 2017

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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 Resubmissions[1]

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:

SUBMISSION COHORT	STANDARD	PRIORITY
NME NDAs and original BLAs	90% in 10 months of the 60 day filing date	90% in 6 months of the 60 day filing date
Non NME NDAs	90% in 10 months of the receipt date	90% in 6 months of the receipt date
Class 1 Resubmissions	90% in 2 months of the receipt date	90% in 2 months of the receipt date
Class 2 Resubmissions	90% in 6 months of the receipt date	90% in 6 months of the receipt date
Original Efficacy Supplements	90% in 10 months of the receipt date	90% in 6 months of the receipt date
Class 1 Resubmitted Efficacy Supplements	90% in 2 months of the receipt date	90% in 2 months of the receipt date
Class 2 Resubmitted Efficacy Supplements	90% in 6 months of the receipt date	90% in 6 months of the receipt date

	PRIOR APPROVAL	ALL OTHER
Manufacturing Supplements	90% in 4 months of the receipt date	90% in 6 months of the receipt date

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.[2] 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.

[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, XIA, XIB 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 web site 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.

4. Assessment of the impact of electronic submissions and data standards on the efficiency and other performance attributes of the human drug review process beginning in FY 2015.

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.