PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2018 THROUGH 2022

PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2018 THROUGH 2022

This document contains the performance goals and procedures for the Prescription Drug User Fee Act (PDUFA) reauthorization for fiscal years (FYs) 2018-2022, known as PDUFA VI. It is commonly referred to as the "goals letter" or "commitment letter." The goals letter represents the product of FDA's discussions with the regulated industry and public stakeholders, as mandated by Congress. The performance and procedural goals and other commitments specified in this letter apply to aspects of the human drug review program that are important for facilitating timely access to safe, effective, and innovative new medicines for patients. While much of FDA's work is associated with formal tracked performance goals, the Agency and industry mutually agree that it is appropriate to manage some areas of the human drug review program with internally tracked timeframes. This provides FDA the flexibility needed to respond to a highly diverse workload, including unanticipated public health needs. FDA is committed to meeting the performance goals specified in this letter and to continuous improvement of its performance regarding other important areas specified in relevant published documents[1] that relate to preapproval drug development and post-approval activities for marketed products. FDA and the regulated industry will periodically and regularly assess the progress of the human drug review program throughout PDUFA VI. This will allow FDA and the regulated industry to identify emerging challenges and develop strategies to address these challenges to ensure the efficiency and effectiveness of the human drug review program.

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

[1] Refer to the Good Review Management Principles and Practices for PDUFA Products guidance (hereinafter referred to as "GRMP guidance") available at http://www.fda.gov/downloads/Drugs/.../Guidances/ucm079748.pdf and the Good Review Management Principles and Practices for Effective IND Development and Review MAPP (hereinafter referred to as "GRMP MAPP") available at http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM349907.pdf

I. ENSURING THE EFFECTIVENESS OF THE HUMAN DRUG REVIEW PROGRAM

A. REVIEW PERFORMANCE GOALS

1. NDA/BLA Submissions and Resubmissions[2]

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.

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

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

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

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

2. Original Efficacy Supplements

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

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

3. Resubmitted Efficacy Supplements

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

b. Review and act on 90 percent of Class 2 resubmitted efficacy supplements within 6 months of receipt.

[2] Refer to Section I.B for a description of the review program for NME NDAs and original BLAs.

4. Original Manufacturing Supplements

a. Review and act on 90 percent of manufacturing supplements requiring prior approval within 4 months of receipt

b. Review and act on 90 percent of all other manufacturing supplements within 6 months of receipt.

5. Review Performance Goal Extensions

a. Major Amendments

i. 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.

ii. 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 Element 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.

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

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

v. 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.

b. Inspection of Facilities Not Adequately Identified in an Original Application or Supplement

i. All original applications, including those in the "Program," (see Section I.B.2) and supplements are expected to include a comprehensive and readily located list of all manufacturing facilities included or referenced in the application or supplement. This list provides FDA with information needed to schedule inspections of manufacturing facilities that may be necessary before approval of the original application or supplement.

ii. If, during FDA's review of an original application or supplement, the Agency identifies a manufacturing facility that was not included in the comprehensive and readily located list, the goal date may be extended.

1) If FDA identifies the need to inspect a manufacturing facility that is not included as part of the comprehensive and readily located list in an original application or efficacy supplement, the goal date may be extended by three months.

2) If FDA identifies the need to inspect a manufacturing facility that is not included as part of the comprehensive and readily located list in a manufacturing supplement, the goal date may be extended by two months.

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

Table 1: 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

Table 2:

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

B. PROGRAM FOR ENHANCED REVIEW TRANSPARENCY AND COMMUNICATION FOR NME NDAs AND ORIGINAL BLAs

To promote transparency and communication between the FDA review team and the applicant, FDA will apply the following model ("the Program") to the review of 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 decision, received from October 1, 2017, through September 30, 2022.[3] The goal of the Program is to promote the efficiency and effectiveness of the first cycle review process and minimize the number of review cycles necessary for approval, ensuring that patients have timely access to safe, effective, and high quality new drugs and biologics.

Approach to Application Review. The standard approach for the review of NME NDAs and original BLAs is described in this section. However, the FDA review team and the applicant may discuss and reach mutual agreement on an alternative approach to the timing and nature of interactions and information exchange between the applicant and FDA, i.e., a Formal Communication Plan for the review of the NME NDA or original BLA. The Formal Communication Plan may include elements of the standard approach (e.g., a mid-cycle communication or a late-cycle meeting) as well as other interactions that sometimes occur during the review process (e.g., a meeting during the filing period to discuss the application, i.e., an "application orientation meeting"). If appropriate, the Formal Communication Plan should specify those elements of the Program that FDA and the sponsor agree are unnecessary for the application under review. If the review team and the applicant anticipate developing a Formal Communication Plan, the elements of the plan should be discussed and agreed to at the pre-submission meeting (see Section I.B.1) and reflected in the meeting minutes. The Formal Communication Plan may be reviewed and amended at any time based on the progress of the review and the mutual agreement of the review team and the applicant. For example, the review team and the applicant may mutually agree at any time to cancel future specified interactions in the Program (e.g., the late-cycle meeting) that become unnecessary (e.g. because previous communications between the review team and the applicant are sufficient). Any amendments made to the Formal Communication Plan should be consistent with the goal of an efficient and timely first cycle review process and not impede the review team's ability to conduct its review.

Expedited Reviews. In certain cases, an application reviewed in the Program will be for a product that the FDA review team identifies as meeting an important public health need. If the FDA review team determines that a first-cycle approval is likely for such an

[3] 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.

application, the team intends to make every effort to conduct an expedited review[4] and act early on the application. FDA conducts expedited reviews to promote timely access to critically needed therapies for patients without compromising FDA's high standards for demonstrating the safety, efficacy, and quality of new medicines. Expedited reviews are typically characterized by frequent contact between the applicant and the FDA review team throughout the review process. Any parameters of the Program that are intended to facilitate expedited reviews are noted throughout Section I.B.

If significant application deficiencies are identified by the review team at any time during an expedited review, FDA intends to revert, for the remainder of the review, to the standard approach to the review of priority NME NDAs and original BLAs (as described in this section), and will inform the applicant accordingly.

The remainder of Section I.B describes the parameters that will apply to FDA's review of applications in the Program.

1. <u>Pre-submission meeting:</u> 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. This meeting will be attended by the FDA review team, including appropriate senior FDA staff.

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. In addition to FDA's preliminary responses to the applicant's questions, other potential discussion topics include preliminary discussions on the need for REMS or other risk management actions, and, where applicable, the development of a Formal Communication Plan and a timeline for review activities associated with a scheduling recommendation under the Controlled Substances Act for drugs with abuse potential. These discussions will be summarized at the conclusion of the meeting and reflected in the FDA meeting minutes.

c. The FDA and the applicant will agree on the content of a complete application for the proposed indication(s) at the pre-submission 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

[4] The term "expedited review" in this letter refers to FDA's review of a human drug application that has received priority review designation where the review team plans to act at least 1 month before the PDUFA goal date provided that no significant application deficiencies prevent an early action. Expedited review is distinguished from FDA's expedited programs: fast track designation, breakthrough therapy designation, accelerated approval, and priority review. The decision to perform an expedited review of an application is independent of decisions regarding these expedited programs. Applications that are identified as candidates for expedited review may be reviewed under any one or more of FDA's expedited programs.

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. These agreements will be summarized at the conclusion of the meeting and reflected in the FDA meeting minutes.

i. 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.

ii. 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. <u>Original application submission:</u> 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.

d. The following parameters will apply to applications that are subject to a Refuse-to-File decision and are subsequently filed over protest:

i. The original submission of the application will be subject to the review performance goal as described in Section I.B.4.

ii. The application will not be eligible for the other parameters of the Program (e.g., mid-cycle communication, late-cycle meeting)

iii. FDA generally will not review amendments to the application during any review cycle. FDA also generally will not issue information requests to the applicant during the agency's review.

iv. The resubmission goals described in Section I.A.1.e and I.A.1.f will not apply to any resubmission of the application following an FDA complete response action. Any such resubmission will be reviewed as available resources permit.

e. 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. Review of unsolicited amendments, including those submitted in response to an FDA communication of deficiencies, will be handled in accordance with the GRMP guidance. 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 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. If applicable, the Day 74 letter will serve as notification to the applicant that the review division intends to conduct an expedited review.

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. An agenda will be sent to the applicant prior to the mid-cycle communication. 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), an update regarding FDA's review activities associated with a scheduling recommendation under the Controlled Substances Act (if applicable), and other projected milestone dates for the remainder of the review cycle.

b. In the case of an expedited review, FDA will communicate the timelines for the Late-Cycle Meeting and the Late-Cycle Meeting background package (see Section I.B.6) which may occur earlier with more condensed timeframes compared to a review that is not expedited.

6. Late-Cycle and Advisory Committee Meetings: 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. Late-cycle meetings will generally be face-to-face meetings; however, the meeting may be held by teleconference if FDA and the applicant agree. Since the application is expected to be complete at the time of submission, FDA intends to complete primary and secondary reviews of the application in advance of the planned late-cycle meeting.

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 AC meeting, the following parameters apply:

i. FDA intends to convene AC meetings no later than 2 months (standard review) or no later than 6 weeks (priority review) prior to the PDUFA goal date. The late-cycle meeting will occur not less than 12 calendar days before the date of the AC meeting.

ii. FDA intends to provide final questions for the AC to the sponsor and the AC not less than 2 calendar days before the AC meeting.

iii. Following an AC Meeting, FDA and the applicant may agree on the need to discuss feedback from the AC for the purpose of facilitating the remainder of the review. Such a meeting will generally be held by teleconference without a commitment for formal meeting minutes issued by the agency.

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.

d. Late-Cycle Meeting Background Packages: The Agency background package for the late-cycle meeting will be sent to the applicant not less than 10 calendar days (or 2 calendar days for an expedited review) before the late-cycle meeting. The package will consist of a brief memorandum from the review team outlining substantive application issues (e.g., deficiencies identified by primary and secondary reviews), the Agency's background package for the AC meeting (incorporated by reference if previously sent to the applicant), potential questions and/or points for discussion for the AC meeting (if planned) and the current assessment of the need for REMS or other risk management actions. If the application is subject to an expedited review, the background package may be streamlined and brief using a bulleted list to identify issues to be discussed.

e. Late-Cycle Meeting Discussion Topics: 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; status update of FDA's review activities associated with a scheduling recommendation under the Controlled Substances Act, if applicable; information requests from the review team to the applicant; and additional data or analyses the applicant may wish to submit.

   i. 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.

7. <u>Inspections:</u> 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.

C. FIRST CYCLE REVIEW MANAGEMENT

FDA and industry share a commitment to ensuring an efficient and effective first cycle review process for all applications subject to the PDUFA program. This commitment was first articulated in the GRMP guidance finalized in 2005. FDA will update this guidance in PDUFA VI to include review activities (e.g., the NME Program, REMS) that have been added to the human drug review program since the guidance was finalized, principles regarding notification to applicants regarding issues identified during FDA's initial review of the application, principles regarding FDA's notification to applicants regarding planned review timelines, and the importance of internal review timelines that govern aspects of the human drug review program that are not part of PDUFA performance goals. FDA will publish a revised draft guidance for public comment no later than the end of FY 2018.

D. REVIEW OF PROPRIETARY NAMES TO REDUCE MEDICATION ERRORS

To enhance patient safety, FDA is committed to 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. The following performance goals apply to FDA's review of drug and biological product proprietary names during development (as early as end-of-phase 2) and during FDA's review of a marketing application:

1. Proprietary Name Review Performance Goals During Drug Development

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 Name Review Performance Goals During Application Review

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.

E. MAJOR DISPUTE RESOLUTION

1. 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.

2. Performance goal:

90% of such answers are provided within 30 calendar days of the Center's receipt of the written appeal.

3. Conditions:

a. 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.

b. 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.

c. 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.

d. 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 (AC).

e. In these cases, once the required information is received by the Agency (including any advice from an AC), the person to whom the appeal was made, again has 30 calendar days from the receipt of the required information in which to either grant or deny the appeal.

f. 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.

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

F. CLINICAL HOLDS

1. 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.

2. Performance goal:

90% of such responses are provided within 30 calendar days of the Agency's receipt of the sponsor's response.

G. SPECIAL PROTOCOL QUESTION ASSESSMENT AND AGREEMENT

1. 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.

a. 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).

b. 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.

c. 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.

d. 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.

e. 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.

2. Performance goal:

90% of special protocol assessments and agreement requests completed and returned to sponsor within the timeframe.

3. Reporting:

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

H. MEETING MANAGEMENT GOALS

Formal PDUFA meetings between sponsors and FDA consist of Type A, B, B(EOP), and C meetings. These meetings are further described below.

- Type A meetings are those meetings that are necessary for an otherwise stalled drug development program to proceed (i.e., a "critical path" meeting) or to address an important safety issue. Post-action meetings requested within three months after an FDA regulatory action other than approval (i.e., issuance of a complete response letter) will also generally be considered Type A meetings.
- Type B meetings include pre-IND meetings and pre-NDA/BLA meetings, while Type B(EOP) meetings are reserved for certain End-of-Phase 1 meetings (i.e. for 21 CFR Part 312 Subpart E or 21 CFR Part 314 Subpart H or similar products) and End-of-Phase 2/pre-Phase 3 meetings. Meetings regarding REMS or postmarketing requirements that occur outside the context of the review of a marketing application will also generally be considered Type B meetings.
- A Type C meeting is any other type of meeting.[5]

1. Responses to Meeting Requests

a. **Procedure:** FDA will notify the requester in writing of the date, time, and place for the meeting, as well as expected Center participants following

[5] Refer to Section I.I.3 of this document that describes a specific type of Type C meeting pertaining to early consultations with FDA regarding the use of new surrogate endpoints as the primary basis of product approval in a proposed context of use.

receipt of a formal meeting request. Table 3 below indicates the timeframes for FDA's response to a meeting request.

Table 3

Meeting Type	Response Time (calendar days)
A	14
B	21
B(EOP)	14
C	21

i. For any type of meeting, the sponsor may request a written response to its questions rather than a face-to-face meeting, videoconference or teleconference. FDA will review the request and make a determination on whether a written response is appropriate or whether a face-to-face meeting, videoconference, or teleconference is necessary. If a written response is deemed appropriate, FDA will notify the requester of the date it intends to send the written response in the Agency's response to the meeting request. This date will be consistent with the timeframes specified in Table 4 below for the specific meeting type.

ii. For pre-IND and Type C meetings, while the sponsor may request a face-to-face meeting, the Agency may determine that a written response to the sponsor's questions would be the most appropriate means for providing feedback and advice to the sponsor. When it is determined that the meeting request can be appropriately addressed through a written response, FDA will notify the requester of the date it intends to send the written response in the Agency's response to the meeting request. This date will be consistent with the timeframes specified in Table 4 below for the specific meeting type.

b. **Performance Goal:** FDA will respond to meeting requests and provide notification within the response times noted in Table 3 for 90% of each meeting type.

2. Scheduling Meetings

a. **Procedure:** FDA will schedule the meeting on the next available date at 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. Table 4 below indicates the timeframes for the scheduled meeting date following receipt of a formal meeting request, or in the case of a written response, the timeframes for the Agency to send the written response. If the requested date for any meeting

type is greater than the specified timeframe, the meeting date should be within 14 calendar days of the requested date.

Table 4

Meeting Type	Meeting Scheduling or Written Response Time
A	30 calendar days from receipt of meeting request
B	60 calendar days from receipt of meeting request
B(EOP)	70 calendar days from receipt of meeting request
C	75 calendar days from receipt of meeting request

b. **Performance goal:** 90% of meetings are held within the timeframe for each meeting type, and 90% of written responses are sent within the timeframe for each meeting type.

3. Meeting Background Packages

The timing of the Agency's receipt of the sponsor background package for each meeting type (including those meetings for which a written response will be provided) is specified in Table 5 below.

Table 5

Meeting Type	Receipt of Background Package
A	At the time of the meeting request
B	30 calendar days before the date of the meeting or expected written response
B(EOP)	50 calendar days before the date of the meeting or expected written response*
C[6]	47 calendar days before the date of the meeting or expected written response*

***** If the scheduled date of a Type B(EOP) or C meeting is earlier than the timeframes specified in Table 4, the meeting background package will be due no sooner than 6 calendar days and 7 calendar days following the response time for Type B(EOP) and C meetings specified in Table 3, respectively.

[6] For Type C meetings that are requested as early consultations on the use of a new surrogate endpoint to be used as the primary basis for product approval in a proposed context of use, the meeting background package is due at the time of the meeting request. Refer to Section I.I.3 of this document.

4. Preliminary Responses to Sponsor Questions

a. **Procedure:** The Agency will send preliminary responses to the sponsor's questions contained in the background package no later than five calendar days before the meeting date for Type B(EOP) and C meetings.

b. **Performance goal:** 90% of preliminary responses to questions for Type B(EOP) meetings are issued by FDA no later than five calendar days before the meeting date.

5. Sponsor Notification to FDA

Not later than three calendar days following the sponsor's receipt of FDA's preliminary responses for a Type B(EOP) or C meeting, the sponsor will notify FDA of whether the meeting is still needed, and if it is, the anticipated agenda of the meeting given the sponsor's review of the preliminary responses.

6. Meeting Minutes

a. Procedure: The Agency will prepare minutes that 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 any meeting type.

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

7. Conditions

For a meeting to qualify for these performance goals:

a. A written request must be submitted to the review division.

b. The written request must provide:

i. A brief statement of the purpose of the meeting and the sponsor's proposal for either a face-to-face meeting or a written response from the Agency;

ii. A listing of the specific objectives/outcomes the requester expects from the meeting;

iii. A proposed agenda, including estimated times needed for each agenda item;

iv. A listing of planned external attendees;

v. A listing of requested participants/disciplines representative(s) from the Center with an explanation for the request as appropriate; and

vi. The date that the meeting background package will be sent to the Center. Refer to Table 5 for timeframes for the Agency's receipt of background packages.

c. 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 or B(EOP) meeting will be honored except in the most unusual circumstances.

8. Guidance

FDA will publish revised draft guidance on formal meetings between FDA and sponsors no later than September 30, 2018.

I. ENHANCING REGULATORY SCIENCE AND EXPEDITING DRUG DEVELOPMENT

To ensure that new and innovative products are developed and available to patients in a timely manner, FDA will build on the success of the FDA's regulatory science program that included advancing the science of meta-analysis methodologies, advancing the use of biomarkers and pharmacogenomics, enhancing communications between FDA and sponsors during drug development, and advancing the development of drugs for rare diseases. The extension and continuation of this work will encompass further evaluation and enhancement of FDA-sponsor communications, ensuring the sustained success of the breakthrough therapy program, establishing early consultations between FDA and sponsors on the use of new surrogate endpoints as the primary basis for product approval, advancing rare disease drug development, advancing the development of combination products, and exploring the use of real world evidence for use in regulatory decision-making.

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

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. Accordingly, FDA will maintain dedicated drug development communication and training staffs in CDER and CBER, focused on enhancing communication between FDA and sponsors during drug development.

One function of the staff is to serve as a liaison that will facilitate general and, in some cases, specific interactions between sponsors and each Center. The liaison 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 liaison will also serve as a secondary point of contact in each Center for sponsors who are

encountering challenges 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 will work with the review team and the sponsor to facilitate resolution of the issue.

The second function of the staff is to provide ongoing training to the review organizations on best practices in communication with sponsors. The content of training includes, but is not limited to, FDA's philosophy regarding timely interactive communication with sponsors during drug development as a core Agency activity, best practices for addressing sponsor requests for advice and timely communication of responses through appropriate mechanisms (e.g., teleconferences, secure email, or when questions are best addressed through the formal meetings process), and the role of the liaison staff in each Center in facilitating communication between the review staff and sponsor community, including the staff's role in facilitating resolution of individual communication requests. The staff will also collaborate with sponsor stakeholders (e.g., through participation in workshops, webinars, and other meetings) to communicate FDA's philosophy and best practices regarding communication with sponsors during drug development.

To continue to enhance timely interactive communication with sponsors during drug development in PDUFA VI, FDA will do the following:

a. **Independent Assessment.** FDA will contract with an independent third party to assess current practices of FDA and sponsors in communicating during drug development. The statement of work for this effort will be published for public comment prior to beginning the assessment. The third party will be expected to separately engage both FDA staff and individual sponsors through contractor-led interviews as part of the assessment. Due to the significant volume of FDA-sponsor interactions in a given year, the assessment will be based on a random subset of drug development programs identified by IND number. The third party will identify best practices and areas for improvement in communication by FDA review staff and sponsors. FDA will publish the final report of the assessment on FDA's website no later than the end of FY 2020.

b. **Public Workshop.** FDA will convene a public workshop by the end of March 2021 to discuss the findings of the independent assessment, including anonymized, aggregated feedback from sponsors and FDA review teams resulting from the contractor interviews.

c. **Guidance.** FDA will consider the third party's recommendations for best practices in communication and update the current draft or final guidance on "Best Practices for Communication Between IND Sponsors and FDA During Drug Development" if appropriate. If FDA determines that the guidance should be updated, based on the recommendations of the third party and the feedback received from the public workshop, FDA will update the guidance no later than one year following the public workshop.

2. Ensuring Sustained Success of Breakthrough Therapy Program

Breakthrough therapy designation is intended to expedite the development and review of drug and biological products, alone or in combination, for serious or life-threatening diseases or conditions when preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies.[7] A breakthrough therapy designation includes the features of the fast track program, intensive FDA guidance on an efficient drug development program, and an organizational commitment by FDA involving senior managers.[8] Additional resources will enable the Agency to continue to work closely with sponsors throughout the breakthrough therapy designation, development, and review processes. Both FDA and the regulated industry are committed to ensuring the expedited development and review of innovative therapies for serious or life-threatening diseases or conditions by investing additional resources into the breakthrough therapy program.

3. Early Consultation on the Use of New Surrogate Endpoints

FDA and industry believe that early consultation between review teams and sponsors is important for development programs where the sponsor intends to use a biomarker as a new surrogate endpoint that has never been previously used as the primary basis for product approval in the proposed context of use. Early consultation in the drug development program allows the review team to consult with FDA senior management to evaluate the sponsor's proposal before providing advice regarding the proposed biomarker as a new surrogate endpoint to support accelerated or traditional approval. Requests to engage with FDA on this topic will be considered a Type C meeting request. The purpose of this meeting is to discuss the feasibility of the surrogate as a primary endpoint, and identify any gaps in knowledge and how they might be addressed. The outcome of this meeting may require further investigation by the sponsor and discussion and agreement with the agency before the surrogate endpoint could be used as the primary basis for product approval. To qualify for this consultation, these Type C meeting requests must be accompanied by the complete meeting background package at the time the request is made that includes preliminary human data indicating impact of the drug on the biomarker at a dose that appears to be generally tolerable.[9] The remaining meeting procedures as described in Section I.H of this document will apply.

4. Advancing Development of Drugs for Rare Diseases

[7] See Section 506(a) of the Federal Food, Drug, and Cosmetic (FD&C) Act, 21 U.S.C. § 356(a).
[8] See FDA Guidance for Industry entitled "Expedited Programs for Serious Conditions – Drugs and Biologics," May 2014. A drug designated as a breakthrough therapy may also qualify for one or more of the other expedited programs as described in this guidance.
[9] Refer to Table 5 in Section I.H of this document.

FDA will build on the success of the Rare Disease Program (RDP) in CDER and CBER by continuing to advance and facilitate the development and timely approval of drugs and biologics for rare diseases, including rare diseases in children. The Rare Disease Program staff in CDER will be integrated into review teams for rare disease development programs and application review to provide their unique expertise on flexible and feasible approaches to studying and reviewing such drugs to include, for example, innovative use of biomarkers, consideration of non-traditional clinical development programs, use of adaptive study designs, evaluation of novel endpoints, application of new approaches to statistical analysis, and appropriate use of FDA's expedited development and review programs (i.e., Fast Track, Breakthrough, Priority Review, and Accelerated Approval). CBER, through its Rare Disease Program Staff, will also ensure that its review offices consider such flexible and feasible approaches in review.

The RDP staff will also continue to provide training to all CDER and CBER review staff related to development, review, and approval of drugs for rare diseases as part of the reviewer training core curriculum. The objective of the training will be 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 drug development and application review. The training will also emphasize the important role of the RDP staff as members of the core review team to help ensure consistency of scientific and regulatory approaches across applications and review teams.

RDP staff will continue to engage in outreach to industry, patient groups, and other stakeholders to provide training on FDA's RDP. The staff will continue to foster collaborations in the development of tools (e.g., patient reported outcome measures) and data (e.g., natural history studies) to support development of drugs for rare diseases. In addition, the staff will also facilitate interactions between stakeholders and FDA review divisions to increase awareness of FDA regulatory programs and engagement of patients in FDA's regulatory decision-making.

FDA will include updates on the activities and success of the RDP in the PDUFA annual performance report to include, for example, the number of training courses offered and staff trained, the number of review programs where RDP staff participated as core team members, and metrics related to engagement with external stakeholders. FDA will also continue to include information on rare disease approvals in its annual reports on innovative drug approvals, including utilization of expedited programs and regulatory flexibility and appropriate comparative metrics to non-rare disease innovative approvals.

5. Advancing Development of Drug-Device and Biologic-Device Combination Products Regulated by CBER and CDER

a. FDA will develop staff capacity and capability across the medical product centers and the Office of Combination Products (OCP) to more efficiently, effectively, and consistently review and respond to submissions that include

combination products. These staff will advance the development of combination products by providing combination product expertise as part of the core review team as applicable, and through promoting best practices for review of combination products. The additional capacity will include staff who will focus on review of cGMP, engineering aspects, human factors and bridging study protocols and study reports, and labeling, to include instructions-for-use materials.

b. FDA will streamline the process for combination product review and improve the Agency's ability to assess workload and allocate resources to the review of combination products.

   i. By no later than December 31, 2017, FDA will complete a lean process mapping for combination product review in order to inform changes to review work flow to improve the inter-center consultation process.

   ii. By no later than December 31, 2017, FDA will begin tracking workload and timelines for cross-center consultations to enable appropriate allocation of resources and regularly assess the progress of combination product review throughout PDUFA VI.

   iii. By no later than September 30, 2018, for each component within FDA that is consulted to participate in review of combination products, FDA will outline in appropriate internal documents the Agency's process for resolving internally any scientific or regulatory issues that arise, as well as a commitment for the medical product centers and OCP to coordinate and complete reviews and related activities when consulted in timelines set forth by PDUFA and other published documents (e.g., the GRMP guidance and GRMP MAPP).

c. FDA will establish Manuals of Policies and Procedures (MAPPs) and Standard Operating Policy and Procedures (SOPPs) to promote efficient, effective, and consistent combination product development and review. The documents will describe processes and procedures for conducting review of combination products, including the expectations for consultation of internal experts outside the reviewing Center. FDA will describe the responsibilities of staff in each Center and Office, expectations for core review team members and for other consultant staff in activities and meetings related to the combination product development program and application review. FDA will define the key terms to be used by staff in review of combination products to foster clear communication within FDA and to regulated industry. The topic areas and expected completion dates of these documents are specified below:

   i. Human Factors Assessments (March 31, 2019)

   ii. Quality assessment of combination products, including coordination of facility inspections (September 30, 2019)

iii. Patient-oriented labeling, including instructions-for-use materials for those drug-device and biologic-device combination products regulated by CBER and CDER (September 30, 2019)

d. By no later than December 31, 2018, FDA will make available on FDA's website key points of contact in OCP and the medical product centers for combination product review. FDA agrees to maintain and update this information periodically.

e. FDA will establish submission procedures for Human Factors protocols no later than September 30, 2018. Beginning in FY 2019, FDA will establish timelines to review and provide comment on the protocols for Human Factors studies of combination drug-device and biologic-device products within 60 days.

i. Procedure for review of human factors protocols for combination products: Upon specific request by a sponsor (including specific questions that the sponsor desires to be answered) consistent with the steps below, the Agency will evaluate human factors 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 human factors protocol design and scientific and regulatory requirements for which the sponsor seeks agreement (e.g., are the study participant groups appropriate to represent intended users, is the study endpoint adequate, are the critical tasks that should be evaluated appropriately identified).

(2) Within 60 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) Performance goals for FDA will be phased in, starting in FY 2019 as follows:

a. By FY 2019, review 50% of human factors protocol submissions within 60 days and provide sponsor with written comments.

b. By FY 2020, review 70% of human factors protocol submissions within 60 days and provide sponsor with written comments.

c. By FY 2021, review 90% of human factors protocol submissions within 60 days and provide sponsor with written comments.

f. By no later than December 31, 2018, FDA will begin staff training related to development, review, and approval of drug-device and biologic-device combination products reviewed in CDER and CBER. The training will be provided to all CDER, CBER, Center for Devices and Radiological Health (CDRH), and Office of Combination Products (OCP) staff, and will be part of the reviewer training core curriculum. The key purposes of this training include familiarizing review staff with the regulatory requirements and challenges associated with combination product applications and strategies to address these challenges; promoting best practices for review and regulation of combination products regulated by CDER and CBER, and helping ensure coordination and consistent approaches within the Centers in the review and regulation of combination product applications. The training will also emphasize the role of various experts in the Centers as members of the review team and OCP's roles and responsibilities in order to help ensure consistency of scientific and regulatory approaches across applications and review teams.

g. FDA will contract with an independent third party to assess current practices for combination drug product review. This study will focus on areas where the needs for inter-center coordination and consistent approaches are greatest, including such areas as the Request-for-Designation, cGMPs/facilities topics, human factors and bridging studies, and labeling. The contractor will be expected to engage both FDA staff and individual sponsors as part of the assessment. The assessment will be based on a randomly selected subset of combination products in various phases of development. The assessment will identify best practices and areas for improvement by FDA review staff and sponsors in the submission and review of combination products for consideration by both FDA and sponsors. FDA will publish the final report of the assessment on FDA's website no later than the end of FY 2020. FDA will consider the assessment findings regarding best practices on the part of FDA review staff and sponsors in any updates to relevant documents such as MAPPs, SOPPs, and submission procedures for human factors protocols, and in the review and submission of Combination Product applications.

h. By the end of FY 2019, FDA will publish draft guidance or update previously published guidance issued by the medical product centers and OCP for review staff and industry describing considerations related to drug-device and biologic-device combination product on the topics noted below. The draft guidance(s) will be finalized by the end of FY 2022.

   i. Bridging studies, including the bridging of data from combination products that employ different device components for the same drug or biologic and the same device component across different drugs and biologics.

   ii. Patient-oriented labeling (e.g., instructions-for-use).

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

As we participate in the current data revolution, it is important that FDA consider the possibilities of using so-called "real world" data as an important tool in evaluating not only the safety of medications but also their effectiveness. To accomplish this will require an understanding of what questions to ask, including how such data can be generated and used appropriately in product evaluation, what the challenges are to appropriate generation and use of these data, and how to address such challenges. Towards this end, FDA will do the following:

a. By no later than the end of FY 2018, FDA will complete one or more public workshop(s) with key stakeholders, including patients, biopharmaceutical companies, and academia, to gather input into issues related to Real World Evidence (RWE) use in regulatory decision-making. The workshop(s) should address, among other things, the following topics:

   - Benefits to patients, regulators, and biopharmaceutical companies of RWE in regulatory decision making;
   - RWE availability, quality, and access challenges, and approaches to mitigate these;
   - Methodological approaches for the collection, analysis, and communication of RWE; and
   - Appropriate contexts of use of RWE in regulatory decision-making regarding effectiveness.

b. By no later than the end of FY 2019, FDA will initiate (or fund by contract), appropriate activities (e.g., pilot studies or methodology development projects) aimed at addressing key outstanding concerns and considerations in the use of RWE for regulatory decision making.

c. By no later than the end of FY 2021, considering available input, such as from activities noted above, FDA will publish draft guidance on how RWE can contribute to the assessment of safety and effectiveness in regulatory submissions, for example in the approval of new supplemental indications and for the fulfillment of postmarketing commitments and requirements. FDA will work toward the goal of publishing a revised draft or final guidance within 18 months after the close of the public comment period.

J. ENHANCING REGULATORY DECISION TOOLS TO SUPPORT DRUG DEVELOPMENT AND REVIEW

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

To facilitate the advancement and use of systematic approaches to collect and utilize robust and meaningful patient and caregiver input that can more consistently inform drug development and, as appropriate, regulatory decision making, FDA will conduct the following activities during PDUFA VI:

a. FDA will strengthen the staff capacity to facilitate development and use of patient-focused methods to inform drug development and regulatory decisions. This staff, composed primarily of clinical, statistical, psychometric, and health outcomes research expertise, will be integrated into review teams as core members of the team during drug development and application review where the sponsor intends to use patient input or clinical outcome assessment (COAs) such as patient-reported outcomes (PROs) as part of the development program. A core responsibility of the staff will be to engage patient stakeholders and provide timely development-phase consultations to sponsors developing new tools to collect patient and caregiver input. This additional capacity is expected to advance the science of COA development and analysis, and the staff will also support the public qualification activities for COAs.

b. FDA will develop a series of guidance documents to focus on approaches and methods to bridge from initial patient-focused drug development meetings, like those piloted under PDUFA V, to fit-for-purpose tools to collect meaningful patient and caregiver input for ultimate use in regulatory decision making. Prior to the issuance of each guidance, as part of the development, FDA will conduct a public workshop to gather input from the wider community of patients, patient advocates, academic researchers, expert practitioners, industry, and other stakeholders.

   i. By the end of FY 2018, FDA will publish a draft guidance describing approaches to collecting comprehensive and representative patient and caregiver input on burden of disease and current therapy. The guidance will address topics including: standardized nomenclature and terminologies, methods to collect meaningful patient input throughout the drug development process, and methodological considerations for data collection, reporting, management, and analysis.

   ii. By the end of FY 2019, FDA will publish a draft guidance describing processes and methodological approaches to development of holistic sets of impacts that are most important to patients. The guidance will address topics including: methods for sponsors, patient organizations, academic researchers, and expert practitioners to develop and identify what are most important to patients in terms of burden of disease, burden of treatment, and other critical aspects. The guidance will address how patient input can inform drug development and review processes, and, as appropriate, regulatory decision making.

   iii. By the end of FY 2020, FDA will publish a draft guidance describing approaches to identifying and developing measures for an identified set of impacts (e.g., burden of disease and treatment), which may facilitate collection of meaningful patient input in clinical trials. The guidance will address methods to measure impacts in a meaningful way, and identify an appropriate set of measure(s) that matter most to patients.

iv. By the end of FY 2021, FDA will publish a draft guidance on clinical outcome assessments, which, when final, will, as appropriate, revise or supplement the 2009 Guidance to Industry on Patient-Reported Outcome Measures. The draft guidance will also address technologies that may be used for the collection, capture, storage, and analysis of patient perspective information. The guidance will also address methods to better incorporate clinical outcome assessments into endpoints that are considered significantly robust for regulatory decision-making.

v. For each of the above, FDA will work toward the goal of publishing a revised draft or final guidance within 18 months after the close of the public comment period on the draft guidance.

c. FDA will create and maintain a repository of publicly available tools on FDA's website as a resource for stakeholders. The repository will also include FDA's clinical outcome assessment compendium, patient-focused drug development meeting resources, and ongoing efforts on patient-focused drug development.

d. As appropriate, FDA will revise existing MAPPs and SOPPs to include suggested approaches for incorporating an increased patient focus in other on-going or planned FDA public meetings (e.g., FDA scientific workshops). In addition, as appropriate, FDA will develop and implement staff training related to processes, tools, and methodologies described in this section.

e. By the end of FY 2019, FDA will conduct a public workshop, through a qualified third party, with the primary purpose of gathering ideas and experiences of the patient and caregiver community and their recommendations on approaches and best practices that would enhance patient engagement in clinical trials. The meeting may also gather input from sponsors, academic researchers, and expert practitioners. The meeting will result in a published report on proceedings and recommendations from discussions at the meeting.

2. Enhancing Benefit-Risk Assessment in Regulatory Decision-Making

FDA will further the agency's implementation of structured benefit-risk assessment, including the incorporation of the patient's voice in drug development and decision-making, in the human drug review program through the following commitments to be accomplished during PDUFA VI:

a. By March 31, 2018, FDA will publish an update to the implementation plan titled "Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making." The update will include a report on the progress made during PDUFA V and a plan for continued implementation during FYs 2018-2022.

b. By the end of FY 2019, FDA will convene and/or participate in, at least one meeting, conducted through a qualified third party, to gather industry, patient,

researcher, and other stakeholder input on key topics. This would include applying the benefit-risk framework throughout the human drug lifecycle, including best approaches to communicating FDA's benefit-risk assessment.

c. By the end of FY 2020, FDA will publish a draft guidance on benefit-risk assessments for new drugs and biologics. This guidance will:

   i. Articulate FDA's decision-making context and framework for benefit-risk assessment, illustrating the application of the benefit-risk framework throughout the human drug lifecycle, using a case study approach, if appropriate.

   ii. Discuss appropriate interactions between a sponsor and FDA during drug development to understand the therapeutic context (i.e., the severity of disease that represents the targeted indication and the extent of unmet medical need in the target population) regarding regulatory decisions for the product at the various stages of drug development and evaluation.

   iii. Discuss appropriate approaches to communicate to the public FDA's thinking on a product's benefit-risk assessment, such as through product-specific discussions using the benefit-risk framework at AC meetings.

d. Beginning in FY 2021, FDA will conduct an evaluation of the implementation of the benefit-risk framework in the human drug review program. This evaluation will assess how reviewers across the organization apply the benefit-risk framework and identify best practices in use of the benefit-risk framework. The evaluation of the benefit-risk framework implementation conducted in PDUFA V will serve as a baseline for this PDUFA VI assessment.

e. As appropriate, FDA will revise relevant MAPPs and SOPPs to include new approaches that incorporate FDA's benefit-risk framework into the human drug review program.

3. Advancing Model-Informed Drug Development

To facilitate the development and application of exposure-based, biological, and statistical models derived from preclinical and clinical data sources, herein referred to as "model-informed drug development" (MIDD) approaches, FDA will conduct the following activities during PDUFA VI:

a. FDA will develop its regulatory science and review expertise and capacity in MIDD approaches. This staff will support the highly-specialized evaluation of model-based strategies and development efforts.

b. FDA will convene a series of workshops to identify best practices for MIDD. Topics will include: (1) physiologically-based pharmacokinetic modeling; (2) design analysis and inferences from dose-exposure-response studies; (3) disease progression model development, including natural history and trial simulation; and (4) immunogenicity and correlates of protection for evaluating

biological products, including vaccines and blood products. Each workshop will focus on current and emerging scientific approaches, including methodological limitations. FDA will produce a written summary of the topics discussed in each workshop.

c. Starting in FY 2018, FDA will conduct a pilot program for MIDD approaches. For sponsors participating in the pilot program, FDA will grant a pair of meetings specifically designed for this pilot program, consisting of an initial and a follow-up meeting on the same drug development issues, to occur within a span of approximately 120 days. These meetings will be led by the clinical pharmacology or biostatistical review components within CDER or CBER.

   i. FDA will publish a Federal Register Notice announcing the pilot program and outlining the eligibility criteria and process for submitting to FDA requests to participate in the pilot program.

   ii. FDA will select 2-4 proposals (e.g., 1-2 per Center) quarterly each year. FDA will convene an internal review group to review proposals on a quarterly basis and provide recommendations on prioritization and selection of proposals and share knowledge and experience. Program selection will take into account development programs where clinical data are limited such that integration across non-traditional sources may be needed, and for which MIDD can assess uncertainties about issues such as dosing, duration, and patient selection in a way that can inform regulatory decision-making.

   iii. Sponsors who do not participate in the pilot will have an opportunity to interact with the Agency through traditional channels.

d. By end of FY 2019, FDA will publish draft guidance, or revise relevant existing guidance, on model-informed drug development.

e. By end of FY 2021, FDA will develop or revise, as appropriate, relevant MAPPs or SOPPs, and/or review templates and training, to incorporate guidelines for the evaluation of MIDD approaches.

4. Enhancing Capacity to Review Complex Innovative Designs

To facilitate the advancement and use of complex adaptive, Bayesian, and other novel clinical trial designs, FDA will conduct the following activities during PDUFA VI:

a. FDA will develop the staff capacity to enable processes to facilitate appropriate use of these types of methods. This staff will support the computationally intensive review work necessary to evaluate complex adaptive, Bayesian, and other novel clinical trial designs, with a particular focus on clinical trial designs for which simulations are necessary to evaluate the operating characteristics.

b. Starting in FY 2018, FDA will conduct a pilot program for highly innovative trial designs for which analytically derived properties (e.g., Type I error) may not be feasible, and simulations are necessary to determine trial operating characteristics. For INDs in the pilot program, FDA will grant a pair of meetings specifically designed for this pilot program, consisting of an initial and follow-up meeting on the same design, to occur within a span of approximately 120 days. These meetings will be led by the biostatistical review components within CDER or CBER. The opportunity for increased interaction with the agency will provide better understanding of the agency's requirements for trial simulations involved in the use of the pilot study design and allow for iteration of design modifications, if needed. In return, FDA's ability to publicly discuss example designs will provide better clarity on the acceptance of different types of trial designs that should facilitate their use in future development programs.

   i. FDA will publish a Federal Register Notice announcing the pilot program, clarifying pilot program eligibility, and describing the proposal submission and selection process.

   ii. FDA will select up to 2 proposals (e.g., 1 per Center) quarterly each year. FDA will convene an internal review group to review proposals on a quarterly basis and provide recommendations on prioritization and selection of proposals and share knowledge and experience. Program selection will be prioritized based on trial design features and therapeutic areas of high unmet need.

   iii. To promote innovation in this area, trial designs developed through the pilot program may be presented by FDA (e.g., in a guidance or public workshop) as case studies, including while the drug studied in the trial has not yet been approved by FDA. Before FDA grants the initial meeting, FDA and the sponsor will agree on the information that FDA may share publicly in these case studies. Participation in the pilot program, including such agreement on information disclosure, will be voluntary and at the discretion of the sponsor.

   iv. FDA may periodically review the progress of the pilot program and determine whether it is appropriate to adjust any aspects of the program.

   v. Sponsors who do not participate in the pilot will have an opportunity to interact with the Agency through traditional channels. The pilot program will not affect FDA's existing procedures for providing advice on trial designs.

c. By end of 2nd Quarter FY 2018, FDA will convene a public workshop to discuss various complex adaptive, Bayesian, and other novel clinical trial designs, with a particular focus on clinical trial designs for which simulations are necessary to evaluate the operating characteristics, and the acceptability of those designs in regulatory decision-making.

d. By end of FY 2018, FDA will publish draft guidance on complex adaptive (including Bayesian adaptive) trial designs.

e. By end of FY 2020, FDA will develop or revise, as appropriate, relevant MAPPs, SOPPs and/or review templates and training to incorporate guidelines on evaluating complex clinical trial designs that rely on computer simulations to determine operating characteristics.

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

To support the enhancement of analysis data standards for product development and review in the human drug review program, FDA will conduct the following activities during PDUFA VI:

a. FDA will develop the staff capacity to efficiently review and provide feedback to sponsors on the readiness of submitted analysis data sets and programs for statistical review. This staff will support pre- and post-submission discussion of standardized datasets and programs, and maintain the knowledge of and engage in collaborations about standards models used in the design, analysis and review of clinical and non-clinical studies. Examples of these standards models could include the Standard for Exchange of Nonclinical Data (SEND), Clinical Data Acquisition Standards Harmonization (CDASH), Study Data Tabulation Model (SDTM), and Analysis Data Model (ADaM).

b. In parallel, FDA will improve staff capacity to assist with FDA development and updating of therapeutic area user guides (TAUGs) to include the appropriate content for the analysis data standards used in submission and review.

c. By end of FY 2019, FDA will convene a public workshop to advance the development and application of analysis data standards.

d. FDA will collaborate with external stakeholders and participate in public workshops held by third parties such as standards development organizations, on development of data standards, processes, documentation and continuous improvement of clinical trials and regulatory science.

e. By end of FY 2020, FDA will develop or revise, as appropriate, relevant guidance, MAPPs, SOPPs and training associated with submission and utilization of standardized analysis datasets and programs used in review, and on the processes, procedures, and responsibilities related to the receipt, handling, and documentation of submitted analysis data and programs.

6. Enhancing Drug Development Tools Qualification Pathway for Biomarkers

To facilitate the enhancement of the drug development tools qualification pathway for biomarkers, FDA will conduct the following activities during PDUFA VI:

a. FDA will develop the staff capacity to enhance biomarker qualification review by increasing base capacity. FDA will also pilot processes to engage external experts to support review of biomarker qualification submissions.

b. By the end of FY 2018, FDA will convene a public meeting to discuss 1) taxonomy for biomarkers used in drug development, and 2) a framework with appropriate standards and scientific approaches to support biomarkers under the taxonomy, including scientific criteria to determine acceptance of a biomarker qualification submission and essential elements of a formal biomarker qualification plan.

c. By the end of FY 2018, FDA will publish draft guidance on proposed taxonomy of biomarker usage and related contexts of use.

d. By the end of FY 2020, FDA will publish draft guidance on general evidentiary standards for biomarker qualification to be supplemented with focused guidance on specific biomarker uses and contexts.

e. FDA will develop or revise, as appropriate and necessary, relevant MAPPs and SOPPs on the biomarker qualification process.

f. FDA will list biomarker qualification submissions that are in the qualification process on a public website, to be updated quarterly. Inclusion of a submission on this list will be based on the consent of the submitter for FDA to publish information about the submission, including stage and current status of qualification and the proposed use of the biomarker. Following qualification of a biomarker FDA will post reviews and summary documents that outline the qualification program and data supporting a qualification decision.

g. Sponsors who do not use this qualification pathway will have an opportunity to interact with the Agency through traditional channels.

K. 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, standardization and integration of REMS into the healthcare system, enhancing communication and coordination between postmarketing and pre-market review staff, and improving tracking, communication and oversight of postmarketing safety issues. 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 A) advancing postmarketing drug safety evaluation through expansion of the Sentinel System and integration into FDA pharmacovigilance activities, and B)

timely and effective evaluation and communication of postmarketing safety findings related to human drugs.

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

FDA will use user fee funds to conduct a series of activities to systematically implement and integrate Sentinel in FDA pharmacovigilance practices. These activities will involve augmenting the quality and quantity of data available through the Sentinel System, improving methods for determining when and how that data is utilized, and comprehensive training of review staff on the use of Sentinel.

a. FDA will work toward expanding the Sentinel System's sources of data and enhancing the system's core capabilities.

b. FDA will enhance its communication with sponsors and the public regarding general methodologies for Sentinel queries, including what the Agency has learned regarding the most appropriate ways to query and use Sentinel data. This can be done through enhancement of existing mechanisms and/or greater frequency of such mechanisms.

c. FDA will evaluate additional ways to facilitate public and sponsor access to Sentinel's distributed data network to conduct safety surveillance.

d. By the end of FY 2019, FDA will hold or support a public meeting engaging stakeholders to discuss current and emerging Sentinel projects and seek stakeholder feedback and input regarding gaps in the current system to facilitate the further development of Sentinel and its system of Active Risk Identification and Analysis (ARIA).

e. By the end of FY 2020, FDA will establish policies and procedures (MAPPs and SOPPs) to facilitate informing sponsors about the planned use of Sentinel to evaluate a safety signal involving their respective products. These MAPPs and SOPPs will address what types of evaluations and what information about the evaluations will be shared with sponsors, and the timing of such communications.

f. By the end of FY 2020, FDA will facilitate integration of Sentinel into the human drug review program in a systematic, efficient, and consistent way through staff development and by updating existing SOPPs and MAPPs, as needed.

g. By the end of FY 2020, FDA will develop a comprehensive training program for review staff (e.g., epidemiologists, statisticians, medical officers, clinical analysts, project managers, and other review team members) to ensure that staff have a working knowledge of Sentinel, can identify when Sentinel can inform important regulatory questions, and are able to consistently participate in use of Sentinel to evaluate safety issues.

h. By the end of FY 2022, FDA will analyze, and report on the impact of the Sentinel expansion and integration on FDA's use of Sentinel for regulatory purposes, e.g., in the contexts of labeling changes, PMRs, or PMCs.

2. Timely and Effective Evaluation and Communication of Postmarketing Safety Findings Related to Human Drugs

FDA will use user fee funds to continue to support the review, oversight, tracking, and communication of postmarketing drug safety issues.

a. FDA will make improvements to its current processes that capture and track information, including enhancements to its information technology systems, as needed, in order to support the management and oversight of postmarketing drug safety issues.

b. By the end of FY 2019, FDA will update existing policies and procedures (MAPPs and SOPPs) concerning tracking postmarketing safety signals to include consistent and timely notification to a sponsor (1) when a serious safety signal involving a product is identified and (2) to the extent practicable, not less than 72 hours before public posting of a safety notice under section 921 of the Food and Drug Administration Amendments Act of 2007.[10]

c. By the end of FY 2022, FDA will conduct, or fund by contract, an assessment of how its data systems and processes, as described in MAPPs and SOPPs, support review, oversight, and communication of postmarketing drug safety issues.

[10] FD&C Act § 505(k)(5), 21 U.S.C. 355(k)(5).

II. ENHANCING MANAGEMENT OF USER FEE RESOURCES

FDA will modernize the user fee structure to improve the predictability of FDA funding and sponsor invoices, improve efficiency by simplifying the administration of user fees, and enhance flexibility of financial mechanisms to improve management of PDUFA program funding. FDA is committed to enhancing management of PDUFA resources and ensuring PDUFA user fee resources are administered, allocated, and reported in an efficient and transparent manner. FDA will conduct a series of resource capacity planning and financial transparency activities to enhance management of PDUFA resources in PDUFA VI.

A. RESOURCE CAPACITY PLANNING AND MODERNIZED TIME REPORTING

FDA is committed to enhancing management of PDUFA resources in PDUFA VI. FDA will conduct activities to develop a resource capacity planning function and modernized time reporting approach in PDUFA VI.

1. FDA will publish a PDUFA program resource capacity planning and modernized time reporting implementation plan no later than the 2nd quarter of FY 2018. FDA will continue to utilize information and recommendations from a third party assessment of resource capacity planning, financial analytics, and modernized time reporting for PDUFA as part of the implementation plan.

2. FDA will staff a resource capacity planning team that will implement and manage a capacity planning system across the PDUFA program in PDUFA VI.

3. FDA will obtain through a contract with an independent accounting or consulting firm an evaluation of options and recommendations for a new methodology to accurately assess changes in the resource and capacity needs of the human drug review program. The report will be published no later than end of FY 2020 for public comment. Upon review of the report and comments, FDA will implement robust methodologies for assessing resource needs of the program. This will include the adoption of a new resource capacity adjustment methodology, in place of the current PDUFA workload adjuster, that accounts for sustained increases in PDUFA workload.

4. FDA recognizes that revenue generated by the workload adjuster and the resource capacity adjustment will be allocated to and used by organizational review components engaged in direct review work to enhance resources and expand staff capacity and capability. FDA will document in the annual financial report how the workload adjuster and resource capacity adjustment fee revenues are being utilized.

B. FINANCIAL TRANSPARENCY AND EFFICIENCY

FDA is committed to ensuring PDUFA user fee resources are administered, allocated, and reported in an efficient and transparent manner. FDA will conduct activities to evaluate the

financial administration of the PDUFA program to help identify areas to enhance efficiency. FDA will also conduct activities to enhance transparency of PDUFA program resources.

1. FDA will contract with an independent third party to conduct an evaluation of PDUFA program resource management during FY 2018 to ensure that PDUFA user fee resources are administered, allocated, and reported in an efficient and transparent manner in PDUFA VI. The study will include, but is not limited, to the following areas:

a. Evaluate all components of the PDUFA program resource planning, request, and allocation process from when FDA receives the user fee funds through when funds are spent. The contractor will recommend options to improve the process and data needed to enhance resource management decisions.

b. Assess how FDA administers PDUFA user fees organizationally, including, but not limited to, billing, user fee collection, and execution. The contractor will recommend options to enhance the efficiency of user fee administration.

c. Evaluate FDA's existing PDUFA program financial and administrative oversight and governance functions. Assess alternative governance models including roles and responsibilities, organizational location, and personnel skill sets required. The contractor will recommend options on the most effective governance model to support the human drug review program.

d. Assess FDA's technical capabilities to conduct effective financial management and planning in the context of generally accepted government resource management and planning practices. The contractor will recommend options for the technical capabilities needed by financial personnel involved in PDUFA resource management to enhance financial management and planning.

e. Evaluate how FDA estimates fee paying units for annual fee setting. The contractor will recommend options to enhance the accuracy of FDA's PDUFA user fee estimation methods.

2. FDA will publish a PDUFA 5-year financial plan no later than the 2nd quarter of FY 2018. FDA will publish updates to the 5-year plan no later than the 2nd quarter of each subsequent fiscal year.

3. FDA will convene a public meeting no later than the third quarter of each fiscal year starting in FY 2019 to discuss the PDUFA 5-year financial plan, along with the Agency's progress in implementing modernized time reporting, resource capacity planning, and the modernized user fee structure.

III. IMPROVING FDA HIRING AND RETENTION OF REVIEW STAFF

To speed and improve development of safe and effective new therapies for patients, enhancements to the human drug review program require that FDA hire and retain sufficient numbers and types of technical and scientific experts to efficiently conduct reviews of human drug applications. In order to strengthen this core function and increase the public health impact of new therapies, the FDA will commit to do the following:

A. COMPLETION OF MODERNIZATION OF THE HIRING SYSTEM INFRASTRUCTURE AND AUGMENTATION OF SYSTEM CAPACITY:

1. Complete implementation of FTE-based position management system capability.

a. FDA will complete development of Position Management baseline accounting of all current positions and FTE counts engaged in the human drug review program for each applicable Center and Office including filled and vacant positions, a governance structure for on-going position management that will be accountable to FDA senior management, and Position Management policy and guidance ratified by FDA senior management, outlining processes for adding new positions, deleting positions, and changing established positions.

b. FDA will complete implementation of the new Position-Based Management System.

2. Complete implementation of an online position classification system

a. FDA will finalize the establishment of an online Position Description (PD) library. The library will include all current well-classified PDs and current standardized PDs. Once operational, any new PDs classified using the on-line classification tools, and any newly created standardized PDs, will be stored and accessible within FDA's PD library and available for FDA-wide use as appropriate.

3. Complete implementation of corporate recruiting

a. For key scientific and technical disciplines commonly needed across offices engaged in the human drug review program, FDA will complete the transition from the use of individual vacancy announcements for individual offices to expanded use of a common vacancy announcement and certificate of eligible job applicants that can be used by multiple offices. As a part of this effort, FDA will complete the transition from use of individual announcements that are posted for a limited period to common vacancy announcements with open continuous posting to maximize the opportunity for qualified applicants to apply for these positions.

B. AUGMENTATION OF HIRING STAFF CAPACITY AND CAPABILITY

In recognition of the chronic and continuing difficulties of recruiting and retaining sufficient numbers of qualified Human Resources (HR) staff, FDA will engage a qualified contractor to provide continuous support throughout PDUFA VI to augment the existing FDA HR staff capacity and capabilities. The utilization of a qualified contractor will assist FDA in successfully accomplishing PDUFA goals for recruitment and retention of human drug review program staff.

C. COMPLETE ESTABLISHMENT OF A DEDICATED FUNCTION TO ENSURE NEEDED SCIENTIFIC STAFFING FOR HUMAN DRUG REVIEW PROGRAM

1. Rapid advances in the science and technology of human drug development and manufacturing require FDA's human drug review program staff to keep pace with science and learn innovative methods and techniques for review of new therapies. FDA will complete the establishment of a new dedicated unit within the Office of Medical Products and Tobacco charged with the continuous recruiting, staffing, and retention of scientific, technical and professional staff for the process for the review of human drug applications.

a. The unit will continuously develop and implement scientific staff hiring strategies and plans, working closely with the center review offices and the FDA HR office, to meet discipline-specific hiring commitments and other targeted staffing needs. It will function as a scientific-focused recruiter conducting ongoing proactive outreach to source qualified candidates, and conducting competitive recruiting to fill vacancies that require top scientific, technical and professional talent.

b. The unit will conduct analyses, no less than annually, of compensation and other factors affecting retention of key staff in targeted disciplines, providing leadership and support for agency compensation oversight boards that currently exist or may be established as needed to ensure retention of key scientific, technical and professional staff.

D. SET CLEAR GOALS FOR HUMAN DRUG REVIEW PROGRAM HIRING

1. FDA will establish priorities for management of the metric goals for targeted hires within the human drug review program staff for the years of PDUFA VI. These goals for targeted hires are summarized in the Table 6 below:

Table 6

	FY 2018	FY 2019	FY 2020	FY 2021	FY 2022
CDER	43	57	45	17	9
CBER	16	8	7	1	0
Other FDA	12	9	6	0	0
Total FTE	71	74	58	18	9

2. FDA will confirm progress in the hiring of PDUFA V FTEs. FDA will report on progress against the hiring goals for FY 2018-2022 on a quarterly basis posting updates to the FDA website PDUFA Performance webpage.

E. COMPREHENSIVE AND CONTINUOUS ASSESSMENT OF HIRING AND RETENTION

FDA hiring and retention of staff for the human drug review program will be evaluated by a qualified, independent contractor with expertise in assessing HR operations and transformation. This will include continuous assessments throughout the course of implementation of the performance initiatives identified in sections III.A-D, and metrics including, but not limited to, those related to recruiting and retention in the human drug review program including, but not limited to, specifically targeted scientific disciplines and levels of experience. The contractor will conduct a comprehensive review of current hiring processes and hiring staff capacity and capabilities that contribute to achievement of successes, potential problems, or delays in human drug review program staff hiring. This includes the entire hiring function and related capabilities. FDA and regulated industry leadership will periodically and regularly assess the progress of hiring and retention throughout PDUFA VI.

1. Initial Assessment: The assessment will include an initial baseline assessment to be conducted and completed no later than December 31, 2017. The initial baseline study will include an evaluation of the current state and provide recommended options to address any identified gaps or areas identified as priorities for improvement, and a study report to be published no later than December 31, 2017. FDA will hold a public meeting no later than December 31, 2017, to present and discuss report findings, and present its specific plans, including agency senior management oversight, and timeline for implementing recommended enhancements to be fully operational by no later than December 31, 2018.

2. Interim Assessment: An interim assessment will be published by March 31, 2020, for public comment. By June 30, 2020, FDA will hold a public meeting during which the public may present their views. FDA will discuss the findings of the interim assessment, including progress relative to program milestones and metrics, and other aggregated feedback from internal customers and participants in HR services that may be included in the continuous assessment. FDA will also address any issues identified to date including actions proposed to improve the likelihood of success of the program.

3. Final Assessment: A final assessment will be published by December 31, 2021, for public comment. FDA will hold a public meeting by no later than March 30, 2022, during which the public may present their views. FDA will discuss the findings of the final assessment, including progress relative to program milestones and metrics, and other aggregated feedback from internal customers and participants in HR services that may be included in the continuous assessment. FDA will also address any issues identified and plans for addressing these issues.

IV. INFORMATION TECHNOLOGY GOALS

A. OBJECTIVE

FDA is committed to achieve the long-term goal of improving the predictability and consistency of the electronic submission process (Section IV.B), and enhancing transparency and accountability of FDA information technology related activities (Section IV.C). FDA is pursuing these objectives through IT investments that support the PDUFA program.

B. IMPROVE THE PREDICTABILITY AND CONSISTENCY OF PDUFA ELECTRONIC SUBMISSION PROCESSES

1. Electronic Submission Documentation:
By December 31, 2017, FDA will publish and maintain up-to-date documentation for the following:

a. The electronic submission process, including key electronic submission milestones and associated sponsor notifications. The description should cover the complete process undergone by a submission from the completion of its upload to the Electronic System Gateway (ESG) through the time the submission is made available to the review team.

b. The rejection process for electronic submissions.

c. The electronic submission validation criteria.

d. Software names and versions for Electronic Common Technical Document (eCTD) validation and data validation tools.

2. Electronic Submission and System Status:
By September 30, 2018, FDA will:

a. Publish targets for and measure ESG availability overall (including scheduled downtime) and during business hours (8am to 8pm Eastern Time). ESG availability is defined for the purposes of this commitment letter as the ability for an external user to complete a submission from each entry point to its delivery to the appropriate FDA Center.

b. Post current ESG operational status on its public website.

c. Publish submission instructions to use in the event of an ESG service disruption.

3. By December 31, 2017, FDA will publish target time frames for the 1) expected submission upload duration(s) and 2) timeframe between key milestones and notifications as defined in 1(a).

4. By September 30, 2018, FDA will implement the ability to communicate electronic submission milestone notifications, including final submission upload status (e.g., successfully processed or rejected), to sender/designated contact.

5. FDA will provide expert technical support for electronic submissions to FDA review staff for submission navigation and troubleshooting.

6. For those systems that sponsors interact with directly, FDA will invite industry to provide feedback and/or participate in user acceptance testing in advance of implementing significant changes that impact industry's interaction with the system.

7. By December 31, 2017, FDA will document and implement a process to provide ample advance notification of systems and process changes commensurate with the complexity of the change and the impact to sponsors for ESG scheduled unavailability and user interface changes.

C. ENHANCE TRANSPARENCY AND ACCOUNTABILITY OF FDA ELECTRONIC SUBMISSION AND DATA STANDARDS ACTIVITIES

1. FDA staff and industry will jointly plan and hold quarterly meetings and will share performance updates prior to each meeting. The meeting will address current challenges and emerging needs.

2. Beginning no later than September 30, 2018, FDA will hold annual public meetings to seek stakeholder input related to electronic submission system past performance, future targets, emerging industry needs and technology initiatives to inform the FDA IT Strategic Plan and published targets.

3. By December 31, 2017, FDA will post, at least annually, historic and current metrics on ESG performance in relation to published targets, characterizations and volume of submissions, and standards adoption and conformance.

4. By December 31, 2017, FDA will incorporate strategic initiatives in support of PDUFA goals into the FDA IT Strategic Plan. Milestones and metrics for PDUFA initiatives will be included in the plan. The plan will be updated and discussed annually during a meeting described in Section IV.C.1..

5. FDA will:

a. Collaborate with Standards Development Organizations and stakeholders to ensure long-term sustainability of supported data standards.

b. Publish a data standards action plan updated at least quarterly.

c. Publish and maintain a current FDA Data Standards Catalog.

V. 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 the human drug review program

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 for the review of human drug applications

8. Improved communication between the FDA and industry

B. STUDIES WILL INCLUDE:

1. Assessment of current practices of FDA and sponsors in communicating during drug development as described in Section I.I.1.

2. Assessment of the current practices for combination drug product review as described in Section I.I.5.

3. Evaluation of how reviewers across the organization apply the benefit-risk framework and identify best practices in use of the benefit-risk framework as described in Section I.J.2.

4. Analysis of the impact of the Sentinel expansion and use for regulatory purposes as described in Section I.K.1.

5. Assessment of how FDA data systems and processes, as described in MAPPs and SOPPs, support review, oversight, and communication of postmarketing drug safety issues, as described in Section I.K.2.

6. Evaluation of options and recommendations for a new methodology to accurately assess changes in the resource and capacity needs of the human drug review program as described in Section II.A.3.

7. Evaluation of PDUFA program resource management to ensure that PDUFA user fee resources are administered, allocated, and reported in an efficient and transparent manner in PDUFA VI as described in Section II.B.1.

8. Comprehensive and continuous assessment of hiring and retention as described in Section III.E.

VI. PROGRESS REPORTING FOR PDUFA VI AND CONTINUING PDUFA V INITIATIVES

A. FDA will include in the annual PDUFA Performance Report information on the Agency's progress in meeting the specific commitments identified in Sections I.I-K of this document.

B. FDA will include in the annual PDUFA Financial Report information on the Agency's progress in the hiring of new staff used to support the new initiatives as identified in Section III.

VII. DEFINITIONS AND EXPLANATION OF TERMS

1. "Human drug applications" refers to new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act and biologics license applications submitted under section 351(a) of the Public Health Service Act, as defined in the Prescription Drug User Fee Act.[11]

2. "Human drug review program" refers to the activities to conduct "the process for the review of human drug applications," as defined in the Prescription Drug User Fee Act.[12]

3. 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.

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

5. 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):

a. Final printed labeling

[11] FD&C Act § 735(1), 21 U.S.C. § 379g(1).
[12] FD&C Act § 735(6), 21 U.S.C. § 379g(6).

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

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

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

7. 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.

8. As used in this commitment letter, "regulatory decision making" may include, for example, FDA's process for making a regulatory decision regarding a drug or biological product throughout the product lifecycle, such as during drug development, following FDA's review of a marketing application, including review of proposed labeling for the product, or in the post-approval period (e.g., FDA's decision regarding a supplement to an approved application).