said, the greenest vessel on the Great Lakes. What a great idea, I thought. But it turns out it isn't even close to being realistic.

Today there are few suppliers of liquefied natural gas in the area. There are no shipyards in the United States that are qualified to convert passenger vessels to run on liquefied natural gas. And it would take close to $50 million just to develop the infrastructure on the land needed to transport fuel to the dock for the Badger.

One day, all the boats on Great Lakes might be powered by natural gas, but that isn't a realistic plan right now or within the next few years. It is just another delaying tactic from the owners of the S.S. Badger. These owners were given a deadline to convert the ship's fuel or dispose of the ash in a responsible way 5 years ago. The Badger has blatantly avoided complying with these EPA regulations.

There has been an effort in the House of Representatives to provide a special exemption for this filthy boat on Lake Michigan forever. They want them declared some sort of a national historic monument or something and say that it shouldn't be governed by environmental regulations.

These are Congressmen whose districts are on Lake Michigan. I have to ask them, what do you think about the lake and its future, when this boat is responsible for six times the solid waste of all the other ships that use Lake Michigan in commerce on an annual basis? Six times. That to me is a horrible thing to continue.

They have had plenty of time to clean up their act and they failed. Now we have to get serious. I am hoping the EPA decides very quickly that it is time to end the coal-fired ferry tradition of the S.S. Badger. This is a vessel that generates and dumps 5 tons of coal ash laced with mercury, lead, and arsenic into Lake Michigan every single day. This great lake cannot take any more toxic dumping, no matter how historic or quaint the source may be.

## LETTERS FROM THE SECRETARY OF HEALTH AND HUMAN SERVICES RE: MEDICAL DEVICE USER FEE PROGRAM

Mr. HARKIN. Mr. President, I ask unanimous consent that, pursuant to Public Law 112–144, the Food and Drug Administration Safety and Innovation Act, the following letters from the Secretary of Health and Human Services to the Chairman of the Committee on Health, Education, Labor, and Pensions of the Senate and the Chairman of the Committee on Energy and Commerce of the House of Representatives be printed into the RECORD.

There being no objection, the material was ordered to be printed in the RECORD, as follows:

### MDUFA PERFORMANCE GOALS AND PROCEDURES

The performance goals and procedures agreed to by the Center for Devices and Radiological Health (CDRH) and the Center for Biologics Evaluation and Research (CBER) of the United States Food and Drug Administration (''FDA'' or ''the Agency'') for the medical device user fee program in the Medical Device User Fee Amendments of 2012, are summarized below.

FDA and the industry are committed to protecting and promoting public health by providing timely access to safe and effective medical devices. Nothing in this letter precludes the Agency from protecting the public health by exercising its authority to provide a reasonable assurance of the safety and effectiveness of medical devices. Both FDA and the industry are committed to the spirit and intent of the goals described in this letter.

#### I. PROCESS IMPROVEMENTS

*A. Pre-Submissions*

FDA will institute a structured process for managing Pre-Submissions. Pre-Submissions subject to this process are defined in Section VIII, Definitions and Explanations of Terms. The Agency will continue to improve the Pre-Submission process as resources permit, but not to the detriment of meeting the quantitative review timelines and statutory obligations. FDA will issue a draft guidance document and final guidance document on Pre-Submissions.

Upon receipt of a Pre-Submission that requests feedback through a meeting or teleconference, FDA intends to schedule the meeting or teleconference to occur within a timely manner. In the Pre-Submission, the applicant will provide at least three suggested dates and times when the applicant is available to meet.

It is FDA's intent that within 14 calendar days of receipt of a request for a meeting or teleconference, FDA will determine if the request meets the definition of a Pre-Submission, and will inform the applicant if it does not meet the definition. FDA will also determine if the request necessitates more than one meeting or teleconference. A determination that the request does not meet the definition of a Pre-Submission will require the concurrence of the branch chief and the reason for this determination will be provided to the applicant. If the request meets the definition of a Pre-Submission, FDA and the applicant will set a mutually agreeable time and date for the meeting.

At least 3 business days prior to the meeting, FDA will provide initial feedback to the applicant by email, which will include: written responses to the applicant's questions; FDA's suggestions for additional topics for the meeting or teleconference, if applicable; or, a combination of both. If all of the applicant's questions are addressed through written responses, to the applicant's satisfaction, FDA and the applicant can agree that a meeting or teleconference is no longer necessary and the written responses provided by email will be considered the final written feedback to the Pre-Submission.

Meetings and teleconferences related to Pre-Submission will generally be limited to 1 hour. A longer meeting or teleconference time can be scheduled by mutual agreement by the applicant and FDA.

Applicants will be responsible for developing draft minutes for a Pre-Submission meeting or teleconference, and provide the draft minutes via email to FDA within 15 calendar days of the meeting. The minutes will summarize the meeting discussions and include agreements and any action items. FDA will provide any edits to the draft minutes to the applicant via email within a timely manner. These minutes will become final 15 calendar days after the applicant receives FDA's edits, unless the applicant indicates that there is a disagreement with how a significant issue or action item has been documented. In this case, within a timely manner, the applicant and FDA will conduct a teleconference to discuss that issue with FDA. At the conclusion of that teleconference, within a timely manner FDA will finalize the minutes either to reflect the resolution of the issue or note that this issue remains a point of disagreement.

FDA intends that feedback the Agency provides in a Pre-Submission will not change, provided that the information submitted in a future investigational device exemption (IDE) or marketing application is consistent with that provided in the Pre-Submission and that the data in the future submission do not raise any important new issues materially affecting safety or effectiveness. Modifications to FDA's feedback will be limited to situations in which FDA concludes that the feedback does not adequately address important new issues materially relevant to a determination of safety or effectiveness. Such a determination will be supported by the appropriate management concurrence consistent with applicable guidance and SOPs.

*B. Submission Acceptance Criteria*

To facilitate a more efficient and timely review process, FDA will implement revised submission acceptance criteria. The Agency will publish guidance outlining electronic copy of submissions (e-Copy) and objective criteria for revised ''refuse to accept/refuse to file'' checklists. FDA will publish draft and final guidance prior to implementation.

*C. Interactive Review*

The Agency will continue to incorporate an interactive review process to provide for, and encourage, informal communication between FDA and applicants to facilitate timely completion of the review process based on accurate and complete information. Interactive review entails responsibilities for both FDA and applicants. As described in the guidance document, *Interactive Review for Medical Device Submissions: 510(k)s, Original [Premarket Approvals] PMAs, PMA Supplements, Original BLAs, and BLA Supplements*, both FDA and industry believe that an interactive review process for these types of premarket medical device submissions should help facilitate timely completion of the review based on accurate and complete information. Interactive review is intended to facilitate the efficient and timely review and evaluation by FDA of premarket submissions. The interactive review process contemplates increased informal interaction between FDA and applicants, including the exchange of scientific and regulatory information.

*D. Guidance Document Development*

FDA will apply user fee revenues to supplement the improvement of the process of developing, reviewing, tracking, issuing, and updating guidance documents. The Agency will continue to develop guidance documents and improve the Guidance Development process as resources permit, but not to the detriment of meeting the quantitative review timelines and statutory obligations.

FDA will update its website in a timely manner to reflect the following:

1. The Agency's review of previously published device guidance documents, including the deletion of guidance documents that no longer represent the Agency's interpretation of, or policy on, a regulatory issue, and notation of guidance documents that are under review by the Agency;

2. A list of prioritized device guidance documents (an ''A-list'') that the Agency intends to publish within 12 months of the date this list is published each fiscal year; and

3. A list of device guidance documents (a ''B-list'') that the Agency intends to publish, as the Agency's guidance-development resources permit each fiscal year.

The Agency will establish a process allowing stakeholders an opportunity to:

1. Provide meaningful comments and/or propose draft language for proposed guidance topics in the ''A'' and ''B'' lists.

2. Provide suggestions for new or different guidance documents; and

3. Comment on the relative priority of topics for guidance.

*E. Third Party Review*

The Agency will continue to support the third party review program and agrees to work with interested parties to strengthen and improve the current program while also establishing new procedures to improve transparency. The Agency will continue to improve the third party review program as resources permit, but not to the detriment of meeting the quantitative review timelines and statutory obligations.

*F. Patient Safety and Risk Tolerance*

FDA will fully implement final guidance on the factors to consider when making benefit-risk determinations in medical device premarket review. This guidance will focus on factors to consider in the premarket review process, including patient tolerance for risk, magnitude of the benefit, and the availability of other treatments or diagnostic tests.

Over the period of MDUFA III, FDA will meet with patient groups to better understand and characterize the patient perspective on disease severity or unmet medical need.

In addition, FDA will increase its utilization of FDA's Patient Representatives as Special Government Employee consultants to CDRH to provide patients' views early in the medical product development process and ensure those perspectives are considered in regulatory discussions. Applicable procedures governing conflicts of interest and confidentiality of proprietary information will be utilized for these consultations.

*G. Low Risk Medical Device Exemptions*

By the end of FY 2013, FDA will propose additional low risk medical devices to exempt from premarket notification. Within two years of such proposal, FDA intends to issue a final rule exempting additional low risk medical devices from premarket notification.

*H. Emerging Diagnostics*

FDA will work with industry to develop a transitional In Vitro Diagnostics (IVD) approach for the regulation of emerging diagnostics.

II. REVIEW PERFORMANCE GOALS—FISCAL YEARS 2013 THROUGH 2017 AS APPLIED TO RECEIPT COHORTS

The overall objective of the review performance goals stated herein is to assure more timely access to safe and effective medical devices.

*A. Original Premarket Approval (PMA), Panel-Track Supplements, and Premarket Report Applications*

The performance goals in this section apply to all Original Premarket Approval, Panel-Track Supplements, and Premarket Report Applications, including those that are accepted for priority review (previously referred to as expedited).

FDA will communicate with the applicant regarding whether the application has been accepted for filing review within 15 calendar days of receipt of the application. This communication consists of a fax, email, or other written communication that (a) identifies the reviewer assigned to the submission, and (b) acknowledges acceptance/rejection of the submission based upon the review of the submission against objective acceptance criteria outlined in a published guidance document.

If the application is not accepted for filing review, FDA will notify the applicant of those items necessary for the application to be considered accepted for filing review.

For those applications that are accepted for filing review, FDA will communicate the filing status within 45 calendar days of receipt of the application.

For those applications that are not filed, FDA will communicate to the applicant the specific reasons for rejection and the information necessary for filing.

If the application is filed, FDA will communicate with the applicant through a Substantive Interaction within 90 calendar days of the filing date of the application for: 65% of submissions received in FY 2013; 75% of submissions received in FY 2014; 85% of submissions received in FY 2015; and 95% of submissions received in FY 2016 through FY 2017.

When FDA issues a major deficiency letter, that letter will be based upon a complete review of the application and will include all deficiencies. Any subsequent deficiencies will be limited to issues raised by the information provided by the applicant in its response, unless FDA concludes that the initial deficiencies identified do not adequately address important new issues materially relevant to a determination of safety or effectiveness. Such a determination will be supported by the appropriate management concurrence consistent with applicable guidance and SOPs. Issues related to post-approval studies, if applicable, and revisions to draft labeling will typically be addressed through interactive review once major deficiencies have been adequately addressed.

For submissions that do not require Advisory Committee input, FDA will issue a MDUFA decision within 180 FDA Days for: 70% of submissions received in FY 2013; 80% of submissions received in FY 2014 and FY 2015; and 90% of submissions received in FY 2016 and FY 2017.

For submissions that require Advisory Committee input, FDA will issue a MDUFA decision within 320 FDA Days for: 50% of submissions received in FY 2013; 70% of submissions received in FY 2014; 80% of submissions received in FY 2015 and FY 2016; and 90% of submissions received in FY 2017.

If in any one fiscal year, the number of submissions that require Advisory Committee input is less than 10, then it is acceptable to combine such submissions with the submissions for the following year(s) in order to form a cohort of 10 or more submissions, upon which the combined years' submissions will be subject to the performance goal for the fiscal year in question. If the number of submissions that require Advisory Committee input is less than 10 for FY 2017, it is acceptable to combine such submissions with the submissions in the prior year in order to form a cohort of 10 or more submissions; in such cases, FDA will be held to the FY 2017 performance goal for the combined years' submissions.

To facilitate an efficient review prior to the Substantive Interaction, and to incentivize submission of a complete application, submission of an unsolicited major amendment prior to the Substantive Interaction extends the FDA Day review clock by the number of FDA Days that have elapsed. Submission of an unsolicited major amendment after the Substantive Interaction extends the FDA Day goal by the number of FDA Days equal to 75% of the difference between the filing date and the date of receipt of the amendment.

For all PMA submissions that do not reach a MDUFA decision by 20 days after the applicable FDA Day goal, FDA will provide written feedback to the applicant to be discussed in a meeting or teleconference, including all outstanding issues with the application preventing FDA from reaching a decision. The information provided will reflect appropriate management input and approval, and will include action items for FDA and/or the applicant, as appropriate, with an estimated date of completion for each party to complete their respective tasks. Issues should be resolved through interactive review. If all of the outstanding issues are adequately presented through written correspondence, FDA and the applicant can agree that a meeting or teleconference is not necessary.

In addition, information about submissions that miss the FDA Day goal will be provided as part of FDA's Performance Reports, as described in Section VI.

*B. 180-Day PMA Supplements*

FDA will communicate with the applicant through a Substantive Interaction within 90 calendar days of receipt of the submission for: 65% of submissions received in FY 2013; 75% of submissions received in FY 2014; 85% of submissions received in FY 2015; and 95% of submissions received in FY 2016 through FY 2017.

FDA will issue a MDUFA decision within 180 FDA Days for: 85% of submissions received in FY 2013; 90% of submissions received in FY 2014 and FY 2015; and 95% of submissions received in FY 2016 through FY 2017.

*C. Real-Time PMA Supplements*

FDA will issue a MDUFA decision within 90 FDA Days for: 90% of submissions received in FY 2013 and FY 2014; and 95% of submissions received in FY 2015 through FY 2017.

*D. 510(k) Submissions*

FDA will communicate with the applicant regarding whether the submission has been accepted for review within 15 calendar days of receipt of the submission. For those submissions that are not accepted for review, FDA will notify the applicant of those items necessary for the submission to be considered accepted.

This communication includes a fax, email, or other written communication that a) identifies the reviewer assigned to the submission, and b) acknowledges acceptance/rejection of the submission based upon the review of the submission against objective acceptance criteria outlined in a published guidance document. This communication represents a preliminary review of the submission and is not indicative of deficiencies that may be identified later in the review cycle.

FDA will communicate with the applicant through a Substantive Interaction within 60 calendar days of receipt of the submission for: 65% of submissions received in FY 2013; 75% of submissions received in FY 2014; 85% of submissions received in FY 2015; and 95% of submissions received in FY 2016 through FY 2017.

Deficiencies identified in a Substantive Interaction, such as a telephone/email hold or Additional Information Letter, will be based upon a complete review of the submission and will include all deficiencies. Any subsequent deficiencies will be limited to issues raised by the information provided by the applicant in its response, unless FDA concludes that the initial deficiencies identified do not adequately address important new issues materially relevant to a determination of substantial equivalence. Such a determination will be supported by the appropriate management concurrence consistent with applicable guidance and SOPs.

For submissions received in FY 2013, FDA will issue a MDUFA decision for 91% of 510(k) submissions within 90 FDA Days.

For submissions received in FY 2014, FDA will issue a MDUFA decision for 93% of 510(k) submissions within 90 FDA Days.

For submissions received in FY 2015 through FY 2017, FDA will issue a MDUFA decision for 95% of 510(k) submissions within 90 FDA Days.

For all 510(k) submissions that do not reach a MDUFA decision within 100 FDA

Days, FDA will provide written feedback to the applicant to be discussed in a meeting or teleconference, including all outstanding issues with the application preventing FDA from reaching a decision. The information provided will reflect appropriate management input and approval, and will include action items for FDA and/or the applicant, as appropriate, with an estimated date of completion for each party to complete their respective tasks. Issues should be resolved through interactive review. If all of the outstanding issues are adequately presented through written correspondence, FDA and the applicant can agree that a meeting or teleconference is not necessary.

In addition, information about submissions that miss the FDA Day goal will be provided as part of FDA's Performance Reports, as described in Section VI.

*E. Clinical Laboratory Improvement Amendments (CLIA) Waiver by Application*

FDA will engage in a Substantive Interaction with the applicant within 90 days for 95% of the applications.

During the pre-submission process, if the applicant informs FDA that it plans to submit a dual submission (510(k) and CLIA Waiver application), FDA will issue a decision for 90% of such applications within 210 FDA days.

For ''CLIA Waiver by application'' submissions FDA will issue a MDUFA decision for 95% of the applications that do not require Advisory Committee input within 180 FDA days.

For ''CLIA Waiver by application'' submissions FDA will issue a MDUFA decision for 95% of the applications that require Advisory Committee input within 330 FDA days.

To provide greater transparency, FDA will issue guidance regarding review and management expectations throughout the entire submission process.

*F. Original Biologics Licensing Applications (BLAs)*

FDA will review and act on standard original BLA submissions within 10 months of receipt for 90% of submissions.

FDA will review and act on priority original BLA submissions within 6 months of receipt for 90% of submissions.

*G. BLA Efficacy Supplements*

FDA will review and act on standard BLA efficacy supplement submissions within 10 months of receipt for 90% of submissions.

FDA will review and act on priority BLA efficacy supplement submissions within 6 months of receipt for 90% of submissions.

*H. Original BLA and BLA Efficacy Supplement Resubmissions*

FDA will review and act on Class 1 original BLA and BLA efficacy supplement resubmissions within 2 months of receipt for 90% of submissions.

FDA will review and act on Class 2 original BLA and BLA efficacy supplement resubmissions within 6 months of receipt for 90% of submissions.

*I. BLA Manufacturing Supplements Requiring Prior Approval*

FDA will review and act on BLA manufacturing supplements requiring prior approval within 4 months of receipt for 90% of submissions.

III. SHARED OUTCOME GOALS

The program and initiatives outlined in this document are predicated on significant interaction between the Agency and applicants. FDA and representatives of the medical device industry agree that the process improvements outlined in this letter, when implemented by all parties as intended, should reduce the average Total Time to Decision for PMA applications and 510(k) submissions, provided that the total funding of the device review program adheres to the assumptions underlying this agreement. FDA and applicants share the responsibility for achieving this objective of reducing the average Total Time to Decision, while maintaining standards for safety and effectiveness. Success of this program will require the cooperation and dedicated efforts of FDA and applicants to reduce their respective portions of the total time to decision.

FDA will be reporting total time performance quarterly as described in Section VI. FDA and industry will participate in the independent assessment of progress toward this outcome, as described in Section V above. As appropriate, key findings and recommendations from this assessment will be implemented by FDA.

*A. PMA*

Beginning in Fiscal Year 2013, FDA will report on an annual basis the average Total Time to Decision as defined in Section VIII.G for the three most recent closed receipt cohorts. For submissions received beginning in Fiscal Year 2013, the average Total Time to Decision goal for FDA and industry is 395 calendar days. For submissions received beginning in Fiscal Year 2015, the average Total Time to Decision goal for FDA and industry is 390 calendar days. For submissions received beginning in Fiscal Year 2017, the average Total Time to Decision goal for FDA and industry is 385 calendar days.

*B. 510(k)*

Beginning in Fiscal Year 2013, FDA will report on an annual basis the average Total Time to Decision as defined in Section VIII.G for the most recent closed receipt cohort. For submissions received beginning in Fiscal Year 2013, the average Total Time to Decision goal for FDA and industry is 135 calendar days. For submissions received beginning in FY 2015, the average Total Time to Decision goal for FDA and industry is 130 calendar days. For submissions received beginning in FY 2017, the average Total Time to Decision goal for FDA and industry is 124 calendar days.

IV. INFRASTRUCTURE

*A. Scientific and Regulatory Review Capacity*

The Agency will apply user fee revenues to reduce the ratio of review staff to front line supervisors in the Pre-Market review program and to enhance and supplement scientific review capacity by hiring device application reviewers and leveraging external experts needed to assist with the review of device applications.

The Agency will seek to obtain streamlined hiring authority for all MDUFA-related positions prior to and during the MDUFA III period.

During MDUFA III, FDA will also work with industry to benchmark best practices for retaining employees (both financial and non-financial).

*B. Training*

Prior to the commencement of MDUFA III, CDRH will implement its Reviewer Certification Program. FDA commits to holding a minimum of two medical device Vendor Days each year.

CDRH will apply user fee revenues to supplement the following training programs:

1) Management training for Branch Chiefs and Division Directors.

2) MDUFA III Training Program for all staff.

3) Reviewer Certification Program for new CDRH reviewers. FDA will publish the curriculum of this program and other course offerings. FDA will consider comments from stakeholders when making updates to courses and determining course offerings.

4) Specialized training to provide continuous learning for all staff.

*C. Tracking System*

FDA will continue efforts to improve its IT systems with a future expectation of facilitating availability of real-time status information for submissions.

V. INDEPENDENT ASSESSMENT OF REVIEW PROCESS MANAGEMENT

FDA and the device industry will participate in a comprehensive assessment of the process for the review of device applications. The assessment will include consultation with both FDA and industry. The assessment shall be conducted in two phases under contract to FDA by a private, independent consulting firm capable of performing the technical analysis, management assessment, and program evaluation tasks required to address the assessment scope described below. For Phase 1, FDA will award the contract no later than the end of the second quarter of FY13. Findings on high-priority recommendations (i.e., those likely to have a significant impact on review times) will be published within six months of award; final comprehensive findings and recommendations will be published within 1 year of contract award. FDA will publish an implementation plan within 6 months of receipt of each set of recommendations. For Phase 2 of the independent assessment, the contractor will evaluate the implementation of recommendations and publish a written assessment no later than February 1, 2016.

The assessment will address FDA's premarket review process using an assessment framework that draws from appropriate quality system standards, including, but not limited to, management responsibility, document controls and records management, and corrective and preventive action.

The scope of the assessment will include, but not be limited to, the following areas:

1. Identification of process improvements and best practices for conducting predictable, efficient, and consistent premarket reviews that meet regulatory review standards.

2. Analysis of elements of the review process (including the Pre-Submission process, IDE, 510(k) and PMA reviews) that consume or save time to facilitate a more efficient process. This includes analysis of root causes for inefficiencies that may affect review performance and total time to decision. This will also include recommended actions to correct any failures to meet MDUFA goals. Analysis of the review process will include the impact of combination products, companion diagnostics products, and laboratory developed tests on the review process.

3. Assessment of FDA methods and controls for collecting and reporting information on premarket review process resource use and performance.

4. Assessment of effectiveness of FDA's Reviewer Training Program implementation.

5. Recommendations for ongoing periodic assessments and any additional, more detailed or focused assessments.

FDA will incorporate findings and recommendations, as appropriate, into its management of the premarket review program. FDA will analyze the recommendations for improvement opportunities identified in the assessment, develop and implement a corrective action plan, and assure its effectiveness. FDA also will incorporate the results of the assessment into a Good Review Management Practices (GRMP) guidance document. FDA's implementation of the GRMP guidance will include initial and ongoing training of FDA staff, and periodic audits of compliance with the guidance.

VI. PERFORMANCE REPORTS

The Agency will report its progress toward meeting the goals described in this letter, as

follows. If, throughout the course of MDUFA III, the Agency and Industry agree that a different format or different metrics would be more useful, the reporting will be modified accordingly as per the agreement of both FDA and Industry.

1. Quarterly reporting at the CDRH Division level/CBER Center level (in recognition of the significantly smaller number of submissions reviewed at CBER):

1.1. For 510(k) submissions, reporting will include:

i. Average and quintiles of the number of calendar days to Substantive Interaction

ii. Average, and quintiles of the number of FDA Days, Industry Days, and Total Days to a MDUFA decision

iii. Average number of review cycles.

iv. Rate of submissions not accepted for review

1.2. For PMA submissions, reporting will include:

i. Average and quintiles of the number of calendar days to Substantive Interaction for Original PMA, Panel-Track PMA Supplement, and Premarket Report Submissions

ii. Average and quintiles of the of FDA Days, Industry Days, and Total Days to a MDUFA decision

iii. Rate of applications not accepted for filing review, and rate of applications not filed

1.3. For Pre-Submissions, reporting will include:

i. Number of all qualified Pre-Submissions received

ii. Average and quintiles of the number of calendar days from submission to meeting or teleconference (if necessary)

iii. Number of Pre-Submissions that require a meeting

1.4. For IDE applications, reporting will include:

i. Number of original IDEs received

ii. Average number of amendments prior to approval or conditional approval of the IDE (this information will be provided beginning no later than the quarter that starts 10/1/2013)

2. CDRH will report quarterly, and CBER will report annually, the following data at the Center level:

2.1. Rate of NSE decisions for 510(k) submissions

2.2. Rate of withdrawals for 510(k) and PMA submissions

2.3. Rate of Not Approvable decisions for PMA submissions

2.4. Key product areas or other issues that FDA identifies as noteworthy because of a potential effect on performance, including significant rates of Additional Information requests

2.5. Specific topic or product area as it relates to performance goals, agreed upon at the previous meeting

2.6. Number of submissions that missed the goals and the total number of elapsed calendar days broken down into FDA days and industry days

2.7. Newly released draft and final guidance documents, and status of other priority guidance documents

2.8. Agency level summary of fee collections

2.9. Independent assessment implementation plan status

2.10. Results of independent assessment and subsequent periodic audits and progress toward implementation of the recommendations and any corrective action

2.11. Number of discretionary fee waivers or reductions granted by type of submission

3. In addition, the Agency will provide the following information on an annual basis:

3.1. Qualitative and quantitative update on how funding is being used for the device review process, including the percentage of review time devoted to direct review of applications

3.2. How funding is being used to enhance scientific review capacity

3.3. The number of Premarket Report Submissions received

3.4. Summary information on training courses available to CDRH and CBER employees, including new reviewers, regarding device review and the percentage of applicable staff that have successfully completed each such course. CDRH will provide information concerning any revisions to the new reviewer training program curriculum.

3.5. Performance on the shared outcome goal for average Total Time to decision

3.6. For 510(k) submissions, reporting will include:

i. Number of submissions reviewed by a Third Party

ii. Number of Special Submissions

iii. Number of Traditional Submissions

iv. Average and number of days to Accept/Refuse to Accept

v. Number of Abbreviated Submissions

3.7. For PMA submissions, reporting will include the number of the following types of PMA submissions received:

i. Original PMAs

ii. Priority PMAs

iii. Premarket Reports

iv. Panel-Track PMA Supplement

v. PMA Modules

vi. 180-Day PMA Supplements

vii. Real-Time PMA Supplements

3.8. For De Novo Classification Petitions, reporting will include:

i. Number of submissions received

ii. Average number of calendar days to a MDUFA decision

3.9. For CLIA waiver applications, reporting will include:

i. Number of CLIA waiver applications received

ii. Average and quintiles of the number of calendar days to Substantive Interaction

iii. Average and quintiles of the number of FDA Days, Industry Days, and Total Days to a MDUFA decision and a discussion of any trends in the data

## VII. DISCRETIONARY WAIVER

The Agency will seek authority to grant discretionary fee waivers or reductions in the interest of public health. Notwithstanding any fee waivers or reductions granted by the Agency under this discretionary authority, FDA remains committed to meeting the goals described in this letter. Any submission subject to a fee waiver or reduction under this discretionary authority shall not be subject to the goals specified in this letter and shall be reviewed by the Agency as resources permit. This discretionary authority will expire at the end of MDUFA III.

## VIII. DEFINITIONS AND EXPLANATIONS OF TERMS

*A. Applicant*

Applicant means a person who makes any of the following submissions to FDA: an application for premarket approval under section 515; a premarket notification under section 510(k); an application for investigational device exemption under section 520(g); a Pre-Submission; a CLIA waiver application.

*B. Electronic Copy (e-Copy)*

An electronic copy is an exact duplicate of a paper submission, created and submitted on a CD, DVD, or in another electronic media format that FDA has agreed to accept, accompanied by a copy of the signed cover letter and the complete original paper submission. An electronic copy is not considered to be an electronic submission.

*C. FDA Days*

FDA Days are those calendar days when a submission is considered to be under review at the Agency for submissions that have been accepted (510(k)) or filed (PMA). FDA Days begin on the date of receipt of the submission or of the amendment to the submission that enables the submission to be accepted (510(k)) or filed (PMA).

*D. MDUFA Decisions*

*Original PMAs*: Decisions for Original PMAs are Approval, Approvable, Approvable Pending GMP Inspection, Not Approvable, Withdrawal, and Denial.

*180-Day PMA Supplements*: Decisions for 180-Day PMA Supplements include Approval, Approvable, and Not Approvable.

*Real-Time PMA Supplements:* Decisions for Real-Time PMA supplements include Approval, Approvable, and not Approvable.

*510(k)s:* Decisions for 510(k)s are substantially equivalent (SE) or not substantially equivalent (NSE).

Submissions placed on Application Integrity Program Hold will be removed from the MDUFA cohort.

*E. Pre-Submission*

A Pre-Submission includes a formal written request from an applicant for feedback from FDA which is provided in the form of a formal written response or, if the manufacturer chooses, a meeting or teleconference in which the feedback is documented in meeting minutes. A Pre-Submission meeting is a meeting or teleconference in which FDA provides its substantive feedback on the Pre-Submission.

A Pre-Submission provides the opportunity for an applicant to obtain FDA feedback prior to intended submission of an investigational device exemption or marketing application. The request must include specific questions regarding review issues relevant to a planned IDE or marketing application (e.g., questions regarding pre-clinical and clinical testing protocols or data requirements). A Pre-Submission is appropriate when FDA's feedback on specific questions is necessary to guide product development and/or application preparation.

The following forms of FDA feedback to applicants are not considered Pre-Submissions. However, if the requested feedback meets the criteria for a Pre-Submission, outlined above, FDA will contact the sponsor, and with the concurrence of the sponsor, may convert the request to a Pre-Submission.

General information requests initiated through the Division of Small Manufacturers, International and Consumer Assistance (DSMICA)

General questions regarding FDA policy or procedures

Meetings or teleconferences that are intended to be informational only, including, but not limited to, those intended to educate the review team on new device(s) with significant differences in technology from currently available devices, or to update FDA about ongoing or future product development, without a request for FDA feedback on specific questions related to a planned submission

Requests for clarification on technical guidance documents, especially where contact is recommended by FDA in the guidance document. However, the following requests will generally need to be submitted as a Pre-Submission in order to ensure appropriate input from multiple reviewers and management: recommendations for device types not specifically addressed in the guidance document; recommendations for nonclinical or clinical studies not addressed in the guidance document; requests to use an alternative means to address recommendations specified in a guidance document.

Phone calls or email messages to reviewers that can be readily answered based on a reviewer's experience and knowledge and do

not require the involvement of a broader number of FDA staff beyond the routine involvement of the reviewer's supervisor and more experienced mentors.

Interactions requested by either the applicant or FDA during the review of a marketing application (i.e., following submission of a marketing application, but prior to reaching an FDA Decision).

*F. Substantive Interaction*

Substantive Interaction is an email, letter, teleconference, video conference, fax, or other form of communication such as a request for Additional Information or Major Deficiency letters by FDA notifying the applicant of substantive deficiencies identified in initial submission review, or a communication stating that FDA has not identified any deficiencies in the initial submission review and any further minor deficiencies will be communicated through interactive review. An approval or clearance letter issued prior to the Substantive Interaction goal date will qualify as a Substantive Interaction.

If substantive issues warranting issuance of an Additional Information or Major Deficiency letter are not identified, interactive review should be used to resolve any minor issues and facilitate an FDA decision. In addition, interactive review will be used, where, in FDA's estimation, it leads to a more efficient review process during the initial review cycle (i.e., prior to a Substantive Interaction) to resolve minor issues such as revisions to administrative items (e.g., 510(k) Summary/Statement, Indications for Use statement, environmental impact assessment, financial disclosure statements); a more detailed device description; omitted engineering drawings; revisions to labeling; or clarification regarding nonclinical or clinical study methods or data.

Minor issues may still be included in an Additional Information or Major Deficiency letter where related to the resolution of the substantive issues (e.g., modification of the proposed Indications for Use may lead to revisions in labeling and administrative items), or if they were still unresolved following interactive review attempts. Both interactive review and Substantive Interactions will occur on the review clock except upon the issuance of an Additional Information or Major Deficiency Letter which stops the review clock.

*G. Total Time to Decision*

Total Time to Decision is the number of calendar days from the date of receipt of an accepted or filed submission to a MDUFA decision.

The average Total Time to Decision for 510(k) submissions is calculated as the trimmed mean of Total Times to Decision for 510(k) submissions within a closed cohort, excluding the highest 2% and the lowest 2% of values. A cohort is closed when 99% of the accepted submissions have reached a decision.

The average Total Time to Decision for PMA applications is calculated as the three-year rolling average of the annual Total Times to Decision for applications (for example, for FY2015, the average Total Time to Decision for PMA applications would be the average of FY2013 through FY2015) within a closed cohort, excluding the highest 5% and the lowest 5% of values. A cohort is closed when 95% of the applications have reached a decision.

*H. BLA-related Definitions*

Review and act on—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.

Class 1 resubmitted applications—applications resubmitted after a complete response letter that includes the following items only (or combinations of these items):

(a) Final printed labeling

(b) Draft labeling

(c) 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)

(d) Stability updates to support provisional or final dating periods

(e) Commitments to perform Phase 4 studies, including proposals for such studies

(f) Assay validation data

(g) Final release testing on the last 1–2 lots used to support approval

(h) A minor reanalysis of data previously submitted to the application (determined by the Agency as fitting the Class 1 category)

(i) Other minor clarifying information (determined by the Agency as fitting the Class 1 category)

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

Class 2 resubmitted applications—resubmissions that include any other items, including any item that would require presentation to an advisory committee

## 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 Resubmissions*[1]

Note: [1] Refer to Section II.A.4 for a description of the review program for NME NDAs and original BLAs.

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.

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:

Note: [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.

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.

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 DECISIONMAKING

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.

GENERIC DRUG USER FEE ACT PROGRAM PERFORMANCE GOALS AND PROCEDURES

The performance efficiencies, metric goals and procedures to which FDA will agree upon commencement of a generic drug user fee act (GDUFA) program (''the program''), as jointly proposed by FDA and industry, are summarized below.

OVERALL PURPOSE OF THE GENERIC DRUG USER FEE PROGRAM

To help FDA ensure that participants in the U.S. generic drug system comply with U.S. quality standards, and to increase the likelihood that American consumers get timely access to low cost, high quality generic drugs, FDA and industry have jointly agreed to a comprehensive user fee program,

to be supplemental to traditional appropriated funding, that is focused on three key aims:

Safety—Ensure that industry participants, foreign or domestic, who participate in the U.S. generic drug system are held to consistent high quality standards and are inspected biennially, using a risk-based approach, with foreign and domestic parity.

Access—Expedite the availability of low cost, high quality generic drugs by bringing greater predictability to the review times for abbreviated new drug applications, amendments and supplements, increasing predictability and timeliness in the review process.

Transparency—Enhance FDA's ability to protect Americans in the complex global supply environment by requiring the identification of facilities involved in the manufacture of generic drugs and associated active pharmaceutical ingredients, and improving FDA's communications and feedback with industry in order to expedite product access.

Recognizing the critical role generic drugs play in providing more affordable, therapeutically equivalent medicine, the Generic Drug User Fee program is designed to keep individual fee amounts as low as possible to supplement appropriated funding to ensure that consumers continue to receive the significant benefits offered by generic drugs which provided more than $824 billion in savings to the nation's health care system in the last decade alone. The additional resources called for under the agreement, an inflation adjusted $299 million annually for each of the five years of the program, will provide FDA with the ability to perform critical program functions that could not otherwise occur. This program is not expected to add significantly to the cost of generic drugs: given that a reported 3.99 billion retail prescriptions per year were dispensed in the United States in 2010, and assuming that 78% of these prescriptions were filled by generic drugs, it equates to less than a dime per prescription for the average cost of a prescription filled by a generic drug in the United States. Moreover, with the adoption of user fees and the associated savings in development time, the overall expense of bringing a product to market may decline and result in reduced costs.

In addition to the public health benefits outlined above, the program described in this letter is expected to provide significant value to small companies and first time entrants in the generic market who will benefit significantly from the certainty associated with performance review metrics that offer the potential to dramatically reduce the time needed to commercialize a generic drug when compared to pre-GDUFA review times.

In addition, the variety of funding sources for the program will assure that participants in the generic drug industry, whether finished dosage form (FDF) manufacturers or Active Pharmaceutical Ingredient (API) manufacturers appropriately share the financial expense and benefits of the program. Given that the total amount of annual user fee funding is expected to be derived from a broad funding source, including an estimated 2000 FDF and API facilities supporting Abbreviated New Drug Applications (ANDAs), as well as approximately 750 ANDAs, 750 prior approval supplements (PASs) and 350 Type II Active Pharmaceutical Drug Master Files (DMFs) annually, user fees are expected to provide a measurable return on investment related to predictability of inspection, and review timelines. The program's goals of ensuring FDA has necessary resources to conduct needed inspections as part of the complete review framework and achieve parity of Good Manufacturing Practice (GMP) inspections for foreign and domestic facilities by the 5th year of the user fee program will also provide significant value to industry participants given that outstanding inspections can result in delays of ANDA approvals.

Taken collectively, the user fee program and associated performance metrics and fees are expected to provide measurable public health benefits and are not expected to competitively disadvantage any company or business sector regardless of size or location.

END NOTES

1. Source: IMS Health Report—GPHA. Savings achieved through the use of generic pharmaceuticals: 2000–2009, July 2010.

2. Source: ''The Use of Medicines in the United States: Review of 2010'', Report by the IMS Institute for Healthcare Informatics, slide 8, available at *http://www.imshealth.com/deployedfiles/imshealth/Global/Content/IMS%20Institute/Static%20File/IHII_UseOfMe_d_report.pdf.*

3. Ibid., slide 22.

## 1. OVERVIEW

### OVERALL PROGRAM SCOPE, ASSUMPTIONS, AND ASPIRATIONS

The goals to which FDA is committing for generic drugs are premised on the following assumptions:

I. Funding for the program from user fees will be at agreed-upon levels of approximately $299 million annually adjusted for inflation and will supplement appropriated funding from Congress as described further below.

II. It is estimated that FDA will receive the funding through approximately 750 abbreviated new drug applications (ANDAs) per year submitted electronically, approximately 750 prior approval supplements (PASs) approximately 350 newly referenced drug master files (DMFs) per year and through approximately 2000 facilities associated with ANDAs. While the total revenue collected can be defined in advance and is constant as the resourcing level must be constant, the individual fee will be determined each year based on the variability of the fee source.

III. Over the five year course of the program, there will be no significant changes in the generic drug facility inventory, either in terms of general number of facilities, or the foreign and domestic facility split.

IV. FDA will have streamlined hiring authority for all GDUFA-related positions prior to or concurrent with the implementation date of the program.

V. FDA expects the program will be implemented starting on the first day of Fiscal Year 2013, October 1, 2012 and continue for five years, with the joint expectation that the program will be continued at the end of five years under terms to be negotiated before the end of FY 2017.

VI. Industry and FDA will populate and maintain databases as necessary for facilities, fee assessments, efficiency and other enhancements as described further below and as needed to support the Generic Drug User Fee Act. Because certain databases to implement this program will need to be built, and existing systems need to be expanded or modified, industry will submit necessary information in electronic format to FDA using appropriate standards to be specified by the agency or as specified in statute.

VII. FDA will aspire to the extent possible to maintain levels of productivity at least similar to pre-GDUFA levels, while hiring and training incremental staff necessary to achieve the program performance goals, building necessary systems and implementing outlined program changes in years 1 and 2 of the program (see goals for years 3–5 metrics).

VIII. FDA will utilize a complete review standard (as defined below), will aspire to hold first cycle deficiency teleconferences with industry to discuss complete response questions at a level at least similar to pre-GDUFA levels in years 1 and 2 of the program (see goals for years 3–5 metrics) and will utilize an approach similar to the NDA review process whereby FDA uses telephone information requests to address easily correctable deficiencies during the review process before and after issuance of complete response letters.

IX. FDA will aspire to complete reviews for applications with only minor administrative amendments pending prior to the expiration date of the controlling patent or applicable exclusivity date regardless of the amendment(s) goal date.

X. FDA will work towards achieving performance goals to reach parity of GMP inspections of foreign and domestic establishments, will prioritize inspections using a risk-based approach, and will prioritize inspections of establishments associated with ANDAs that are otherwise approvable or eligible for tentative approval except for an outstanding inspection, as well as establishments associated with ANDAs that have not been inspected previously. In appropriate circumstances FDA can rely on a routine surveillance inspection in lieu of an application-specific inspection. Generally, among other considerations, FDA relies on a previous inspection of a finished product site occurring within 2 years of the current good manufacturing practice (CGMP) evaluation for a pending application, 3 years for an active pharmaceutical ingredient (API) site or a control testing laboratory, and 4 years for a packaging-only site. There are exceptions to this general practice, which are usually related to the nature of the drug being processed or the complexity of the associated processing operations. FDA intends to continue the practice of using a risk-based assessment in determining the length of time since the last inspection, guided by a 2-year cycle for finished dosage product sites and a 3-year cycle for API sites and consideration of the type of finished product or API in the application. Practically, this means that in making decisions about pending applications for which FDA does not have current inspection information within the time period indicated, FDA may use previous FDA inspection information and/or use inspection information from another regulatory authority as appropriate.

XI. FDA will strive to review and act on all ANDAs that are submitted on the first day that any valid Paragraph IV application for the drug in question is submitted within 30 months of submission to avoid causing first applicants to inadvertently forfeit 180-day exclusivity eligibility under 21 U.S.C. §355(j)(5)(D)(i)(IV).

XII. Because the agreed generic drug user fee program is intended to be additive to budget appropriations, agreed upon legislative language will require that annual program appropriations from Congress must be equal to or exceed the FDA appropriation for FY 2009.

XIII. In order to generate the agreed upon levels of user fee funding to achieve the enclosed performance goals, metrics and efficicienies, legislative language will require that approximately 70% of GDUFA fees shall be derived from facility fees (for facilities producing or pending review to produce active pharmaceutical ingredients or finished dosage forms for a generic drug application), approximately 30% of GDUFA fees shall be derived from application fees (DMF Fees and ANDA and PAS (Prior Approval Supplement) Fees). As discussed and agreed by the various industry business segments, overall fees will be divided 80 percent to 20 percent between the finished dosage form (FDF) and API and manufacturers, respectively in industry. In the first year of the

program, $50 million of the total GDUFA user fee funding shall be generated by a one time backlog fee for ANDAs pending (except for ANDAs that are pending but have received tentative approval) on October 1, 2012.

XIV. For appeals of decisions concerning procedural or scientific matter involving review of pending ANDAs, ANDA amendments and ANDA supplements FDA will aspire that the response to appeals of decisions will occur within 30 calendar days of OGD receipt of the written appeal when possible, though no reportable performance goals are required.

Note: If these assumptions differ significantly from actuality, FDA may not be able to achieve the goals and efficiency enhancements outlined in this goals letter, despite the supplemental funding provided by the program.

SUMMARY OF MAJOR PROGRAM GOALS INCLUDING FIVE YEAR GOALS

Major Program (including 5 year) goals can be summarized as follows:

Note that FDA agrees to additional 5 year goals, as set forth later in this goals letter, such as goals on amendments, controlled correspondence, and prior approval supplements, as well as goals for years prior to year 5 of the program. The goals summarized in this section are a subset of the complete year 5 goals, and are intended simply to illustrate the scope of the program.

*Application metrics*—For Abbreviated New Drug Applications (ANDAs) in the year 5 cohort, FDA will review and act on 90 percent of complete electronic ANDAs within 10 months after the date of submission. Certain amended applications may have differing metrics as discussed below.

*Backlog metrics*—FDA will review and act on 90 percent of all ANDAs, ANDA amendments and ANDA prior approval supplements regardless of current review status (whether electronic, paper, or hybrid) pending on October 1, 2012 by the end of FY 2017.

*CGMP Inspection metrics*—FDA will conduct risk-adjusted biennial CGMP surveillance inspections of generic API and generic finished dosage form (FDF) manufacturers, with the goal of achieving parity of inspection frequency between foreign and domestic firms in FY 2017.

*Efficiency Enhancements*—FDA will implement various efficiency enhancements discussed below on October 1, 2012 or upon enactment of the program, whichever is later.

*Regulatory Science*—FDA will continue, and for some topics begin undertaking various regulatory science initiatives discussed below on October 1, 2012 or upon enactment of the program, whichever is later, focusing first on the initiatives discussed below and with additional initiatives to be identified with input from an industry working group. Details follow.

2. EFFICIENCY ENHANCEMENTS TO BE UNDERTAKEN ON OCTOBER 1, 2012, OR UPON ENACTMENT OF THE PROGRAM, WHICHEVER IS LATER

A. ANDA REVIEW EFFICIENCY ENHANCEMENTS

Starting on October 1, 2012 or upon enactment of the program, whichever is later, FDA will issue complete response letters, rather than discipline specific letters, for all ANDAs, including those pending on October 1, 2012.

Complete response letters will reflect full division-level review of deficiencies from all relevant review disciplines, including inspections, and address other matters relating to the ANDA and associated DMFs as well as consults with other agency components (these will be subsumed into the application metrics).

FDA reviewers will make every reasonable effort to communicate promptly to applicants easily correctable deficiencies found in the ANDA and will utilize an approach similar to the NDA review process whereby FDA uses telephone information requests to address easily correctable deficiencies during the review process before and after issuance of complete response letters.

When requested by the ANDA sponsor within 10 business days of FDA issuing a first cycle complete response letter, as provided by the sponsor in a written request that outlines specific written questions the applicant would like to discuss (limited to the content of the letter), FDA will schedule a 30 minute teleconference to clarify issues and answer questions. Priority for such teleconferences will be given to expedited and first major amendment applications. Although FDA will begin to develop procedures and tracking systems for such teleconferences coincident with the start of the program, there will be no teleconference goals for the first two years of the program although FDA will aspire to conduct such teleconferences as requested when reportable performance goals are not otherwise required. In the first two years, FY 2013 and FY 2014, FDA would aspire to hold teleconferences with industry to address complete response questions at a level similar to pre-GDUFA levels. Subsequently, the goals for number of reportable teleconferences (although FDA may conduct more such teleconferences) will be:

Closing out the teleconference request for 200 meetings in FY 2015;

Closing out the teleconference request for 250 meetings in FY 2016;

Closing out the teleconference request for 300 meetings in FY 2017.

FDA will develop enhanced refusal to receive standards for ANDAs and other related submissions by the end of year 1 of the program and will publish such standards in advance of implementation.

For ANDAs in the year 1 and 2 cohorts, FDA will expedite review of Paragraph IV applications that are submitted on the first day that any valid Paragraph IV application for the drug in question is submitted. Expedited review will be implemented consistent with existing procedure for expediting applications as set forth in CDER's MAPP 5240.3, and will also include those applications that become eligible for approval during the review period as a result of no blocking exclusivities, patent(s) and/or applicable stays based on appropriate documentation submitted.

Review metric goals (described below) only apply to submissions made electronically, following the eCTD format in effect at the date of submission.

Backlog review metric goals (described below) apply to all ANDA applications, amendments, and supplements regardless of current review status in the queue as of October 1, 2012, regardless of whether they were submitted in paper, electronic, or hybrid format.

B. DRUG MASTER FILE (DMF) REVIEW EFFICIENCY ENHANCEMENTS

After the program's implementation date, upon payment of the DMF fee by DMF holders anticipating reference by a generic drug manufacturer, FDA will conduct a completeness assessment of Type II API DMFs. Following a satisfactory completeness assessment, FDA will deem the DMF available for reference, placing the DMF number in a publicly available list of Type II API DMFs available for reference.

Review metric goals (described below) will only apply to Type II API DMFs submitted after the program's implementation date, if they are submitted electronically. Electronic DMFs will follow the eCTD format in effect at date of submission.

FDA will issue a letter detailing all identified deficiencies, rather than discipline specific letters, for all DMFs including those under review at the time of enactment of the implementing legislation.

The DMF deficiency letters will reflect full division-level deficiency review of deficiencies from all relevant review disciplines, including inspections, and address other matters relating to the DMF review such as consults with other agency components (these will be subsumed into the DMF metrics).

FDA reviewers will make every reasonable effort to communicate promptly to applicants easily correctable deficiencies found in the DMF and will continue to utilize an approach similar to the NDA review process whereby FDA uses telephone information requests to address easily correctable deficiencies during the review process before and after issuance of complete response letters.

When requested by a DMF holder within 10 business days of FDA issuing a first cycle DMF deficiency letter, as provided by the DMF holder in a written request that outlines specific written questions the DMF holder would like to discuss (limited to the content of the letter), FDA will schedule a 30 minute teleconference with a limit of one teleconference per DMF holder per month, with the total number of teleconferences not to exceed the number of teleconferences for ANDAs, a teleconference to clarify issues and answer questions. Priority for such teleconferences will be given to DMFs referenced in expedited and first major deficiency applications. Although FDA will begin to develop procedures and tracking systems for such teleconferences coincident with the start of the program, there will be no teleconference goals for the first two years of the program although FDA will aspire to conduct such teleconferences as requested when reportable performance goals are not otherwise required. In the first two years, FY 2013 and FY 2014, FDA would aspire to hold teleconferences with industry to address DMF deficiency questions at a level similar to pre-GDUFA levels (although FDA may conduct more such teleconferences).

Once a DMF has undergone a complete review and the ANDA referencing same is either approved or tentatively approved—at such time there being no further outstanding deficiencies to the DMF—FDA will issue the DMF holder a letter to indicate that the DMF does not have any further open matters as part of the review associated with the referencing ANDA.

C. INSPECTION EFFICIENCY ENHANCEMENTS

To maximize the number of applications that can be reviewed within the metric goals and to assist in securing the pharmaceutical supply chain, FDA will employ a risk-adjusted biennial CGMP surveillance inspection model for inspection of generic API and FDF manufacturers, with the goal of achieving parity of inspection frequency between foreign and domestic establishments in FY 2017 and will prioritize inspections of establishments associated with ANDAs that are otherwise approvable or eligible for tentative approval except for an outstanding inspection, as well as establishments that have not been inspected previously.

FDA will make inspection classification results and date of the last facility inspection available to the public and industry on FDA's website on timely basis.

During the five years of the program, FDA will undertake a study of foreign government regulator inspections (CGMP and bioequivalence), report findings publicly, and develop a program to utilize foreign inspection classifications when and where appropriate.

D. OTHER EFFICIENCY ENHANCEMENTS

FDA will develop new and/or enhance existing facility databases (API and FDF manufacturing and clinical/ bioequivalence site) to be populated by industry. These databases will, at a minimum, contain information for generics-related firms, including addresses and Data Universal Numbering System (DUNS) numbers, and will link facilities to DMFs and ANDAs and will contain other information as necessary.

FDA will develop a current chemistry manufacturing and controls (CMC) records database to aid in the efficiency of review and inspection.

FDA will develop and issue electronic data submission standards.

Because certain databases to implement this program will need to be built, and existing systems need to be expanded or modified, industry will submit necessary information in electronic format to FDA using appropriate standards to be specified by the agency or as specified in statute.

3. REGULATORY SCIENCE INITIATIVES

A. WORKING GROUP

FDA will convene a working group and consider suggestions from industry and other stakeholders to develop an annual list of regulatory science initiatives for review by CDER Director.

B. FY 2013 PLAN

The FY 2013 plan is appended.

4. METRIC GOALS/MEASUREMENTS

A. HUMAN RESOURCES METRICS

FDA will hire and train at least 25 percent of incremental staff in FY 2013, 50 percent in FY 2014 and will strive to complete GDUFA-funded human resources hiring goals in FY 2015 as necessary to achieve the program's performance metrics and goals.

B. ANDA, ANDA AMENDMENT, AND ANDA PRIOR APPROVAL SUPPLEMENT REVIEW METRICS AND DMF REVIEWS AS SUBSUMED IN EACH

ANDAs will be categorized according to cohort year.

Once an ANDA is in a given year's cohort, dates of submission of a subsequent amendment will not change the cohort year. Regardless of the year in which an amendment is submitted, any additional time periods to be added to the base review period will be calculated using the time periods corresponding to the original cohort year.

Original (complete) ANDA Review (Certain amended applications may have differing metrics as discussed below.)

FDA will review and act on 60 percent of original ANDA submissions within 15 months from the date of submission for the year 3 cohort.

FDA will review and act on 75 percent of original ANDA submissions within 15 months from the date of submission for the year 4 cohort.

FDA will review and act on 90 percent of original ANDA submissions within 10 months from the date of submission for the year 5 cohort.

For ANDAs in the year 1 and 2 cohorts, FDA will expedite review of Paragraph IV applications that are submitted on the first day that any valid Paragraph IV application for the drug in question is submitted.

Amendment Review

All amendment metric goals are incremental, and the time periods specified are calculated from the date of submission. They will be added to the original review goal, but in no case shall they shorten the original goal date. (In other words, an amendment with a 6 month metric which was submitted 4 months prior to original goal date would add 2 months to the review clock).

An amendment pre Complete Response Letter adjusts the goal date for the original application.

Subsequent amendments pre Complete Response Letter also adjust the goal date for the application and are additive.

An amendment post Complete Response Letter sets a new goal date for the application.

Subsequent amendments post Complete Response Letter also adjust the goal date for the application and are additive.

Delaying amendments or amendments containing information that FDA would otherwise ask for as a result of post ANDA submission reference listed drug changes do not add to the count of amendments.

If any amendment contains multiple elements, the longest goal date shall apply.

Amendments shall be grouped as Tier 1, Tier 2 or Tier 3. FDA agrees that unsolicited amendments that are submitted to a pending ANDA that are neither Tier 1, Tier 2 or Tier 3 amendments, but rather are routine or administrative in nature and do not require scientific review (e.g., requests for final ANDA approval, patent amendments, general correspondence, and USP monograph updates), will not lengthen or impact the original review goal date.

Tier 1 amendments include:

All solicited first major and the first five minor amendments

All unsolicited amendments indicated by sponsor and agreed by FDA to be a result of either delaying actions as determined by FDA's Office of Generic Drugs taking into account the facts and information supplied by the ANDA applicant or that otherwise would eventually be solicited.

Tier 2 amendments include:

All unsolicited amendments not arising from delaying actions as determined by FDA's Office of Generic Drugs taking into account the facts and information supplied by the ANDA applicant excepting those amendments which only remove information for review.

Tier 3 amendments include:

Any solicited major amendment subsequent to the first major amendment

Any solicited minor amendment subsequent to the fifth minor amendment

Tier 1 amendment goals:

First major amendment

FDA will review and act on 60 percent of first major amendment submissions within 10 months from the date of submission for the year 3 cohort.

FDA will review and act on 75 percent of first major amendment submissions within 10 months from the date of submission for the year 4 cohort.

FDA will review and act on 90 percent of first major amendment submissions within 10 months from the date of submission for the year 5 cohort.

Minor amendments (first—third)

FDA will review and act on 60 percent of first through third minor amendment submissions within 3 months from the date of submission for the year 3 cohort.

FDA will review and act on 75 percent of first through third minor amendment submissions within 3 months from the date of submission for year 4 cohort.

FDA will review and act on 90 percent of first through third minor amendment submissions within 3 months from the date of submission for the year 5 cohort.

Minor amendments (fourth—fifth)

FDA will review and act on 60 percent of fourth through fifth minor amendment submissions within 6 months from the date of submission for the year 3 cohort.

FDA will review and act on 75 percent of fourth through fifth minor amendment submissions within 6 months from the date of submission for year 4 cohort.

FDA will review and act on 90 percent of fourth through fifth minor amendment submissions within 6 months from the date of submission for the year 5 cohort.

Except that if any Tier 1 amendment requires an inspection, the goal shall be 10 months.

Tier 2 amendment goals:

FDA will review and act on 60 percent of amendment submissions within 12 months from the date of submission for the year 3 cohort.

FDA will review and act on 75 percent of amendment submissions within 12 months from the date of submission for year 4 cohort.

FDA will review and act on 90 percent of amendment submissions within 12 months from the date of submission for the year 5 cohort.

Tier 3 amendment goals:

There will be no GDUFA metrics for tier 3 amendments.

Review of Complete Prior Approval Supplements (PASs) (Certain amended PASs may have differing metrics as discussed above in the Amendment Review section).

FDA will review and act on 60 percent of PASs not requiring inspection within 6 months from the date of submission for receipts in FY 2015; FDA will review and act on 60 percent of PASs requiring inspection within 10 months from the date of submission for receipts in FY 2015.

FDA will review and act on 75 percent of PASs not requiring inspection within 6 months from the date of submission for receipts in FY 2016; FDA will review and act on 75 percent of PASs requiring inspection within 10 months from the date of submission for receipts in FY 2016.

FDA will review and act on 90 percent of PASs not requiring inspection within 6 months from the date of submission for receipts in FY 2017; FDA will review and act on 90 percent of PASs requiring inspection within 10 months from the date of submission for receipts in FY 2017.

C. CONTROLLED CORRESPONDENCE METRICS

Controlled Correspondence

FDA will respond to 70 percent of controlled correspondence in 4 months from date of submission in FY 2015.

FDA will respond to 70 percent of controlled correspondence in 2 months from date of submission in FY 2016.

FDA will respond 90 percent of controlled correspondence in 2 months from date of submission in FY 2017.

If the controlled correspondence requires input from the clinical division, one additional month will be added to the goals outlined above.

In the case of controlled correspondence which raises an issue or question that is the same as or related to the issue or question that is the subject of one or more pending citizen petitions, or petitions for stay or reconsideration, the above goals will apply from the date FDA issues responses to the pending petitions.

D. CGMP INSPECTION METRICS

FDA will conduct risk-adjusted biennial CGMP surveillance inspections of generic API and generic finished dosage form (FDF) manufacturers, with the goal of achieving parity of inspection frequency between foreign and domestic firms in FY 2017.

E. BACKLOG METRICS

FDA will review and act on 90 percent of all ANDAs, ANDA amendments, and ANDA prior approval supplements regardless of current review status (whether electronic, paper, or hybrid) pending on October 1, 2012 by the end of FY 2017.

DEFINITIONS

For the purposes of this goals letter:

*Act on an application*—means FDA will either issue a complete response letter, an approval letter, a tentative approval letter for an ANDA, or a refuse to receive action.

*Active pharmaceutical ingredient*—means (A) a substance, or a mixture when the substance is unstable or cannot be transported on its own, intended to be used as a component of a drug and intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the human body; or (B) a substance intended for final crystallization, purification, or salt formation, or any combination of those activities, to become the final active pharmaceutical ingredient as defined in paragraph (A).

*Backlog*—refers to the queue of pending ANDAs, ANDA amendments and ANDA supplements pending as of October 1, 2012.

*Delaying amendments*—refers to amendments to an ANDA from the ANDA sponsor to address actions by a third party that would cause delay or impede application review or approval timing and that were not or may not have been initially recognized by FDA as necessary when the application was first submitted. FDA's Office of Generic Drugs shall have broad discretion to determine what constitutes a delaying event caused by actions generally outside of the applicants control taking into account facts and information supplied by the ANDA sponsor.

*Closing out a request for a first cycle review teleconference*—means: 1) holding the teleconference; or 2) responding to questions in the sponsor's teleconference request in writing in lieu of holding the teleconference.

*Cohort*—The program is structured based on 5 cohorts of submission dates (original ANDAs, PASs and DMFs), corresponding to the five fiscal years to be covered by the program. The year 1 cohort refers to the dates of submissions made electronically in FY 2013 (October 1, 2012 to September 30, 2013). The year 2 cohort refers to the dates of submissions made electronically in FY 2014 (October 1, 2013 to September 30, 2014). The year 3 cohort refers to the dates of submissions made electronically in FY 2015 (October 1, 2014 to September 30, 2015). The year 4 cohort refers to submissions made electronically in FY 2016 (October 1, 2015 to September 30, 2016). The year 5 cohort refers to submissions made electronically in FY 2017 (October 1, 2016 to September 30, 2017).

*Complete response letter*—refers to a written communication to an applicant or DMF holder from FDA usually describing all of the deficiencies that the agency has identified in an abbreviated application (including pending amendments) or a DMF that must be satisfactorily addressed before the ANDA can be approved. Complete response letters will reflect a complete review and will require a complete response from industry to restart the clock. Refer to 21 CFR 314.110 and *http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084138.htm* for additional details. When a citizen petition may impact the approvability of the ANDA, FDA will strive to address, where possible, valid issues raised in a relevant citizen petition in the complete response letter. If a citizen petition raises an issue that would delay only part of a complete response, a response that addresses all other issues will be considered a complete response.

*Complete review*—refers to a full division-level review from all relevant review disciplines, including inspections, and includes other matters relating to the ANDA and associated DMFs as well as consults with other agency components.

*Controlled correspondence*—FDA'S Office of Generic Drugs provides assistance to pharmaceutical firms and related industry regarding a variety of questions posed as ''controlled documents.'' See *http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm120610.htm*. Controlled correspondence does not include citizen petitions, petitions for reconsideration or requests for stay.

*DMF* or *Type II Active Pharmaceutical Ingredient Drug Master File*—means a submission of information to the Secretary by a person that intends to authorize the Food and Drug Administration to reference the information to support approval of a generic drug submission without the submitter having to disclose the information to the generic drug submission applicant.

*Electronic*—refers to submissions in an all electronic eCTD format in effect at the date of submission.

*Expedited review of application*—While generally, review of original ANDAs, ANDA amendments and ANDA supplements are reviewed in the order received, (first-in, first-reviewed), certain applications may be identified at the date of submission for expedited review, as described in CDER's MAPP 5240.3. (See *http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm079787.pdf*) which includes expedited review of the original submission and amendment(s) associated with the expedited review qualifying application. Products to respond to current and anticipated public health emergencies, products under special review programs, such as the President's Emergency Plan for AIDS Relief (PEPFAR), products for which a nationwide shortage has been identified, and first generic products for which there are no blocking patents or exclusivities on the reference listed drug currently may qualify for expedited review. For ANDAs in the year 1 and 2 cohorts, FDA will expedite review of Paragraph IV applications that are submitted on the first day that any valid Paragraph IV application for the drug in question is submitted.

*Facility*—means business or other entity under one management either direct or indirect and at one geographic location or address engaged in manufacturing or processing an active pharmaceutical ingredient or a finished dosage form, but does not include a business or other entity whose only manufacturing or processing activities are one or more of the following: repackaging, relabeling, or testing. For purposes of this definition, separate buildings within close proximity are considered to be at one geographic location or address if the activities in them are closely related to the same business enterprise, under the supervision of the same local management, and are capable of being inspected by the Food and Drug Administration during a single inspection.

*Finished Dosage Form*—means (A) a drug product in the form in which it will be administered to a patient, such as a tablet, capsule, solution, or topical application; (B) a drug product in a form in which reconstitution is necessary prior to administration to a patient, such as oral suspensions or lyophilized powders; or (C) any combination of an active pharmaceutical ingredient, as defined in paragraph (m)(2), with another component of a drug product for purposes of production of such a drug product.

*First major deficiency application*—means an ANDA which has been issued its first complete response letter classified as having major deficiency(ies).

*Generic Drug Program*—refers to all agency activities related to the determination of approvability of an ANDA.

*Major and minor amendments*—All references to ''major'' and ''minor'' amendments in this goals letter are intended to refer to the distinctions that FDA described in its Guidance for Industry: Major, Minor, Telephone Amendments to Abbreviated New Drug Applications. See *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072888.pdf*

*Parity*—in reference to inspections, as between foreign and domestic facilities, means inspection at an equal frequency plus or minus 20 percent with comparable depth and rigor of inspection.

*Refuse to receive*—means refusal to file an application. See 21 CFR 314.101 and *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080561.pdf1993*

*Solicited amendment*—an amendment submitted in response to a Complete Response letter.

*Submission date*—is the date an ANDA, ANDA amendment, ANDA supplement, or Type II active pharmaceutical drug master file arrives in the appropriate electronic portal of the FDA.

*Prior Approval Supplements*—A prior approval supplement is a submission to allow a company to make a change in a product that already has an approved ANDA. CDER must approve all important ANDA changes (in packaging or ingredients, for instance) to ensure the conditions originally set for the product are still met. (Source: *http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm#S)*

*Unsolicited amendment*—an amendment with information not requested by the FDA except for those unsolicited amendments considered routine or administrative in nature and that do not require scientific review (e.g., requests for final ANDA approval, patent amendments, general correspondence, and USP monograph updates).

FY 2013 REGULATORY SCIENCE PLAN

Topic 1: Bioequivalence of local acting orally inhaled drug products

Impact: Continue to develop new and improved PD endpoints and study designs or establishment of alternative approaches to ensure equivalent local delivery of orally inhaled drug product to the lung would lead to more efficient development of generic products in a sector that lacks any generic competition

Topic 2: Bioequivalence of local acting topical dermatological drug products

Impact: Continue developing new bioequivalence methods in order to reduce the need for relatively insensitive clinical endpoint bioequivalence studies. Development of in vitro release tests or other product characterization to ensure consistent drug release or product performance

Topic 3: Bioequivalence of local acting gastro-intestinal drug products

Impact: Developing new bioequivalence methods for direct measurement of drug concentrations in the GI tract and establishing better correlations between pharmacokinetic measurements and GI concentration would allow more efficient demonstration of bioequivalence than by clinical endpoint studies.

Topic 4: Quality by design of generic drug products

Impact: Continue developing science-based recommendations for product development, raw material, APIs and process controls, and life-cycle management of complex dosage forms (e.g. orally inhaled drug products and modified-release dosage forms)

Topic 5: Modeling and simulation

Impact: Modeling and simulation (including in-vitro and in-vivo correlations) is essential to efficient implementation of quality by design and can help to identify and eliminate unneeded in-vitro and/or in-vivo studies. Models (PK/PD, exposure-response, clinical use simulation) support generic drug evaluation policies especially for NTI drugs and complex products.

Topic 6: Pharmacokinetic studies and evaluation of anti-epileptic drugs

Impact: Improving public confidence in bioequivalent generic epilepsy drugs.

Topic 7: Excipient effects on permeability and absorption of BCS Class 3 Drugs

Impact: Extension of biowaivers to BCS Class 3 Drugs and eliminating the need for unnecessary in vivo bioequivalence studies

Topic 8: Product- and patient-related factors affecting switchability of drug-device combination products (e.g., orally inhaled and nasal drug products and injection drug products)

Impact: Establishing a systematic, science- and risk-based approach to ensure device switchability, and improving the patient's compliance and acceptability of generic devices

Topic 9: Postmarketing surveillance of generic drug usage patterns and adverse events.

Impact: Improved data collection about usage patterns (which strengths are used in which populations, extent of switchability, back switches to RLD products, medication errors) will be fed back into regulatory policy development including those for excipients and impurities. Baseline data collection on adverse event reports on switching to an authorized generic would improve the ability to investigate reports.

Topic 10: Evaluation of drug product physical attributes on patient acceptability

Impact: Laboratory and human studies on physical attributes such as tablet size, shape, coating, odor perception (residual solvents), score configuration, taste masking or color on the ability of patient to use (for example swallow) or perceive quality (for example smell) will allow OGD to provide better guidance to applicants on how these physical attributes should be controlled and compared to the RLD.

Topic 11: Postmarking assessment of generic drugs and their brand-name counterparts

Impact: Stronger public confidence in generic drugs because of pro-active responses to product concerns. An integrated response to product concerns involving laboratory investigations and post-marketing data collection.

Topic 12: Physicochemical characterization of complex drug substances

Impact: Developing analytical methods for demonstrating pharmaceutical equivalence for complex drug substances (non-small molecules) characterized by natural source origin, polydisperse mixture, and/or supramolecular structure, and therefore expanding the boundary of the generic drug program for these complex drug products

Topic 13: Develop a risk-based understanding of potential adverse impacts to drug product quality resulting from changes in API manufacturing and controls.

Impact: The ability to predict the potential impacts of manufacturing changes on product quality will allow manufacturers to target assessments and controls on high-risk areas for regulators to focus their reviews on these areas too.

FY 2014 REGULATORY SCIENCE PRELIMINARY TOPICS FOR CONSIDERATION

In addition to those topics to be identified by the Working Group described in section 3.A of this letter, topics will include recommendations for draft guidances to clarify FDA recommendations with regard to complex product development and to help limit deficiencies in applications.

BIOSIMILAR BIOLOGICAL PRODUCT AUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FOR FISCAL YEARS 2013 THROUGH 2017

FDA proposes the following goals contingent on the allocation of resources for each of the fiscal years 2013–2017 of at least the inflation-adjusted value of $20 million in non-user fee funds, plus collections of biosimilar user fees, to support the process for the review of biosimilar biological applications.

I. REVIEW PERFORMANCE GOALS

*A. Biosimilar Biological Product Application Submissions and Resubmissions*

*FY 2013*

1. Review and act on 70 percent of original biosimilar biological product application submissions within 10 months of receipt.

2. Review and act on 70 percent of resubmitted original biosimilar biological product applications within 6 months of receipt.

*FY 2014*

1. Review and act on 70 percent of original biosimilar biological product application submissions within 10 months of receipt.

2. Review and act on 70 percent of resubmitted original biosimilar biological product applications within 6 months of receipt.

*FY 2015*

1. Review and act on 80 percent of original biosimilar biological product application submissions within 10 months of receipt.

2. Review and act on 80 percent of resubmitted original biosimilar biological product applications within 6 months of receipt.

*FY 2016*

1. Review and act on 85 percent of original biosimilar biological product application submissions within 10 months of receipt.

2. Review and act on 85 percent of resubmitted original biosimilar biological product applications within 6 months of receipt.

*FY 2017*

1. Review and act on 90 percent of original biosimilar biological product application submissions within 10 months of receipt.

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

*B. Supplements with Clinical Data*

1. Review and act on 90 percent of original supplements with clinical data within 10 months of receipt.

2. Review and act on 90 percent of resubmitted supplements with clinical data within 6 months of receipt.

*C. Original Manufacturing Supplements*

1. Review and act on 90 percent of manufacturing supplements within 6 months of receipt.

*D. Goals Summary Tables*

ORIGINAL AND RESUBMITTED APPLICATIONS AND SUPPLEMENTS

| Submission cohort | Performance goal | | | | |
|---|---|---|---|---|---|
| | 2013 | 2014 | 2015 | 2016 | 2017 |
| Original Biosimilar Biological Product Application Submissions | 70% in 10 months of the receipt date. | 70% in 10 months of the receipt date. | 80% in 10 months of the receipt date. | 85% in 10 months of the receipt date. | 90% in 10 months of the receipt date |
| Resubmitted Original Biosimilar Biological Product Applications | 70% in 6 months of the receipt date. | 70% in 6 months of the receipt date. | 80% in 6 months of the receipt date. | 85% in 6 months of the receipt date. | 90% in 6 months of the receipt date |

| | |
|---|---|
| Original Supplements with Clinical Data | 90% in 10 months of the receipt date |
| Resubmitted Supplements with Clinical Data | 90% in 6 months of the receipt date |
| Manufacturing Supplements | 90% in 6 months of the receipt date |

II. FIRST CYCLE REVIEW PERFORMANCE

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

1. Performance Goal: For original biosimilar biological product applications and supplements with clinical data, 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 biosimilar biological product applications and supplements with clinical data, 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 biosimilar biological product 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 supplements with clinical data.

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 a biosimilar biological product is highly similar to the reference product, 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 biosimilar biological products, communication

of the deficiencies identified in the application will generally occur through issuance of a discipline review (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 VIII.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 (under Section II.B.1 and 2) 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 biosimilar biological product 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 biosimilar biological product 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.

III. 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—Biosimilar Biological Product Proprietary Names*

1. Proprietary names submitted during the biosimilar biological product development (BPD) phase

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 biosimilar biological product application

a) Review 90% of biosimilar biological product application 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 (during the BPD phase) 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.

IV. MAJOR DISPUTE RESOLUTION

A. Procedure: For procedural or scientific matters involving the review of biosimilar biological product applications and supplements (as defined in BsUFA) 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. Note: 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.

V. 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.

VI. 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 related 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., are the clinical endpoints adequate to assess whether there are clinically meaningful differences between the proposed biosimilar biological product and the reference product).

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 any necessary clinical study or studies to prove biosimilarity and/or interchangeability (e.g., protocols for comparative clinical trials that will form the primary basis for demonstrating that there are no clinically meaningful differences between the proposed biosimilar biological product and the reference product, and protocols for clinical trials intended to support a demonstration of interchangeability). For such protocols to qualify for this comprehensive protocol assessment, the sponsor must have had a BPD Type 2 or 3 Meeting, as defined in section VIII (F and G), below, 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. 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:

For FY 2013, 70% of special protocols assessments and agreement requests completed and returned to sponsor within timeframes.

For FY 2014, 70% of special protocols assessments and agreement requests completed and returned to sponsor within timeframes.

For FY 2015, 80% of special protocols assessments and agreement requests completed and returned to sponsor within timeframes.

For FY 2016, 85% of special protocols assessments and agreement requests completed and returned to sponsor within timeframes.

For FY 2017, 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.

VII. MEETING MANAGEMENT GOALS

*A. Responses to Meeting Requests*

1. Procedure: Within 14 calendar days of the Agency's receipt of a request and meeting package from industry for a BPD Type 1 Meeting, or within 21 calendar days of the Agency's receipt of a request and meeting package from industry for a Biosimilar Initial Advisory Meeting or a BPD Type 2, 3, or 4 Meeting, as defined in section VIII(D–H), below, CBER and CDER should notify the requester in writing of the date, time, place, and format (i.e., a scheduled face-to-face, teleconference, or videoconference) for the meeting, as well as expected Center participants.

2. Performance Goal: FDA will provide this notification within 14 days for 90 percent of BPD Type 1 Meeting requests and within 21 days for 90 percent of Biosimilar Initial Advisory Meeting and BPD Type 2, 3 and 4 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.

a) Biosimilar Initial Advisory Meeting should occur within 90 calendar days of the Agency receipt of the sponsor-submitted meeting request and meeting package.

b) BPD Type 1 Meetings should occur within 30 calendar days of the Agency receipt of the sponsor-submitted meeting request and meeting package.

c) BPD Type 2 Meetings should occur within 75 calendar days of the Agency receipt of the sponsor-submitted meeting request and meeting package.

d) BPD Type 3 Meetings should occur within 120 calendar days of the Agency receipt of the sponsor-submitted meeting request and meeting package.

e) BPD Type 4 Meetings should occur within 60 calendar days of the Agency receipt of the sponsor-submitted meeting request and meeting package.

2. Performance goal:

For FY 2013, 70% of Biosimilar Initial Advisory Meetings and BPD Type 1–4 Meetings are held within the timeframe.

For FY 2014, 70% of Biosimilar Initial Advisory Meetings and BPD Type 1–4 Meetings are held within the timeframe.

For FY 2015, 80% of Biosimilar Initial Advisory Meetings and BPD Type 1–4 Meetings are held within the timeframe.

For FY 2016, 85% of Biosimilar Initial Advisory Meetings and BPD Type 1–4 Meetings are held within the timeframe.

For FY 2017, 90% of Biosimilar Initial Advisory Meetings and BPD Type 1–4 Meetings are held 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.

2. Performance Goal: FDA will provide meeting minutes within 30 days of the date of the meeting for 90 percent of Biosimilar Initial Advisory Meetings and BPD Type 1–4 Meetings.

*D. Conditions*

For a meeting to qualify for these performance goals:

1. A written request (letter or fax) and supporting documentation (i.e., the meeting package) should be submitted to the appropriate review division or office. The request should provide:

a) A brief statement of the purpose of the meeting, the sponsor's proposal for the type of meeting, and the sponsor's proposal for a face-to-face meeting or a teleconference;

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 list of questions, grouped by discipline. For each question there should be a brief explanation of the context and purpose of the question.

e) A listing of planned external attendees; and

f) A listing of requested participants/disciplines representative(s) from the Center.

g) Suggested dates and times (e.g., morning or afternoon) for the meeting that are within or beyond the appropriate time frame of the meeting type being requested.

2. The Agency concurs that the meeting will serve a useful purpose (i.e., it is not premature or clearly unnecessary). However, requests for BPD Type 2, 3 and 4 Meetings will be honored except in the most unusual circumstances.

The Center may determine that a different type of meeting is more appropriate and it may grant a meeting of a different type than requested, which may require the payment of a biosimilar biological product development fee as described in section 744B of the Federal Food, Drug, and Cosmetic Act before the meeting will be provided. If a biosimilar biological product development fee is required under section 744B, and the sponsor does not pay the fee within the time frame required under section 744B, the meeting will be cancelled. If the sponsor pays the biosimilar biological product development fee after the meeting has been cancelled due to non-payment, the time frame described in section VII.A.1 will be calculated from the date on which FDA received the payment, not the date on which the sponsor originally submitted the meeting request.

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

3. FDA will develop and publish for comment draft guidance on Biosimilar Initial Advisory Meetings and BPD Type 1–4 Meetings by end of second quarter of FY 2014.

VIII. 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, supplement with clinical data, 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 risk evaluation and mitigation strategy (REMS) with elements to assure safe use (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. A Biosimilar Initial Advisory Meeting is an initial assessment limited to a general discussion regarding whether licensure under section 351(k) of the Public Health Service Act may be feasible for a particular product, and, if so, general advice on the expected content of the development program. Such term does not include any meeting that involves substantive review of summary data or full study reports.

E. A BPD Type 1 Meeting is a meeting which is necessary for an otherwise stalled drug development program to proceed (e.g. meeting to discuss clinical holds, dispute resolution meeting), a special protocol assessment meeting, or a meeting to address an important safety issue.

F. A BPD Type 2 Meeting is a meeting to discuss a specific issue (e.g., proposed study design or endpoints) or questions where FDA will provide targeted advice regarding an ongoing biosimilar biological product development program. Such term includes substantive review of summary data, but does not include review of full study reports.

G. A BPD Type 3 Meeting is an in depth data review and advice meeting regarding an ongoing biosimilar biological product development program. Such term includes substantive review of full study reports, FDA advice regarding the similarity between the proposed biosimilar biological product and the reference product, and FDA advice regarding additional studies, including design and analysis.

H. A BPD Type 4 Meeting is a meeting to discuss the format and content of a biosimilar biological product application or supplement submitted under 351(k) of the PHS Act.

## VIOLENCE AGAINST WOMEN REAUTHORIZATION ACT

Mr. LEAHY. Mr. President, I have been saying for weeks and months that we are overdue to pass into law the Leahy-Crapo Violence Against Women Reauthorization Act, which the Senate approved in April with 68 bipartisan votes. I am disappointed that the House still has not picked up this bipartisan effort and that we are not getting the job done this year. I want everyone to know that I will be back next year, and we will get it done.

Just yesterday we were reminded again why this legislation is so important. In Colorado, a man just released from jail on domestic violence charges shot his way into a house, murdering his ex-girlfriend, and her sister, and her sister's husband, before killing himself. We have seen enough horrific violence. It is past time to act.

The Leahy-Crapo bill would support the use of techniques proven to help identify high-risk cases and prevent domestic violence homicides. It will help