PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2023 THROUGH 2027

I. ENSURING THE EFFECTIVENESS OF THE HUMAN DRUG REVIEW PROGRAM

A. Review Performance Goals

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

C. New Molecular Entity (NME) Milestones and Postmarketing Requirements (PMRs)

D. Split Real Time Application Review (STAR) Pilot Program

E. Expedited Reviews

F. Review of Proprietary Names to Reduce Medication Errors

G. Major Dispute Resolution

H. Clinical Holds

I. Special Protocol Question Assessment and Agreement

J. Meeting Management Goals

K. Enhancing Regulatory Science and Expediting Drug Development

L. Enhancing Regulatory Decision Tools to Support Drug Development and Review

M. Enhancement and Modernization of the FDA Drug Safety System

N. Enhancements Related to Product Quality Reviews, Chemistry, Manufacturing, and Controls Approaches, and Advancing the Utilization of Innovative Manufacturing Technologies

O. Enhancing CBER's Capacity to Support Development, Review, and Approval of Cell and Gene Therapy Products

P. Supporting Review of New Allergenic Extract Products

II. CONTINUED ENHANCEMENT OF USER FEE RESOURCE MANAGEMENT

A. Resource Capacity Planning

B. Financial Transparency

PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2023 THROUGH 2027

This document contains the performance goals and procedures for the Prescription Drug User Fee Act (PDUFA) reauthorization for fiscal years (FYs) 2023-2027, known as PDUFA VII. 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 VII. 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 supplements 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.

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.

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

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

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[3]	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[4] 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

[3] FDA will report the number filed, on time, and overdue for Class 1 & Class 2 resubmitted original applications separately, but for review goal performance purposes (percentage on time), these will be consolidated into one performance goal.

[4] FDA will report the number received, on time, and overdue for Class 1 & Class 2 resubmitted efficacy supplements separately, but for review goal performance purposes (percentage on time), these will be consolidated into one performance goal.

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, 2022, through September 30, 2027.[5] 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 applicant 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.

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

1. **Pre-submission meeting:** The applicant is strongly encouraged to discuss the planned content of the application with the appropriate FDA review division at a pre-NDA/BLA meeting. This meeting will be attended by the FDA review team, including appropriate senior FDA staff.

[5] 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.

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

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

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

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

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 Sections 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 (See Section I.E).

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-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 and rationale regarding:

        1. risk management,
        2. the potential need for any post-marketing requirement(s) (PMRs), and
        3. the ability of adverse event reporting and FDA's Active Risk Identification and Analysis (ARIA) system under the Sentinel Initiative to provide sufficient information about product risk.

    b. The update should also include 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.

    c. 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:

        1. 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.

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

3. 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 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 and current assessment of the sufficiency of adverse event reporting and the ARIA system to provide information on product risk and the rationale for potential need for a PMR to characterize product risk 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. **Inspections:** FDA's goal is to complete all GCP, GLP, and GMP inspections for applications in the Program within 6 months of the date of original receipt for priority applications and within 10 months of the date of original receipt for standard applications. This will allow 2 months at the end of the review cycle to attempt to address any deficiencies identified by the inspections.

C. NEW MOLECULAR ENTITY (NME) MILESTONES AND POSTMARKETING REQUIREMENTS (PMRs)

FDA will continue to review, oversee, track, and communicate postmarketing drug safety issues.

1. **Pre-approval review of PMRs:** The Agency recognizes the importance of PMRs to ensure the timely availability of information on the safety and efficacy of therapies to the United States public. Therefore, FDA will establish processes to support consistency and predictability for both the Agency and applicants throughout the identification, determination, and evaluation of postmarketing studies.

   FDA will establish the following pre-approval process enhancements and guidelines in PDUFA VII:

   a. For standard NME NDAs and original BLAs, FDA will communicate details on anticipated PMRs required under Section 505(o)(3), PREA, Accelerated Approval, and the Animal Rule to the applicant no later than 8 weeks prior to the PDUFA action goal date.

   b. For priority NME NDAs and original BLAs, FDA will communicate details on anticipated PMRs required under Section 505(o)(3), PREA, Accelerated Approval, and the Animal Rule to the applicant no later than 6 weeks prior to the PDUFA action goal date.

   c. The communications described above in clauses (a) and (b) will summarize FDA's preliminary evaluation of required postmarketing studies, including the study purpose, critical study design elements including type of study and study population, timelines for discussions and engagement on the PMR for the remainder of the review cycle, and for 505(o)(3) PMRs the specific serious risk.

   d. If a major safety issue which requires a PMR is identified based on data submitted subsequent to submission of the application these timelines may not apply.

   FDA's performance goals for standard NME NDAs and original BLAs will be phased in, starting in FY 2023 as follows:

   a. In FY 2023, communicate anticipated PMRs to the applicant no later than 8 weeks prior to the PDUFA action goal date for 60% of standard NME NDAs and original BLAs.

   b. In FY 2024, communicate anticipated PMRs to the applicant no later than 8 weeks prior to the PDUFA action goal date for 70% of standard NME NDAs and original BLAs.

   c. In FY 2025, communicate anticipated PMRs to the applicant no later than 8 weeks prior to the PDUFA action goal date for 80% of standard NME NDAs and original BLAs.

d. In FY 2026, communicate anticipated PMRs to the applicant no later than 8 weeks prior to the PDUFA action goal date for 80% of standard NME NDAs and original BLAs.

e. In FY 2027, communicate anticipated PMRs to the applicant no later than 8 weeks prior to the PDUFA action goal date for 80% of standard NME NDAs and original BLAs.

FDA's performance goals for priority NME NDAs and original BLAs will be phased in, starting in FY 2023 as follows:

a. In FY 2023, communicate anticipated PMRs to the applicant no later than 6 weeks prior to the PDUFA action goal date for 60% of priority NME NDAs and original BLAs.

b. In FY 2024, communicate anticipated PMRs to the applicant no later than 6 weeks prior to the PDUFA action goal date for 70% of priority NME NDAs and original BLAs.

c. In FY 2025, communicate anticipated PMRs to the applicant no later than 6 weeks prior to the PDUFA action goal date for 80% of priority NME NDAs and original BLAs.

d. In FY 2026, communicate anticipated PMRs to the applicant no later than 6 weeks prior to the PDUFA action goal date for 80% of priority NME NDAs and original BLAs.

e. In FY 2027, communicate anticipated PMRs to the applicant no later than 6 weeks prior to the PDUFA action goal date for 80% of priority NME NDAs and original BLAs.

For the purposes of tracking and reporting metrics on all PMR goals described above, FDA will calculate metrics based on all NME and original BLA applications with issued PMRs, including Section 505(o)(3), PREA, Accelerated Approval, and the Animal Rule.

In addition, FDA will enhance clarity and transparency for the NME Review Program by updating all relevant Manuals of Policies and Procedures (MAPPs), Standard Operating Procedures and Policies (SOPPs), and guidances regarding the pre-approval processes for establishing PMRs beginning FY 2023 and finalizing by the end of FY 2027. The Agency will also conduct training for all relevant review and program support staff on updated processes related to postmarketing studies beginning FY 2023, including:

a. Preliminary communication with applicants at mid-cycle for PMRs, PMCs, and REMS.

b. Processes and procedures for ARIA sufficiency determination.

2. **Post-approval review of existing PMRs:** In addition to mechanisms currently in place for FDA to review existing PMRs (e.g., Annual Status Reports (ASRs), protocol submissions), applicants may also request review of existing PMRs for release. FDA will

establish an additional process for reviewing sponsor-initiated requests as summarized below:

a. The applicant will submit a request summarizing their rationale for why an existing PMR is no longer needed, including all necessary supporting data and information.

b. The relevant FDA review division/office[6] and discipline will initiate review of the request. FDA will notify the applicant of any additional information considered necessary to evaluate the request within 45 days of receipt.

c. FDA will respond to the applicant with a decision within 60 days of receipt of the original request or within 60 days of receipt of the additional information requested by FDA described in the previous step, whichever is later. FDA's response can be an agreement letter or a non-agreement letter. In a case of a non-agreement letter, the FDA will provide a rationale for their decision.

d. If FDA's response is a non-agreement letter, the applicant may submit a request to the review division for reconsideration by the appropriate committee(s) described in (e) below with justification, and any additional information, and/or data if appropriate.

e. Upon receipt of a reconsideration request, the review division/office will discuss with the appropriate internal committee that includes senior Agency leadership (e.g., Medical Policy and Program Review Committee, Medical Policy Coordinating Committee, and Pediatric Review Committee).

f. The review division/office will issue a written response within 45 days of receipt of the reconsideration request. FDA's response can be an agreement letter or a non-agreement letter. In a case of a non-agreement letter, the FDA will provide a rationale for their decision.

The process and timelines described above will be incorporated into all relevant MAPPs, SOPPs, and guidances beginning FY 2023 and finalizing by the end of FY 2027 and will not be PDUFA-tracked metrics or subject to performance goals.

D. SPLIT REAL TIME APPLICATION REVIEW (STAR) PILOT PROGRAM

FDA will establish a STAR pilot program,[7] which has the goal of shortening the time from the date of complete submission to the action date, in order to allow earlier patient access to therapies that address an unmet medical need. The STAR pilot program will apply to efficacy supplements across all therapeutic areas and review disciplines that meet specific criteria. Accepted STAR applications will be submitted in a "split" fashion, specifically in two parts (with the components submitted approximately 2 months apart).

[6] In CDER, initial reviews will be conducted by the relevant review division based on discipline. In CBER, initial reviews will be conducted by the relevant review office based on discipline.

[7] Real Time Oncology Review (RTOR) is separate from the STAR pilot program. Sponsors developing oncology products can still utilize the RTOR program.

1. **Scope:** The STAR program will seek to expedite patient access to novel uses for existing therapies by supporting initiation of review earlier than would otherwise occur and therefore allowing earlier approval for qualified efficacy supplements. This program will apply across all therapeutic areas and review disciplines for applications that meet specific criteria. An application will be considered eligible for STAR if each of the following criteria are met:

    a. Clinical evidence from adequate and well-controlled investigation(s) indicates that the drug may demonstrate substantial improvement on a clinically relevant endpoint(s) over available therapies.

        i. Breakthrough Therapy Designation (BTD) or Regenerative Medicine Advanced Therapy Designation (RMAT) is not required, but above criteria must be met.

    b. The application is for a drug intended to treat a serious condition with an unmet medical need.

    c. No aspect of the submission is likely to require a longer review time (e.g., requirement for new REMS, etc.).

    d. There is no chemistry, manufacturing, or control information that would require a foreign manufacturing site inspection (i.e., domestic site inspections may be allowed if it does not affect the expedited timeframe).

2. **Process and Timeline:** The following steps summarize the process for applying to and participating in the STAR program:

    a. An applicant who believes an efficacy supplement qualifies for review under the STAR program will request an informal pre-submission teleconference with FDA and provide FDA with topline trial results and proposed labeling.

        i. Alternatively, the preliminary discussion may take place as part of a pre-sNDA/sBLA meeting.

    b. If FDA agrees that the pre-submission request meets the STAR program eligibility criteria, the application will be accepted into the STAR program, and the applicant will agree to provide the complete application in two parts (these two parts are described in the Split Submission Components section below or as agreed to with the Review Division).

    c. FDA will initiate review of the data upon receipt of the Part 1 submission.

    d. The PDUFA timeline will begin upon receipt of the Part 2 submission (which completes the application). FDA intends to follow the expedited review timelines (as described in Section I.E below). These timelines target taking an action at least 1 month earlier than the applicable PDUFA goal date.

    e. The filing meeting will be scheduled within 30 days of FDA's receipt of the Part 2 submission. During the filing meeting, FDA will determine an action date at least 1 month in advance of the priority 6-month PDUFA goal date.

i. FDA will notify the applicant of the intended action date in the filing letter. The PDUFA goal date will remain unchanged.

3. **Split Submission Components:** Applications reviewed under the STAR program will comprise two separate submissions.

   a. The Part 1 submission initiates FDA's review and will contain:

      i. All components of the NDA/BLA efficacy supplement (e.g., complete datasets, proposed labeling, clinical protocols and amendments, topline efficacy and safety results), except for final clinical study reports for the adequate and well-controlled investigation(s) supporting the proposed claim and the eCTD module 2 clinical summaries, and

      ii. A document providing topline results for each of the adequate and well-controlled investigations will also be provided in the Part 1 submission.

      Any modifications to submission content are at the discretion of the OND/CDER clinical division or CBER review office and must be agreed to in advance.

   b. The Part 2 submission initiates the PDUFA timeline and will contain:

      i. The clinical study reports for the adequate and well-controlled investigation(s) (e.g., Phase 3 studies) intended to support the proposed indication, and

      ii. The eCTD module 2 clinical summaries not included in the Part 1 submission.

   Part 1 will be submitted approximately 2 months, and not longer than 3 months, in advance of Part 2. If the Part 1 submission is incomplete (i.e., it does not include every component described in Section D.3.a. above, except for easily correctable minor deficiencies of components not essential to initiating review, as determined by the OND/CDER division or CBER review office), the review will not be initiated until the application is complete and the application will no longer be considered within the STAR program.

4. **Transparency:** The Agency will develop a public-facing webpage outlining detailed criteria for potential acceptance and participation in the STAR program by October 1, 2022. FDA will conduct an interim assessment that includes internal activities related to STAR by the end of FY 2025. FDA will also conduct a public workshop by the end of Q2 in FY 2026 to discuss the potential value and feasibility of expanding the pilot program to select NME NDAs and BLAs and solicit feedback on experiences with the pilot program from industry stakeholders. Outputs from the assessment and workshop will be published in a publicly available report summarizing both overall metrics for the pilot program and external stakeholder feedback, including the percentage of applications accepted into the program based on the number of requests and the percentage of applications that had an action date at least 1 month in advance of the priority 6-month PDUFA goal date. FDA will also commit to training review staff on STAR processes and providing a publicly available report summarizing training activities conducted.

5. **Implementation:** The STAR program will be available to applicants beginning in FY 2023. Expediting reviews will be fully implemented by FY 2024 to allow time for FDA to hire necessary staff to support the expedited timeline.

E. EXPEDITED REVIEWS

The term "expedited review" in this letter refers to FDA's review of either 1) a human drug application in the Program that has received priority review designation and the FDA review team identifies as meeting an important public health need, or 2) an efficacy supplement in the STAR pilot program, 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. In such cases the FDA review team intends to make every effort to conduct an expedited review 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. 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 normal priority review approach, and will inform the applicant accordingly.

F. 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 applicant 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 (investigational new drug (IND) phase after end-of-phase 2) and has received tentative acceptance.

c. If the proprietary name is found to be unacceptable, the applicant 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.

G. 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.

H. 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.

I. 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.

J. MEETING MANAGEMENT GOALS

Formal PDUFA meetings between sponsors and FDA consist of Type A, B, B(EOP), C, Type D and INTERACT meetings. FDA plays an active role during drug development by providing advice and feedback to sponsors on the overall drug development programs during meetings conducted between sponsors and FDA. In general, FDA's guidance provided at these meetings describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. 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 type of meeting[8] other than Type A, B, B(EOP), D, or INTERACT.
- A Type D meeting is focused on a narrow set of issues (e.g., often one, but typically not more than two issues and associated questions). Requests could include:
    - A follow-up question that raises a new issue after a formal meeting (i.e., more than just a clarifying question about an FDA response from a prior meeting);
    - A narrow issue on which the sponsor is seeking Agency input with only a few associated questions; or
    - A general question about an innovative development approach that does not require extensive, detailed advice.

Type D meetings should be limited to no more than 2 focused topics. If the sponsor has several issues or a complex single issue with multiple questions, a Type C meeting should be requested rather than requesting several Type D meetings. In addition, the issue should not require input from more than 3 disciplines or Divisions. If the scope of the meeting is broad or includes complex questions/issues that require input from more than 3 disciplines or Divisions, then FDA will inform the sponsor that the Agency will be converting the meeting to the appropriate meeting type (Type B or C) and the sponsor can either withdraw their request or accept the FDA's meeting-type conversion without re-submitting a new meeting request.

1. **INitial Targeted Engagement for Regulatory Advice on CBER/CDER ProducTs** (INTERACT) meetings are intended for novel questions and unique challenges in early development (i.e., prior to filing of an IND). The issues typically relate to IND requirements for example: questions regarding design of IND-enabling toxicity studies (e.g., species, endpoints), complex manufacturing technologies or processes, development of innovative devices used with a drug or biologic, or the use of cutting-edge testing methodologies. INTERACT meetings are intended to facilitate IND-enabling efforts where the sponsor is facing a novel, challenging issue that might otherwise delay progress of the product towards entry into the clinic in the absence of this early FDA input. Typically, the issue is early in a development program—prior to when a pre-IND meeting might be requested—and the issue may delay initiation of, or progress of, IND-enabling studies. The sponsor needs to have selected a specific investigational product or a product-derivation strategy to evaluate in a clinical study before requesting an INTERACT meeting.

[8] Refer to Section I.K.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.

a. Questions and topics within the scope of an INTERACT meeting include:

   i. Novel questions for all CDER and CBER products (i.e., questions where there is no existing guidance or other information in writing the company could reference from FDA).

   ii. These meetings are intended to provide FDA input on issues that a sponsor needs to address prior to a pre-IND meeting, including issues such as:

      1) Choice of appropriate preclinical models or necessary toxicology studies for novel drug platforms or drug candidates;

      2) CMC issues or testing strategies aimed to demonstrate product safety, adequate to support first-in-human study;

      3) Overall advice related to the design of proof-of-concept or other pilot safety/biodistribution studies necessary to support administration of an investigational product in a first-in-human clinical trial;

      4) General recommendations regarding a future first-in-human trial in a target clinical population where the population is novel and there is no prior precedent or guidance;

      5) Recommendations on approach for further development of an early-stage product with limited CMC, pharmacology/toxicology, and/or clinical data that were collected outside of a US IND; and

      6) Other topics that would be agreed upon by FDA.

2. 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 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
D	14
INTERACT	21

i. For any type of meeting, the sponsor may request a written response to its questions rather than a face-to-face[9] or teleconference meeting. FDA will review the request and make a determination on whether a written response is appropriate or whether a face-to-face or teleconference meeting 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, Type C, Type D, and INTERACT 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. If the sponsor believes a face-to-face Pre-IND meeting is valuable and warranted, then the sponsor may provide a rationale in a follow-up correspondence explaining why a face-to-face meeting is valuable and warranted, and FDA will convert where possible WRO to a face-to-face meeting for requests that includes novel approaches to clinical development and/or where precedents are not well established.

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.

3. 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.

[9] A "face-to-face" meeting includes both in-person meetings and virtual meetings on IT platforms that allow for both audio and visual communication.

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
D	50 calendar days from receipt of meeting request
INTERACT	75 calendar days from receipt of meeting request

b. **Performance goal:**

i. Type A, B, B(EOP) and C meetings: 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.

ii. Type D meeting: performance goals for FDA will be phased in, starting in FY 2023 as follows:

1) By FY 2023, hold 50% of Type D meetings, or send written response, within 50 calendar days from receipt of meeting request.

2) By FY 2024, hold 60% of Type D meetings, or send written response, within 50 calendar days from receipt of meeting request.

3) By FY 2025, hold 70% of Type D meetings, or send written response, within 50 calendar days from receipt of meeting request.

4) By FY 2026, hold 80% of Type D meetings, or send written response, within 50 calendar days from receipt of meeting request.

5) By FY 2027, hold 90% of Type D meetings, or send written response, within 50 calendar days from receipt of meeting request.

iii. INTERACT meeting: performance goals for FDA will be phased in, starting in FY 2023 as follows:

1) By FY 2023, hold 50% of INTERACT meetings, or send written response, within 75 calendar days from receipt of meeting request.

2) By FY 2024, hold 60% of INTERACT meetings, or send written response, within 75 calendar days from receipt of meeting request.

3) By FY 2025, hold 70% of INTERACT meetings, or send written response, within 75 calendar days from receipt of meeting request.

4) By FY 2026, hold 80% of INTERACT meetings, or send written response, within 75 calendar days from receipt of meeting request.

5) By FY 2027, hold 90% of INTERACT meetings, or send written response, within 75 calendar days from receipt of meeting request.

4. 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[10]	47 calendar days before the date of the meeting or expected written response*
D	At the time of the meeting request
INTERACT	At the time of the meeting request

***** 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.

5. 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), C, D, and INTERACT meetings. For all other meeting types, the FDA intends to send the requester its preliminary responses no later than 2 calendar days before the meeting.

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

6. 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), D, INTERACT, or C meeting, the sponsor will notify FDA

[10] 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.K.3 of this document.

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.

7. Meeting Minutes

a. **Procedure:** The Agency will prepare minutes that will be available to the sponsor 30 calendar days after the meeting for Type A, B, B(EOP), C, and D. 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. For INTERACT meetings, preliminary responses will be annotated and resent within 30 calendar days if advice provided changes as a result of the meeting. In cases of a WRO, the WRO will serve as meeting minutes from FDA.

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

8. 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/virtual/teleconference 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.

9. Guidance, Clarity, and Transparency

a. By September 30, 2023, FDA will issue a revised draft of the existing draft guidance on "Formal Meetings Between the FDA and Sponsors or Applicants of

PDUFA Products" with information pertaining to INTERACT, Type D meetings, and the follow-up opportunity described below. In addition, FDA will update relevant MAPPs and SOPPs.

b. **Follow-up opportunity:** For all meeting types, to ensure the sponsor's understanding of FDA feedback from meeting discussions or a WRO, sponsors may submit clarifying questions to the agency. Only questions of a clarifying nature will be permitted, i.e., to confirm something in minutes or a WRO issued by FDA, rather than raising new issues or new proposals. FDA will develop criteria and parameters for permissible requests, and FDA may exercise discretion about whether requests are in-scope. The clarifying questions should be sent in writing as a "Request for Clarification" to the FDA within 20 calendar days following receipt of meeting minutes or a WRO. For questions that meet the criteria, FDA will issue a response in writing within 20 calendar days of receipt of the clarifying questions. FDA's response will reference the original meeting minutes or WRO.

c. **Training:** FDA will conduct external training to ensure the best practices outlined in the draft guidances are communicated to Industry.

K. 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 continue to advance 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, continuing 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.

Best Practices for meetings are the responsibility of both Industry and FDA. Efforts from both Industry and FDA are needed in order to continue advancement, improvement, and updating of best practices. To continue to enhance timely interactive communication with sponsors during drug development in PDUFA VII, FDA will do the following:

a. **Public Workshop.** FDA will hold a public meeting to discuss best practices for meeting management by July 30, 2024, including issues related to submission of meeting requests, efficient time management, coordinating meeting agenda, development and submission of meeting background packages and lessons learned from the Coronavirus Disease 2019 ("COVID-19") pandemic including virtual meeting platforms. Learnings from the public meeting could inform FDA's internal process improvement efforts and, as appropriate, be reflected in updating guidances, as noted below. This public workshop will also discuss and share experience and metrics related to all PDUFA meeting activities, including Type D and INTERACT meetings. FDA will discuss the number of meeting requests granted and denied for INTERACT meetings, including a summary of rationales for denied meeting requests. Reported metrics will include the number of requests granted and denied for in-person pre-IND, Type C, Type D, and INTERACT meetings. FDA and Industry will agree on the information that FDA may share publicly in this meeting.

b. **Guidance.** Based on the discussion at the public meeting mentioned above in paragraph (a), and FDA's experience with conducting meetings effectively, FDA will update public documents, as appropriate, including publishing revised draft or final version of the Best Practices for Communication Between IND Sponsors and FDA During Drug Development guidance mentioned below, 18 months after the public meeting is held.

c. **Training.** FDA will conduct external training to ensure the best practices outlined in the guidances are communicated to Industry.

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.[11] 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.[12] FDA will continue to retain current resources to 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.[13] The remaining meeting procedures as described in Section I.J of this document will apply.

4. Advancing Development of Drugs for Rare Diseases

FDA will build on the success of rare disease programs 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 Diseases Team staff in CDER will continue to be integrated into review teams for rare disease

---

[11] See Section 506(a) of the Federal Food, Drug, and Cosmetic (FD&C) Act, 21 U.S.C. § 356(a).

[12] 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.

[13] Refer to Table 5 in Section I.J of this document.

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 rare disease 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 rare disease staff as members of the core review team to help ensure consistency of scientific and regulatory approaches across applications and review teams.

Rare disease staff will continue to engage in outreach to industry, patient groups, and other stakeholders to provide training on FDA's rare disease programs. 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 rare disease programs 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 rare disease 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.

a. Rare Disease Endpoint Advancement (RDEA) Pilot Program

The lack of regulatory precedent, small trial populations, and/or limited understanding of disease natural history associated with rare diseases creates unique challenges when determining the appropriate efficacy endpoint(s) for clinical trials intended to evaluate the effectiveness of rare disease therapies. Though difficult to establish, well-developed efficacy endpoints, especially those that could apply to other rare diseases with similar manifestations, drive the general advancement of rare disease drug development. In addition to challenges associated with developing endpoints that appropriately capture key signs and symptoms of a rare disease and directly measure how patients feel, function, or

survive, surrogate endpoint development is also challenging in diseases with slow progression, small patient populations, or other challenges commonly associated with drug development in rare diseases.

Current mechanisms for sponsors of rare disease drug development programs to collaborate with FDA are not structured to provide repeated, intensive interactions with the Agency. To support the advancement of rare disease treatments, FDA will establish a pilot program for supporting efficacy endpoint development for drugs that treat rare diseases by offering additional engagement opportunities with the Agency to sponsors of development programs that meet specific criteria. In addition, FDA will develop the staff capacity to enable and facilitate appropriate development and use of these types of novel endpoints. This staff will support the complex and intensive review work necessary to evaluate novel endpoint development with a focus on the challenges of trial designs utilizing small populations.

i. **Scope.** The RDEA pilot program will seek to advance rare disease drug development programs by providing a mechanism for sponsors to collaborate with FDA throughout the efficacy endpoint development process. An endpoint, or endpoints, will be considered eligible for proposal submission to RDEA if each of the following criteria are met:

    (1) The associated development program should be active and address a rare disease, with an active IND or pre-IND for the rare disease.

        (a) Sponsors who do not yet have an active development program but have, or are initiating, a natural history study where the proposed endpoint is intended to be studied are also eligible to apply.

        (b) The FDA may also consider accepting a proposal for a development program for a common disease that includes innovative or novel endpoint elements, including the specific endpoint and/or the methodology being developed, if there is sufficient justification that the proposal could be applicable to a rare disease.

    (2) The proposed endpoint is a novel efficacy endpoint intended to establish substantial evidence of effectiveness for a rare disease treatment.

        (a) An endpoint is considered novel if it has never been used to support drug approval or if it has been substantially modified from previous use to support drug approval.

        (b) Preference will be given to proposals that have the potential to impact drug development more broadly, such as one that uses a novel approach to develop an efficacy endpoint or an endpoint that could potentially be relevant to other diseases. Preference will also be given to accepting

proposals that reflect a range of different types of endpoints.

(c) For surrogate endpoint proposals, preference will be given to those with novel approaches for collecting additional clinical data in the pre-market stage to advance the validation of these endpoints. If the sponsor is proposing to develop a surrogate endpoint as part of a rare disease application, participation in a prior Type C Surrogate Endpoint meeting is encouraged.

(3) FDA will select a limited number of qualified proposals for admission into RDEA that increases after the first year of PDUFA VII:

(a) FY 2023: Sponsors may submit proposals beginning in Q4, and FDA will accept a maximum of 1 proposal.

(b) FY 2024 – FY 2027: FDA will accept up to 1 proposal per quarter with a maximum of 3 proposals per year.

(c) Expansion of the program may be dependent on FDA staffing.

ii. **Process and Timeline.** The following steps summarize the process for applying to and participating in the RDEA pilot program:

(1) A sponsor who believes a development program qualifies for participation in RDEA will submit a proposal to FDA that includes a justification addressing each of the criteria described above, including scientific justification for why the endpoint is being explored to measure meaningful clinical benefit in the disease/condition, relevant summaries of pertinent information related to the endpoint from prior studies, as well as a statement indicating if the company is willing to allow disclosure of information for broader development and educational purposes.

(2) FDA will confirm receipt of the sponsor's proposal within 14 days of receipt.

(3) FDA will notify the sponsor with a final selection decision no later than 60 days following the end of the FY quarter during which it is submitted.

(4) Before FDA grants the initial meeting, FDA and the sponsor will agree on the information that FDA may share publicly. When feasible, FDA will notify a sponsor in advance when the sponsor's program is the planned focus of a public discussion. Participation in the pilot program, including such agreement on information disclosure, will be voluntary and at the discretion of the sponsor. If FDA and the sponsor of an accepted proposal are unable to reach agreement on elements for public disclosure, however, that

proposal will no longer be part of the RDEA pilot program and the Agency will proceed with an alternate submission.

(5) Sponsors admitted to the RDEA pilot may participate in up to 4 focused meetings with relevant FDA staff to discuss endpoint development.

(a) The sponsor will provide a briefing document upon submission of each meeting request.

(b) Each meeting will be scheduled within 45 days following FDA's receipt of the sponsor's meeting request and complete briefing document.

(c) The scheduling timeline may be shortened for meeting requests to discuss narrow issues and/or questions at FDA's discretion.

(d) The timing between each meeting is flexible and depends on how much time the sponsor needs to identify new issues and/or questions and prepare required materials for the next meeting.

(6) Sponsors who have completed the maximum of 4 RDEA meetings or do not have additional endpoint-focused questions or issues to discuss with FDA may proceed with the standard regulatory submission process.

(a) FDA's advice provided during and between RDEA meetings does not constitute a regulatory decision and is considered non-binding. Completing the 4 RDEA meetings does not guarantee approval for a regulatory submission that includes efficacy endpoints discussed during RDEA meetings.

(b) After completion of 4 RDEA meetings, the sponsor can request additional input from FDA, as needed, through other formal meeting mechanisms, such as Type B, Type C, Type C Surrogate Endpoint, or Type D meetings.

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

iii. **Transparency and Endpoint Advancement.** As part of RDEA, FDA will conduct up to 3 public workshops by the end of FY 2027 to discuss various topics relevant to endpoint development for rare diseases, such as the use of multidomain analysis methods. To promote innovation and evolving science, novel endpoints developed through RDEA may be presented by FDA, such as in guidance documents, on a public-facing website, or at public workshops as case studies, including prior to FDA's approval for the drug studied in the trial. However, as noted above, before

FDA grants the initial RDEA meeting the Agency and the sponsor will agree on the information that FDA may share publicly in these case studies. When feasible, FDA will notify a sponsor in advance when the sponsor's program is the planned focus of a public discussion.

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

a. For Use-Related Risk Analysis (URRA)

Sponsors employ URRA to identify the need for risk mitigation strategies and to design a human factors (HF) validation study. Based on a URRA, a sponsor may propose that a HF validation study is not needed to be submitted to support the safe and effective use of a drug-device or biologic-device combination product. FDA will establish the following procedures for review of URRAs for combination products:

i. The sponsor should submit a request for review of their URRA to their IND. The submission should include specific questions, justification that a HF validation study is not needed to be submitted including any supporting information, and scientific and regulatory requirements for which the sponsor seeks agreement.

ii. Within 60 days of Agency receipt of the URRA and specific questions, the Agency will provide a written response to the sponsor that includes a succinct assessment of the URRA and answers to the questions posed by the sponsor. If the Agency does not agree that either the URRA or the sponsor's justification are adequate to support the absence of a HF validation study, the reasons for the disagreement will be explained in the response.

iii. URRA submission: performance goals for FDA will be phased in, starting FY 2024 as follows:

1) By FY 2024, review and notify sponsor of agreement or non-agreement with comments for 50% of filed submissions, within 60 days of receipt of submission.

2) By FY 2025, review and notify sponsor of agreement or non-agreement with comments for 70% of filed submissions, within 60 days of receipt of submission.

3) By FY 2026, review and notify sponsor of agreement or non-agreement with comments for 90% of filed submissions, within 60 days of receipt of submission.

4) By FY 2027, review and notify sponsor of agreement or non-agreement with comments for 90% of filed submissions, within 60 days of receipt of submission.

iv. By the end of FY 2024, FDA will publish new draft or revised guidance for review staff and industry describing considerations related to drug-device and biologic-device combination products on the topics noted below.

    Guidance that will convey FDA's current thinking regarding how a URRA along with other information can be used to inform when the results from an HF validation study may need to be submitted to a marketing application. The guidance will provide a comprehensive, systematic and stepwise approach with examples, when applicable, to illustrate how to make this determination.

v. Sponsors may still elect to submit a URRA with a HF validation protocol and will only be subject to timelines in Section I.K.5.b, For Human Factor Validation Study Protocols.

b. For Human Factor Validation Study Protocols

Human factors studies are conducted to evaluate the user interface of a drug-device or biologic-device combination product to eliminate or mitigate use-related hazards that may affect the safe and effective use of the combination product. Over the past decade, more combination products have been developed to deliver therapeutics via different routes of administration (e.g., parenteral, inhalation) with complex engineering designs. HF validation protocols are reviewed during the IND stage with the goal towards developing a final finished combination product that supports the marketing application. To achieve this objective, FDA will establish the following procedures for review of HF validation study protocols:

i. The sponsor should submit a human factors protocol to the IND with specific questions, including 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).

ii. 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.

Performance goals for FDA will be as follows:

i. Beginning in FY 2023, review and provide sponsor with written comments for 90% of human factors validation protocol submissions within 60 days of receipt of protocol submission.

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

In accordance with Section 3022 of the 21st Century Cures Act, and by providing earlier and increased Agency advice, the Advancing RWE Program seeks to improve the quality and acceptability of RWE-based approaches in support of new intended labeling claims, including approval of new indications of approved medical products or to satisfy post-approval study requirements. Specifically, FDA will do the following:

a. By no later than December 31, 2022, FDA will establish and communicate publicly a pilot Advancing RWE Program intended to:

   i. Identify approaches for generating RWE that meet regulatory requirements in support of labeling for effectiveness (e.g., new indications, populations, dosing information) or for meeting post-approval study requirements;

   ii. Develop agency processes that promote consistent decision-making and shared learning regarding RWE;

   iii. Promote awareness of characteristics of RWE that can support regulatory decisions by allowing FDA to discuss study designs considered in the Advancing RWE Program in a public forum.

b. The Advancing RWE Program will include but not be limited to the following activities and components:

   i. FDA will solicit applications for the Advancing RWE Program twice (i.e., two cycles) each year, asking sponsors to describe—before protocol development or study initiation—the regulatory question(s) they seek to address with RWE, the proposed RWE study design, and the potential real-world data (RWD) source(s) to support that design;

   ii. FDA will use a structured review process to evaluate and rank applications, based on the information they present that the data may be fit-for-use, the study design will be adequate, and the proposed study conduct can be anticipated to meet regulatory requirements. Consideration will be given to promoting diversity of data sources, study designs, analytical methodologies and regulatory indications, as well as to diversity of diseases under study and FDA Centers and Offices involved;

   iii. FDA will accept one to two eligible and appropriate proposals each cycle in the first and second year (FY 2023-2024) of the Advancing RWE Program and one to four eligible and appropriate proposals each cycle thereafter (FY 2025-2027);

   iv. FDA will notify sponsors regarding acceptance or non-acceptance of their submission within 45 days of the application deadline;

   v. FDA will convene the first of up to four dedicated Advancing RWE Program meetings within 75 days of the application deadline, with subsequent meetings to be scheduled within 45 days after receiving a request for such meetings from the sponsor;

vi. The Advancing RWE Program represents an optional pathway for sponsors submitting RWE proposals to an IND with CDER or CBER. Regardless of whether an Advancing RWE application is accepted, not accepted, or was never submitted to the Advancing RWE Program, established procedures (e.g., formal PDUFA meetings with the review division) will continue to be available;

vii. Before FDA grants the initial meeting, FDA and the sponsor will agree on the information that FDA may share publicly. When feasible, FDA will notify a sponsor in advance when the sponsor's program is the planned focus of a public discussion. Participation in the pilot program, including such agreement on information disclosure, will be voluntary and at the discretion of the sponsor;

viii. If FDA and the sponsor of an accepted proposal are unable to reach agreement on elements for public disclosure, however, that proposal will no longer be part of the Advancing RWE Program and the Agency will proceed with an alternate submission (The timelines for meetings described above would shift based on the dates of accepting alternate submissions, if applicable.);

ix. Discussions at Advancing RWE program-related meetings will focus on data, design, and regulatory issues that have the potential to generate RWE in support of a proposed regulatory decision;

x. FDA participation in the Advancing RWE Program, including the selection process and program-related meetings, will include representatives from relevant review divisions, other offices with RWE expertise, and senior leadership with expertise in RWE;

xi. Sponsors and FDA can decide that four meetings may not be necessary if an agreed-upon protocol is identified. Conversely, if FDA determines that key data- or design-related problems make the protocol unlikely to support the intended regulatory decision, then subsequent meetings within the Advancing RWE Program may not be conducted;

xii. FDA and sponsors agree that the goal of the Advancing RWE Program is general agreement on key design elements. The acceptability of evidence generated from any completed study is a subsequent review issue;

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

c. By no later than June 30, 2024, FDA will report aggregate and anonymized information, on at least an annual basis and based on available sources (e.g., information provided by review divisions), describing RWE submissions to CDER and CBER. The reports will describe application type (e.g., primary focus on safety or effectiveness), data sources used (e.g., medical claims, electronic health records, registries, digital health technologies), study design employed (e.g., randomized trial, externally controlled trial, observational study), and regulatory request (e.g., new indication, population, dosing information, post-

approval study requirement for a marketed product). This reporting will include but not be limited to protocols emerging from the Advancing RWE Program.

d. By no later than December 31, 2025, FDA will convene a public workshop or meeting to discuss RWE case studies with a particular focus on approaches for generating RWE that can potentially meet regulatory requirements in support of labeling for effectiveness (e.g., new indications, populations, dosing information) or for meeting post-approval study requirements.

e. By no later than December 31, 2026, experience gained with the Advancing RWE Program, as well as CDER's and CBER's RWE program in general, will be used to update existing RWE-related guidance documents or generate new draft guidance, as appropriate.

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

Delivering new medicines to patients through biomedical innovation requires advances in regulatory decision tools to support drug development and review. FDA will build on the successes of its efforts on Patient Focused Drug Development (PFDD), benefit-risk assessment in regulatory decision-making, and the drug development tools qualification pathway for biomarkers. FDA will also continue to advance modern approaches to enhance the efficiency of the drug development and review processes, such as complex adaptive, Bayesian, and other novel clinical trial designs and model-informed drug development (MIDD).

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 VII:

a. FDA will continue to strengthen capacity to facilitate development and use of Patient-Focused methods to inform drug development and regulatory decisions. This includes expanded internal staff training and external outreach to industry sponsors and other involved stakeholders with emphasis on patient-focused drug development (PFDD) methods and tools-related guidance and practice to achieve broad acceptance and integration into regulatory decision making across review divisions and industry development programs. FDA will also engage external experts, through a mechanism called the Intergovernmental Personnel Act, to support the review of patient experience data. These external methodological experts will possess extensive knowledge in methods and approaches related to patient experience data and will augment existing internal expertise.

   i. FDA will undertake a broad-based effort to conduct outreach and training across review divisions, with follow-up consultation as these methods gain broad acceptance and integration, including development of methodology

training courses for review staff that will be conducted at least two times per year.

ii. FDA will conduct targeted outreach to industry and methodological consulting organizations to provide presentations, sessions, and resources to increase understanding, acceptance, and integration into development programs.

b. FDA will issue a Request for Information (RFI) to elicit public input on methodological issues, including the submission and evaluation of patient experience data in the context of the benefit-risk assessment and product labeling, and other areas of greatest interest or concern to public stakeholders. This RFI will be issued by no later than the end of June 2023.

   i. FDA will issue a Federal Register Notice summarizing the input to the RFI by no later than the end of December 2023 and, based on the input received in response to the RFI, FDA will plan to conduct at least 2 public workshops focused on methodological issues.

   ii. The first workshop will be held no later than the end of FY 2024.

   iii. The second workshop will be held no later than the end of FY 2025.

   iv. Based on the RFI and the learnings from the workshops, FDA will produce a written summary with identified priorities for future work no later than the end of FY 2026.

c. FDA will continue to work to develop a virtual catalog of standard core sets of Clinical Outcome Assessments (COAs) and Related Endpoints, pursuing non-user fee funding for the work to develop standard core sets, which will be available for public use. FDA will also work to enhance understanding of how patient preference informs meaningful benefit or benefit-risk tradeoffs in therapeutic areas.

d. A public input process through either the Federal Register or Public Meetings will allow FDA to understand stakeholder's perspectives on diseases and domains of greatest need or highest priority for development of Standard Core COAs and Endpoints as well as priority areas where decisions are preference-sensitive and patient preference information (PPI) data can inform regulatory decision-making.

e. By September 30, 2026, FDA will publish draft guidance on use and submission of patient preference information to support regulatory decision making. FDA will work towards the goal of publishing final guidance within 18 months after the close of the public comment period on the draft guidance. If, after receiving comments on the draft guidance, FDA determines that the guidance requires substantive changes on which further public comments are warranted, FDA will issue a revised draft guidance within those 18 months instead. It then will work towards publishing a final guidance within 18 months after the close of the public comment period on the revised draft guidance.

2. Benefit-Risk Assessment in Regulatory Decision-Making

Benefit-risk assessment is a foundation of FDA's regulatory review of marketing applications for new human drugs and biologics. FDA currently includes the Benefit-Risk Framework in its NDA and BLA review training, processes, and templates to support the conduct and communication of its benefit-risk assessment. CBER incorporates benefit-risk assessment through interdisciplinary review and has integrated the Benefit-Risk Framework into its clinical review template for its new BLA and supplement assessments. CDER has similarly integrated the Benefit-Risk Framework into its clinical review and decisional memo templates.

FDA is committed to continuing its implementation and application of structured benefit-risk assessment in its regulatory review processes and documentation. FDA will continue to explore additional opportunities to enhance its use and communication of its benefit-risk assessments for new drug and biological review.

3. Advancing Model-Informed Drug Development

FDA will build on the success of the "model-informed drug development" (MIDD) approaches by continuing to advance and integrate the development and application of exposure-based, biological, and statistical models derived from preclinical and clinical data sources in drug development and regulatory review. FDA will conduct the following activities during PDUFA VII:

a. By no later than the end of 1st Quarter of FY 2023, FDA will publish a Federal Register Notice announcing the continuation of the MIDD paired meeting program, outlining program eligibility, and describing the proposal submission and selection process.

b. For sponsors participating in the MIDD paired meeting program, FDA will grant a pair of meetings specifically designed for this program, consisting of an initial and a follow-up meeting on the same drug development issues. The second meeting will occur within approximately 60 days of receiving the briefing materials. These meetings will be led by the clinical pharmacology or biostatistical review components within CDER or CBER in partnership with clinical staff at the relevant center to ensure alignment with decision makers.

c. Starting in FY 2023, FDA will select 1-2 eligible and appropriate proposals per quarter each year (i.e. up to 8 per year). Additional proposals that meet the eligibility criteria may be selected depending upon the availability of resources. The internal review group instituted by FDA will continue to review proposals on a quarterly basis and provide recommendations on prioritization and selection of proposals and share knowledge and experience.

d. Sponsors who do not participate in the MIDD paired meeting program will have an opportunity to interact with the Agency through traditional channels.

e. FDA will issue a Request for Information (RFI) to elicit public input for identifying priority focus areas for future policy or guidance development and

stakeholder engagement. This RFI will be issued by no later than the end of FY 2024.

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 VII:

a. FDA will continue to develop CDER and CBER 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. FDA will also engage external experts through existing FDA mechanisms (e.g., Intergovernmental Personnel Act assignment) to support the review of complex innovative designs. These methodological experts will possess extensive knowledge in the aforementioned topics and will augment existing internal expertise.

b. FDA will maintain the paired meeting program, selecting 1-2 eligible and appropriate proposals per quarter each year (i.e. up to 8 per year) 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. Additional proposals that meet the eligibility criteria may be selected depending upon the availability of resources. For INDs in the program, FDA will grant a pair of meetings, consisting of an initial and follow-up meeting on the same design. The second meeting will occur within approximately 90 days of receiving the briefing materials. Management of the overall program as well as specific meetings to discuss innovative designs will be led by the biostatistical review components within CDER or CBER in partnership with clinical staff at each center. 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 as agreed upon with participating sponsors will provide better clarity on the acceptance of different types of trial designs that should facilitate their use in future development programs.

    i. By no later than the end of 1st Quarter of FY 2023, FDA will publish a Federal Register Notice announcing the continuation of the paired meeting program, outlining program eligibility, and describing the proposal submission, selection process, and example topics that will advance the use of complex innovative designs and inform the development of a guidance document.

    ii. FDA will select up to 8 proposals each year from proposals submitted to either CDER or CBER. The selections are expected to be made on a quarterly basis. 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 paired meeting program may be presented by FDA (e.g., in a guidance, at public workshops and conferences, on the Complex Innovative Design website) 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. When feasible, FDA will notify a sponsor in advance when the sponsor's program is the planned focus of a public discussion. Participation in the paired meeting program, including such agreement on information disclosure, will be voluntary and at the discretion of the sponsor.

c. In order to encourage increased submissions by CBER-regulated sponsors to the complex innovative design (CID) paired meeting program, CBER staff will continue to engage in outreach to industry and other stakeholders. Such outreach will include providing information on the paired meeting program and its benefits, such as enhanced attention regarding CID proposals and advancing the leveraging and sharing of knowledge to support efficient product development; clarifying policies and procedures for submitting CID proposals for review; and presenting FDA's current thinking on CID-related technical topics.

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

e. By the end of 2nd Quarter FY 2024, FDA will convene a public workshop to discuss aspects of complex adaptive, Bayesian, and other novel clinical trial designs. Discussion topics will include considerations for external data sources, Bayesian statistical methods, simulations, and clinical trial implementation (e.g. examples of defining and mitigating bias when using select trial design methods) and will be based on FDA accumulated experience both within and outside of the paired meeting program.

f. By the end of FY 2025, FDA will publish draft guidance on the Use of Bayesian Methodology in Clinical Trials of Drugs and Biologics. FDA will work towards the goal of publishing final guidance within 18 months after the close of the public comment period on the draft guidance. If, after receiving comments on the draft guidance, FDA determines that the guidance requires substantive changes on which further public comments are warranted, FDA will issue a revised draft guidance within those 18 months instead. It then will work towards publishing a final guidance within 18 months after the close of the public comment period on the revised draft guidance.

5. 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 VII:

a. FDA will continue to retain and enhance 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. FDA will continue to publish information on its website regarding biomarker qualification submissions under section 507 of the FD&C Act, consistent with the requirements in section 507(c), and to update the website quarterly.

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

M. ENHANCEMENT AND MODERNIZATION OF THE FDA DRUG SAFETY SYSTEM

FDA will continue to use user fees to enhance the drug safety system, including adopting new scientific approaches, improving the utility of existing tools for the detection, evaluation, prevention, and mitigation of adverse events, modernizing REMS assessments, and coordinating regulatory activity in the pre-market and post-market settings. Enhancements to the drug safety system will improve public health by increasing patient protection while continuing to enable access to needed medical products.

User fees will provide support for 1) modernization and improvement of REMS assessments and 2) optimization of the Sentinel Initiative through a) maintenance of Sentinel Initiative capabilities and continued integration into FDA drug safety activities and b) enhancement of the analytic capabilities of the Sentinel Initiative to address questions of product safety and advance the understanding of how real-world evidence can be used for studying effectiveness.

1. Modernization and Improvement of REMS Assessments

FDA will use user fee funds to modernize and improve REMS assessments by incorporating REMS assessment planning into the design of REMS, clarifying its expectations regarding methods to evaluate the performance of REMS, increasing the efficiency of FDA's review of REMS assessment reports, and establishing FDA performance goals for review of REMS assessment methods and study protocols.

a. By March 31, 2024, update relevant guidances to incorporate REMS assessment planning into the design of the REMS by providing recommendations regarding: 1) linking the design with the assessments 2) ensuring sufficient and appropriate data collection, and 3) identifying key metrics for success (e.g., primary and secondary).

b. By March 31, 2024, FDA will issue new or update existing policies and procedures for reviewing methodological approaches and study protocols used to assess a REMS program.

c. Improve the efficiency of FDA's review of REMS assessment reports.

   i. By March 31, 2024, FDA will issue new or update existing policies and procedures to systematically determine, as part of the review of REMS assessment reports, if modifications to the REMS or revisions to the REMS assessment plan are needed, including the timing of the REMS

assessments and to determine whether the REMS is still necessary to ensure the benefits outweigh the risks of the drug.

ii. By March 31, 2026, FDA will develop draft guidance regarding the format and content of a REMS assessment report, including the type of data that can support elimination of a REMS. FDA will work towards the goal of publishing final guidance within 18 months after the close of the public comment period on the draft guidance. If, after receiving comments on the draft guidance, FDA determines that the guidance requires substantive changes on which further public comments are warranted, FDA will issue a revised draft guidance within those 18 months instead. It then will work towards publishing a final guidance within 18 months after the close of the public comment period on the revised draft guidance.

d. Establish FDA review performance goals and provide feedback and comments on REMS methodological approaches and study protocols used to assess a REMS program for products within 90 days of receipt. FDA proposes the following staged implementation of review performance goals for review of methodological approaches and study protocols for REMS assessments in PDUFA VII:

i. In FY 2024, review and notify sponsor with concurrence or comments within 90 days of receipt for 50% of REMS assessment methods and protocols

ii. In FY 2025, review and notify sponsor with concurrence or comments within 90 days of receipt for 70% of REMS assessment methods and protocols

iii. In FY 2026 and FY 2027, review and notify sponsor with concurrence or comments within 90 days of receipt for 90% of REMS assessment methods and protocols

2. Optimization of the Sentinel Initiative

The user fee funds initially provided in PDUFA VI to expand the Sentinel program will continue to systematically implement and integrate Sentinel and BEST (Biologics Effectiveness and Safety) Systems in FDA drug safety activities by sustaining the high quality and large quantity of data available, allowing continued application of advanced methods for determining when and how those data are utilized, and ensuring comprehensive training of review staff on the use of Sentinel and BEST. These capabilities will support the use of the Sentinel Initiative for regulatory decision making to address questions of product safety and advance our understanding of how real-world evidence can be used for studying effectiveness.

a. Maintenance of the Sentinel Initiative Capabilities and Continued Integration into FDA Drug Safety Activities

FDA will use user fee funds to maintain the quality and quantity of data available through the Sentinel Initiative (Sentinel and BEST), to maintain the processes and tools for determining when and how those data are utilized, and to support comprehensive training of review staff on the use of Sentinel.

i. FDA will maintain the Sentinel's sources of data and core capabilities for the safety surveillance of drugs and biologics, including the multisite ARIA system.

ii. FDA will continue 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.

iii. By the end of FY 2025, FDA will publish on its website an update on facilitation of public and sponsor access to Sentinel's distributed data network to conduct safety surveillance.

iv. FDA will continue to post study results, study parameters and analysis code online and maintain a strong Sentinel web presence to host this information.

v. FDA will continue to maintain a comprehensive FDA Sentinel training program for all relevant staff (e.g., epidemiologists, statisticians, project managers, medical officers, clinical analysts, 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 decisions, and are able to consistently participate in use of Sentinel to evaluate safety issues.

vi. By the end of FY 2025, FDA will analyze, and report on the use of Sentinel for regulatory purposes, e.g., in the contexts of labeling changes, PMRs, or PMCs.

vii. For FY 2023-2027, FDA will report its obligations for updated PDUFA VI commitments for PDUFA VII Sentinel Initiative annually in the PDUFA Financial Report. This reporting will provide detail for spending categories (e.g., data infrastructure, analytical capabilities, safety issue analyses, dissemination of relevant product and safety information, and Sentinel system development).

b. Enhancement of the Analytic Capabilities of the Sentinel Initiative to Address Questions of Product Safety and Advance the Understanding of How Real-World Evidence Can Be Used for Studying Effectiveness

FDA will use user fee funds to advance the analytic capabilities of the Sentinel Initiative by i) developing a consistent approach to post-market requirements and commitments during NDA and BLA review related to assessing the outcomes of pregnancies in women exposed to drugs and biological products and clarifying the optimal use and value of pregnancy registries and electronic healthcare data for assessing pregnancy safety and ii) supporting the use of real-world evidence to address questions of product safety and advancing our understanding of how real-world evidence may be used for studying effectiveness.

i. Pregnancy Safety

The goal of pregnancy safety post-market requirements and commitments studies is to inform labeling on the safety of use in pregnancy and to detect or evaluate safety signals in a timely manner.

(1) FDA will develop a framework describing how data from different types of post-market pregnancy safety studies might optimally be used, incorporating knowledge of how different types of post-market studies have been used by FDA and industry and identifying gaps in knowledge needed to be filled by demonstration projects. The framework would consider factors such as, but not limited to, purpose of study, types of post-market studies, anticipated exposure in females of reproductive potential (FRP) and pregnant women, potential toxicity of the drug and proposed risk mitigation, benefits of the drug, and magnitude and type of risk to be detected. The framework would specifically address the use of pregnancy registries and electronic healthcare data sources including Sentinel, with a goal of ensuring the most efficient means of obtaining highest quality safety data available.

(a) FDA will review published literature and conduct a review of types of post-market pregnancy data that have been included in pregnancy labeling.

(b) By September 30, 2023, FDA will hold a public workshop on post-market safety studies in pregnant women to facilitate determination of the ideal post-market study design(s), including industry experience and use of Sentinel Initiative and other real-world data resources.

(c) By September 30, 2024, FDA will publish a workshop report describing the proposed framework.

(2) Incorporating feedback from (1), conduct 5 demonstration projects to address gaps in knowledge about performance characteristics of different study designs. FDA will initiate the following demonstration projects which may be modified as needed, before September 30, 2024:

(a) Assess the performance of pregnancy registries versus electronic healthcare database studies to detect a signal when the exposure to medication in pregnancy is relatively common.

(b) Assess the performance of single arm safety studies versus signal identification methods using electronic healthcare data to detect a signal when the exposure to medication in pregnancy is anticipated to be low.

(c) Assess the performance of pregnancy registries versus electronic healthcare database studies to evaluate a signal

when the exposure to medication in pregnancy is relatively common.

(d) Assess the performance of major congenital malformations (MCM) as a composite outcome in signal detection and evaluation when there is true risk for some but not all specific malformations.

(e) Assess the performance of an algorithm using electronic health record (EHR) and claims-linked healthcare data for a pregnancy-related outcome, or composite of outcomes (e.g., spontaneous abortion, stillbirth, congenital malformations), after use of vaccines in pregnant women. The parameters of the pregnancy-outcome algorithm will be developed to have general usability with therapeutic products.

(3) By September 30, 2027, based on the results of demonstration projects in (2) update the proposed framework and develop a guidance or MAPP/SOPP as appropriate to implement a standardized process for determining necessity and type of pregnancy postmarketing studies including PMRs.

ii. Use of Real-World Evidence – Negative Controls

FDA is building Sentinel/BEST methodology to improve understanding of robustness evaluations used to address the consistency of RWE with respect to study design, analysis, or variable measurement. FDA will develop new methods to support causal inference in Sentinel/BEST that could address product safety questions and advance our understanding of how RWE may be used for studying effectiveness.

(1) By September 30, 2023, FDA will hold a public workshop on use of negative controls for assessing the validity of non-interventional studies of treatment and the proposed Sentinel Initiative projects.

(2) FDA will initiate two methods development projects by September 30, 2024 to 1) develop an empirical method to automate the negative control identification process in Sentinel and integrate it into the Sentinel System tools; and 2) develop a method to use a double negative control adjustment to reduce unmeasured confounding in studying effectiveness of vaccines.

(3) By September 30, 2027, FDA will publish a report on the results of the development projects.

N. ENHANCEMENTS RELATED TO PRODUCT QUALITY REVIEWS, CHEMISTRY, MANUFACTURING, AND CONTROLS APPROACHES, AND ADVANCING THE UTILIZATION OF INNOVATIVE MANUFACTURING TECHNOLOGIES

To ensure new and innovative products are developed and available to patients in a timely manner, FDA and industry will focus on enhancing communications during drug development and application review, enhancing support for CMC development and facilitating the CMC readiness of products with accelerated clinical development timelines, and advancing the implementation of innovative manufacturing technologies.

1. Enhancing Communication Between FDA and Sponsors During Application Review

To promote an efficient and effective application review process, FDA will conduct the following activities during PDUFA VII to enhance communication between the FDA review teams and sponsors:

a. The four essential components of CMC information requests (referred to as Four-Part Harmony) are intended to ensure that the FDA requests information that is appropriate to address the question or issue, in an efficient manner, and at the appropriate timepoint within the review cycle or product lifecycle, as applicable. Use of Four-Part Harmony includes acknowledging what was provided and where (e.g., modules, page numbers, as applicable), identifying the issue or deficiency, clearly identifying the information needed to achieve resolution and make a regulatory decision, and identifying specific references or other information to support FDA's request. These four essential components of Four-Part Harmony are:

   i. What was provided
   ii. What is the issue or deficiency
   iii. What is needed
   iv. Why it is needed

   By the end of FY 2023, to promote FDA reviewers' use of Four-Part Harmony, FDA will update and conduct training on CDER MAPP 5016.8, "Communication Guidelines for Quality-Related Information Request and Deficiencies" and CBER SOPP 8401.1, "Issuance of and Review of Responses to Information Request Communications to Pending Applications" describing the guidelines for the content of information requests, based on the principles of Four-Part Harmony.

b. By the end of FY 2023, FDA will update and conduct training on CMC assessment processes associated with mid-cycle and late-cycle review meetings with the goal of ensuring that mid-cycle and late-cycle meeting expectations are met, including communicating the status of the NDA and BLA CMC assessment and any identified issues that would preclude approval.

c. FDA will contract with an independent third party to assess current practices of FDA (CDER and CBER) and sponsors in communicating through product quality information requests (IRs) during application review, not including supplements.

The assessment will focus on the application of Four-Part Harmony as described in the MAPPs and SOPPs (e.g., did FDA state why the information is needed for the review of the application) as well as seek to identify trends across IRs. 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. The contractor-led interviews will be designed to provide feedback from individual sponsors on the effectiveness of Four-Part Harmony. Due to the significant volume of IRs in a given year, the assessment will be based on a subset of drug and biologic applications, not including supplements, balanced across CDER and CBER, proportional to the number of applications received by each Center. The third party will identify best practices and areas for improvement in communication between FDA review staff and sponsors through IRs. FDA will publish the final report of the assessment on FDA's website no later than June 30, 2025, for public comment.

2. Enhancing Inspection Communication for Applications, not Including Supplements

FDA and industry believe enhanced communication between review teams and industry on certain pre-license inspections and pre-approval inspections can facilitate an efficient application review process.

When FDA determines for an application, not including supplements, that it is necessary to conduct the inspection at a time when the product identified in the application is being manufactured, FDA's goal is to communicate its intent to inspect a manufacturing facility at least 60 days in advance of BLA Pre-license Inspections and NDA Pre-approval Inspections and no later than mid-cycle. FDA reserves the right to conduct manufacturing facility inspections at any time during the review cycle, whether or not FDA has communicated to the facility the intent to inspect.

3. Alternative Tools to Assess Manufacturing Facilities Named in Pending Applications

During the COVID-19 public health emergency, the FDA expanded its use of alternate tools for assessing facilities named in applications, including exercising its authority to request records and other information in advance of or in lieu of an inspection, granted per section 704(a)(4) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 374(a)). Where appropriate, the agency also increased the use of information, including inspection reports, shared by trusted foreign regulatory partners through mutual recognition agreements and other confidentiality agreements. As FDA continues to gain experience and lessons learned from the use of these tools, FDA will communicate its thinking on the use of such methods beyond the pandemic.

By September 30, 2023, FDA will issue draft guidance on the use of alternative tools to assess manufacturing facilities named in pending applications (e.g., requesting existing inspection reports from other trusted foreign regulatory partners through mutual recognition and confidentiality agreements, requesting information from applicants, requesting records and other information directly from facilities and other inspected

entities, and, as appropriate, utilizing new or existing technology platforms to assess manufacturing facilities). The guidance will incorporate best practices, including those in existing published documents, from the use of such tools during the COVID-19 pandemic. FDA will work towards the goal of publishing final guidance within 18 months after the close of the public comment period on the draft guidance. If, after receiving comments on the draft guidance, FDA determines that the guidance requires substantive changes on which further public comments are warranted, FDA will issue a revised draft guidance within those 18 months instead. It then will work towards publishing a final guidance within 18 months after the close of the public comment period on the revised draft guidance.

4. Facilitating Chemistry, Manufacturing, and Controls Readiness for Products with Accelerated Clinical Development

Development programs for CDER- and CBER-regulated drugs and biologics intended to diagnose, treat, or prevent a serious disease or condition where there is an unmet medical need may have accelerated clinical development timelines. Products with accelerated clinical development activities often face challenges in expediting CMC development activities to align with the accelerated clinical timelines. Overcoming these CMC challenges often requires additional interaction with FDA during product development and the use of science- and risk-based regulatory approaches so that the clinical benefits of earlier patient access to these products can be realized.

a. **MAPP:** By December 31, 2022, FDA will issue a new MAPP on approaches to address CMC challenges for CDER-regulated products (drugs, biologics) with accelerated clinical development timelines (e.g., products used to diagnose, treat, or prevent a serious disease or condition where there is unmet medical need). To address the CMC challenges, the MAPP will describe early engagement with sponsors of such products and the different science- and risk-based approaches, including those described in the FDA Guidance for Industry: Expedited Programs for Serious Conditions-Drugs and Biologics, that may be warranted and utilized in CMC development based upon the anticipated clinical benefit of earlier patient access to the product. The MAPP will incorporate modern pharmaceutical principles as well as modern regulatory tools, such as those detailed in ICH Q12.

b. **Pilot:** Starting in FY 2023, FDA (CDER and CBER) will conduct a CMC Development and Readiness Pilot (CDRP) to facilitate the expedited CMC development of products under an IND application, where warranted, based upon the anticipated clinical benefit of earlier patient access to the products. The goal of the Pilot will be to facilitate CMC readiness for CBER- and CDER-regulated products with accelerated clinical development timelines. Due to the differences in product complexity between CBER- and CDER-regulated products, Pilot selection criteria may differ between the Centers. In order to accelerate CMC development and facilitate CMC readiness, the Pilot will incorporate, as applicable, contemporary learnings and the use of science- and risk-based approaches and submission strategies, such as those described in the FDA Guidance for Industry: Expedited Programs for Serious Conditions-Drugs and Biologics.

For sponsors participating in the CMC Development and Readiness Pilot, FDA will provide specific CMC advice during product development by providing two additional CMC-focused Type B meetings and an additional limited number of CMC-focused discussions based on readiness and defined CMC milestones. The increased communication between FDA review staff and applicants is intended to ensure a mutual understanding of what activities must be completed, and what information should be provided at the appropriate timepoint (i.e., at the time of NDA or BLA submission, prior to the end of the review cycle, or post-approval), to ensure CMC readiness of the product.

i. By December 31, 2022, FDA will publish a Federal Register Notice (FRN) announcing the Pilot and outlining the eligibility criteria and process for submitting a request to participate in the Pilot. For CDER, the eligibility criteria will focus on the selection of products with accelerated clinical development timelines that could expand or enhance the approaches in the CDER MAPP described above. For CBER, the eligibility criteria will include considerations for products with accelerated clinical development timelines (e.g., vaccines and cell and gene therapies).

   The FRN will give more specifics on products to be included in the Pilot and will consider Industry's interest in CBER-regulated products such as cell and gene therapies. FDA will select between 8 – 10 proposals per fiscal year over a 4-year period.

ii. To promote innovation and understanding in this area, lessons learned through the Pilot may be presented by FDA (e.g., in a public workshop) as case studies, including when the product studied in the Pilot has not yet been approved by FDA. To be eligible for the Pilot, the sponsor and FDA will reach an agreement on the information to be publicly disclosed. When feasible, FDA will notify a sponsor in advance when the sponsor's program is the planned focus of a public discussion. Participation in the pilot program, including such agreement on information disclosure, will be voluntary and at the discretion of the sponsor.

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

c. **Public Workshop**: By July 31, 2025, FDA will conduct a public workshop, potentially through a qualified third party, focused on CMC aspects of expedited development including case studies, lessons learned, and stakeholder input regarding the CMC Development and Readiness Pilot. The workshop will solicit and include industry and public feedback.

   Topics for the workshop will include, but are not limited to, the use of science- and risk-based approaches and submission strategies to accelerate CMC development, including predictive stability modeling, risk-based approaches to product specification setting, and alternate process validation approaches, as well as experiences related to quality by design and platform technologies.

d. **Strategy Document**: Following the close of the public comment period for the public workshop, and no later than April 30, 2026, FDA will issue a strategy document outlining the Agency's plans, including proposed timeframes, to develop or revise, as appropriate, relevant MAPPs or SOPPs, and other applicable documents (e.g., guidance and process documents) to incorporate lessons learned from the Agency's experiences with the CMC Development and Readiness Pilot and other submissions for products with accelerated clinical development timelines, as well as industry and public input, including feedback from the public workshop.

5. Advancing Utilization and Implementation of Innovative Manufacturing

By the end of FY 2023, FDA will conduct a public workshop on the utilization of innovative manufacturing technologies for CDER- and CBER-regulated products, including barriers to their adoption and submission strategies. The workshop will solicit and include industry and public feedback.

Topics for the workshop will include but are not limited to:

a. Best practices and lessons learned from both the CDER Emerging Technology Team and CBER Advanced Technology Team programs from both industry and regulatory perspectives;

b. Case studies from previous innovative technology submissions presented by sponsors;

c. Barriers (technical, regulatory, etc.) to the adoption of innovative manufacturing technologies;

d. Regulatory strategies for the adoption of advanced manufacturing technologies, including, but not limited to, submission strategies for the implementation of certain innovative technologies across multiple commercial products and/or multiple manufacturing sites; and

e. Science- and risk-based approaches for developing and assessing innovative technologies across platform products and sites to streamline adoption.

Following the close of the public comment period for the public workshop, and no later than September 30, 2024, FDA will issue a draft strategy document for public comment that outlines the specific actions the agency will take over the course of PDUFA VII to facilitate the utilization of innovative manufacturing technologies, including addressing barriers to their adoption. The actions described in the draft strategy document will be based on lessons learned from the Agency's experiences with submissions involving advanced manufacturing technologies as well as feedback from the workshop and other public input. The strategy document may include updating or creating new procedures, MAPPs, SOPPs, guidances, and scientific/other relevant programs related to the topics discussed in the workshop. The strategy document will also include proposed timeframes for the specific actions outlined in the document.

FDA will consider public input and finalize the strategy document within 9 months after the close of the public comment period on the draft strategy document.

O. ENHANCING CBER's CAPACITY TO SUPPORT DEVELOPMENT, REVIEW, AND APPROVAL OF CELL AND GENE THERAPY PRODUCTS

To ensure that new and innovative cell and gene therapy products are developed and available to patients in a timely manner, FDA will build on the success of the Cell and Gene Therapy Program (CGTP) in CBER to further support and advance a balanced approach to product development and regulation. To this end, FDA will substantially strengthen staff capacity and capability in order to meet the increasing challenges and demands in this growing field. Increasing staff capacity will overcome existing resource limitations, allowing staff to spend additional time on meetings and submission reviews including those with breakthrough or regenerative medicine advanced therapy designations, expand stakeholder outreach, invest in new policy and guidance, and facilitate development and use of regulatory tools and scientific technologies.

The CGTP will be augmented with additional resources to sustain and expand the program Staff will be hired for direct review activities, indirect activities (e.g., policy, external outreach, postmarket safety), and supporting activities in the CGTP, with a focus on hiring staff with technical, scientific, clinical, or other specialized expertise necessary to understand and advance cell and gene therapies. Recruiting and hiring of staff will be actively pursued as a CBER priority and be facilitated by support staff whose dedicated focus will be attracting and retaining talent for the CGTP. CBER recognizes the importance of integration of new staff into the CGTP and will effectively facilitate growth in staffing using external consultants when appropriate. For PDUFA VII, resources will also support onboarding and integration of new staff, regulatory support and outreach (e.g., webinars, recorded training) to facilitate industry and stakeholder education and interaction.

CBER will continue to maintain a highly trained and experienced CGTP staff, with an emphasis on remaining current in regulatory science, and the latest scientific, manufacturing, and clinical advances. The current staff training will be reviewed, with input from external consultants, and modified as needed to accommodate and facilitate training of new staff and maintain the competency of existing staff.

CBER will continue to organize and manage the CGTP for optimal performance, leveraging and implementing best practices from relevant sources. The current CGTP organization will be evaluated, with input from external consultants, to determine the optimal organization to effectively integrate new staff and facilitate operations and customer service. As part of CBER's modernization program, CBER will evaluate, streamline, and harmonize CGTP procedures, processes, and interactions to facilitate communications, enhance regulatory consistency and review standards, reduce regulatory burden, optimize operational efficiency, and update relevant SOPPS and documents as needed. Change management will be tailored to ensure success of organizational changes and business modernization.

The CGTP staff will enhance communications with stakeholders, on an individual and collective level, by refining and improving best practices for communication, through public meetings and

workshops, and issuance of guidance, updating relevant SOPPS, and other mechanisms. CBER will continue to issue new guidance on current cell and gene therapy topics and update existing guidance to be current with evolving science and approaches. Staff will increase awareness of FDA's regulatory programs through on-demand training (e.g., recorded webcast), to facilitate navigation by industry through the phases of product development and approval. CGTP staff will continue to engage in outreach to industry, patient groups, and other stakeholders in several areas soliciting views on specific topics and proposals.

Staff will continue to participate in external collaborations, including public-private partnerships and international organizations in a variety of areas, including development of tools (e.g., standards), technologies, and approaches that support development of cell and gene therapies. Interactions will also focus on advancing manufacturing and testing, including facilitating implementation of new technologies. With stakeholders, staff will continue discussing use of existing approaches (e.g., surrogate endpoints, real world evidence, complex innovative designs, natural histories) and explore new approaches for obtaining efficacy and safety information with specific consideration and attention to rare and ultra-rare diseases.

To advance the field and support the next generation of cell and gene therapy products, CBER will conduct the following activities during PDUFA VII.

1. **Patient Focused Drug Development**

    a. By the end of FY 2023, FDA will convene a public patient focused drug development meeting with key stakeholders, including patients and patient advocacy organizations, to better understand patient perspectives on gene therapy products, including cell-mediated gene therapy. This meeting should address, among other things, the patient and caregiver's level of understanding and expectations regarding the benefits and risks of these therapies, and their involvement in clinical study design and execution. Within 6 months of the public meeting, FDA will issue a report summarizing the views expressed at the meeting including:

        i. Analysis of current tools or methods used to capture patient experience data, and/or patient involvement in clinical studies, including identification of existing challenges and gaps;

        ii. Whether there is a need for the community to develop specific tools or methods to capture patient experience data, and/or patient involvement in clinical studies that are unique to these products, and if so, suggestions for community engagement strategies; and

        iii. Approaches to leveraging existing tools or methods to capture patient experience and patient preference data that are unique to these products;

2. **Novel Approaches to Development of Cell and Gene Therapy**

    a. FDA will continue to work with stakeholders including public-private partnerships to seek public input on questions and challenges faced by cell and gene therapy developers, including the use of novel endpoints and the role of less

defined natural histories, and to facilitate development and approval for cell and gene therapies, including but not limited to, individualized therapies, rare disease and therapies for small patient populations.

b. By the end of FY 2025, FDA will issue a draft guidance on the evaluation of efficacy in small patient populations using novel trial designs and statistical methods, and how these concepts can be applied to more common diseases. FDA will work towards the goal of publishing final guidance within 18 months after the close of the public comment period on the draft guidance. If, after receiving comments on the draft guidance, FDA determines that the guidance requires substantive changes on which further public comments are warranted, FDA will issue a revised draft guidance within those 18 months instead. It then will work towards publishing a final guidance within 18 months after the close of the public comment period on the revised draft guidance.

c. In order to promote development of cell and gene therapy products, FDA will issue a Questions and Answers draft guidance by the end of FY 2024 based on frequently asked questions, and commonly faced-issues identified by sponsors or by public-private partnerships. FDA will work towards the goal of publishing final guidance within 18 months after the close of the public comment period on the draft guidance. If, after receiving comments on the draft guidance, FDA determines that the guidance requires substantive changes on which further public comments are warranted, FDA will issue a revised draft guidance within those 18 months instead. It then will work towards publishing a final guidance within 18 months after the close of the public comment period on the revised draft guidance.

d. By the end of FY 2024, FDA will convene a public meeting to solicit input on methods and approaches (e.g., use of RWE, registries) for capturing post-approval safety and efficacy data for cell and gene therapy products. Within 6 months of the public meeting, FDA will issue a summary report or a transcript of the meeting. Input from this meeting will be used to inform development of a draft guidance on this topic. FDA will issue a draft guidance on this topic by the end of FY 2025. FDA will work towards the goal of publishing final guidance within 18 months after the close of the public comment period on the draft guidance. If, after receiving comments on the draft guidance, FDA determines that the guidance requires substantive changes on which further public comments are warranted, FDA will issue a revised draft guidance within those 18 months instead. It then will work towards publishing a final guidance within 18 months after the close of the public comment period on the revised draft guidance.

3. Expedited Programs for the Development of Regenerative Medicine Therapies:

a. By the end of FY 2025, FDA will update the Guidance for Industry: Expedited Programs for Regenerative Medicine Therapies for Serious Conditions. Updates will include, for example, additional thinking on post-approval requirements, including the use of real-world evidence to confirm clinical benefit, for products approved under accelerated approval, as well as for safety monitoring and long-term follow-up. Updates will also include additional thinking on approaches and

processes relating to CMC including considerations regarding CMC readiness to take advantage of the expedited programs. FDA will work towards the goal of publishing final guidance within 18 months after the close of the public comment period on the draft guidance. If, after receiving comments on the draft guidance, FDA determines that the guidance requires substantive changes on which further public comments are warranted, FDA will issue a revised draft guidance within those 18 months instead. It then will work towards publishing a final guidance within 18 months after the close of the public comment period on the revised draft guidance.

4. Leveraging Knowledge

a. FDA will continue to work with organizations, including public-private partnerships, that foster development and accessibility of non-proprietary knowledge (e.g., standards), manufacturing advances, and manufacturing components for use in cell and gene therapy products. FDA will continue to participate in international organizations sharing knowledge and perspective to harmonize cell and gene therapy guidance as appropriate.

b. By the end of FY 2025, FDA will convene a public meeting to solicit the perspective of cell and gene therapy manufacturers on how individual sponsors might leverage internal prior knowledge and public knowledge, including Chemistry, Manufacturing, and Controls, non-clinical, and clinical knowledge, across therapeutic contexts in order to facilitate product development and application review. Input from this meeting will be used to inform development of a draft guidance on this topic that FDA will issue by the end of FY 2026. FDA will work towards the goal of publishing final guidance within 18 months after the close of the public comment period on the draft guidance. If, after receiving comments on the draft guidance, FDA determines that the guidance requires substantive changes on which further public comments are warranted, FDA will issue a revised draft guidance within those 18 months instead. It then will work towards publishing a final guidance within 18 months after the close of the public comment period on the revised draft guidance.

P. SUPPORTING REVIEW OF NEW ALLERGENIC EXTRACT PRODUCTS

FDA will use fee revenues to support the review of new allergenic extract products that have been incorporated in the PDUFA program by PDUFA VII. Allergenic extract products licensed after October 1, 2022 will generally be included in user fees. Allergenic extract products licensed before October 1, 2022, and standardized allergenic extract products submitted pursuant to a notification to the applicant from the Secretary regarding the existence of a potency test that measures the allergenic activity of an allergenic extract product licensed by the applicant before October 1, 2022 will remain excluded from PDUFA. All performance goals, procedures, and commitments in this letter apply to the allergenic products included in the PDUFA program under PDUFA VII.

II. CONTINUED ENHANCEMENT OF USER FEE RESOURCE MANAGEMENT

FDA is committed to ensuring the sustainability of PDUFA program resources and to enhancing the operational agility of the PDUFA program. FDA will build on the financial enhancements included in PDUFA VI and continue activities in PDUFA VII to ensure optimal use of user fee resources and the alignment of staff to workload through the continued maturation and assessment of the Agency's resource capacity planning capability. FDA will also continue activities to promote transparency of the use of financial resources in support of the PDUFA program.

A. RESOURCE CAPACITY PLANNING

FDA will continue activities to mature the Agency's resource capacity planning function, including utilization of modernized time reporting, to support enhanced management of PDUFA resources in PDUFA VII and help ensure alignment of user fee resources to staff workload.

1. Resource Capacity Planning Implementation

a. By the end of the 2nd quarter of FY 2023, FDA will publish an implementation plan that will describe how resource capacity planning and time reporting will continue to be implemented during PDUFA VII. This implementation plan will address topics relevant to the maturation of resource capacity planning, including, but not limited to, detailing FDA's approach to:

   i. The continued implementation of the Agency's resource capacity planning capability, including:

      1) The continual improvement of the Capacity Planning Adjustment (CPA); and

      2) The continual improvement of time reporting and its utilization in the CPA.

   ii. The integration of resource capacity planning analyses in the Agency's resource and operational decision-making processes.

b. FDA will provide annual updates on the FDA website on the Agency's progress relative to activities detailed in this implementation plan by the end of the 2nd quarter of each subsequent fiscal year.

c. FDA will document in the annual PDUFA Financial Report how the CPA fee revenues are being utilized.

2. Resource Capacity Planning Assessment

By the end of FY 2025, an independent contractor will complete and publish an evaluation of the resource capacity planning capability. This will include an assessment of the following topics:

a. The ability of the CPA to forecast resource needs for the PDUFA program, including an assessment of the scope of the workload drivers in the CPA and their ability to represent the overall workload of the PDUFA program;

b. Opportunities for the enhancement of time reporting toward informing resource needs; and

c. The integration and utilization of resource capacity planning information within resource and operational decision-making processes of the PDUFA program.

The contractor will provide options and recommendations in the evaluation regarding the continued enhancement of the above topics as warranted. The evaluation findings and any related recommendations will be discussed at the FY 2026 PDUFA 5-year financial plan public meeting. After review of the findings and recommendations of the evaluation, FDA will, as appropriate, continue improving the resource capacity planning capability and the CPA.

B. FINANCIAL TRANSPARENCY

1. FDA will publish a PDUFA 5-year financial plan no later than the end of the 2nd quarter of FY 2023. The plan shall recognize that the retention of the strategic hiring and retention adjustment required by section 736(b)(1)(C) of the FD&C Act is subject to renegotiation under a subsequent reauthorization of PDUFA. FDA will publish updates to the 5-year plan no later than the end of the 2nd quarter of each subsequent fiscal year. The annual updates will include the following topics:

a. The changes in the personnel compensation and benefit costs for the process for the review of human drug applications that exceed the amounts provided by the personnel compensation and benefit costs portion of the inflation adjustment; and

b. FDA's plan for managing costs related to strategic hiring and retention after the adjustment required by section 736(b)(1)(C) of the FD&C Act expires at the end of fiscal year 2027, given this adjustment is not intended to be reauthorized in a subsequent reauthorization of PDUFA.

2. FDA will convene a public meeting no later than the end of the 3rd quarter of each fiscal year to discuss the PDUFA 5-year financial plan and the Agency's progress in implementing resource capacity planning, including the continual improvement of the CPA and time reporting, and the integration of resource capacity planning in resource and operational decision-making processes.

3. FDA will include in the annual PDUFA Financial Report an accounting of appropriated user fee funds included in the operating reserve at the end of each fiscal year, as well as the carryover balance of user fee funds that are considered unappropriated and therefore not included in the operating reserve.

III. IMPROVING FDA HIRING AND RETENTION OF REVIEW STAFF

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. During PDUFA VII, FDA will commit to do the following:

A. 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 VII. These goals for targeted hires are summarized in Table 6 below:

   Table 6

	FY 2023	FY 2024	FY 2025	FY 2026	FY 2027
CBER	132	48	29	15	4
CDER	77	31	15	0	0
Other FDA	1	0	0	0	0
Total FTE	210	79	44	15	4

2. FDA will confirm progress in the hiring of PDUFA VI new staff. FDA will also report on progress against the hiring goals for FY 2023-2027 on a quarterly basis posting updates to the FDA website PDUFA Performance webpage.

B. ASSESSMENT OF HIRING AND RETENTION

The Directors of CDER and CBER will utilize a qualified, independent contractor with expertise in assessing HR operations to conduct a targeted assessment of the hiring and retention of staff for the human drug review program. The contractor will assess the factors that contribute to HR successes and challenges, including factors outside of FDA's control. The assessment will build upon the findings of previous evaluations conducted under PDUFA VI with a focus on the changes and adjustments that have improved FDA's hiring and retention outcomes and which challenges remain. In addition to evaluating the outcomes of various hiring changes, the assessment will include metrics related to recruiting and retention in the human drug review program, including, but not limited to, specific targeted scientific disciplines, attrition, and utilization of pay authorities. The report will include the contractor's findings and recommendations on further enhancements to hiring and retention of staff for the human drug review program, if warranted.

The assessment will be published on FDA's website no later than the June 30th, 2025 for public comment. FDA will also hold a public meeting no later than the September 30th, 2025 to discuss the report, its findings, and the Agency's specific plans to address the report recommendations.

IV. INFORMATION TECHNOLOGY AND BIOINFORMATICS GOALS

A. ENHANCING TRANSPARENCY AND LEVERAGING MODERN TECHNOLOGY

Under PDUFA VII, FDA will:

1. **Enhance Transparency**

   FDA will further enhance transparency of its IT activities and modernization plans, as well as continue to ensure the usability and improvement of the electronic submissions gateway (ESG):

   a. Quarterly, FDA and industry will jointly plan and conduct meetings on challenges, emerging needs, and progress on initiatives relevant to PDUFA, including continued sustainability of initiatives after completion in PDUFA VII, progress or activities on harmonization and convergence, where appropriate, across Center systems for streamlined compatibility, interoperability, and extensibility. Agendas and meeting materials will be shared prior to each meeting.

   b. Annually, appropriate FDA and industry IT leadership (e.g., enterprise IT leadership, Center IT leadership) will participate in a review of PDUFA IT initiatives and provide an opportunity for industry input.

   c. FDA will engage industry to provide feedback and/or participate in pilot testing in advance of implementing significant changes that impact industry's interaction with the enterprise-wide systems.

   d. FDA will maintain a current published FDA Data Standards Catalog, and quarterly publish an updated data standards action plan.

2. **Develop Data and Technology Modernization Strategy**

   FDA will progress a Data and Technology Modernization Strategy ("Strategy") that provides FDA's strategic direction for current and future state data-driven regulatory initiatives.

   a. No later than Q4 FY 2023, FDA will establish a Data and Technology Modernization Strategy that reflects the vision in FDA's Technology and Data Modernization Action Plans, including:

      i. outlining key areas of focus and approach including leveraging cloud technologies to support Applicant-FDA regulatory interaction;

      ii. articulating enterprise-wide approaches for both technology and data governance; and

      iii. aligning strategic initiatives in support of PDUFA review goals, drawing a line of sight between initiatives and the enterprise strategy (i.e. the agency-wide strategy also supporting components outside PDUFA).

b. The Strategy will be shared and annually updated to reflect progress and any needed adjustments. Milestones and metrics for PDUFA initiatives will be included in the updates.

3. **Promote Convergence**

As appropriate, FDA will engage with stakeholders and international consortia (e.g., ICH, ICMRA) on technology and innovation initiatives that promote convergence in data interoperability and interpretability for current and future FDA initiatives throughout the regulatory lifecycle.

a. FDA will seek to adopt international standards where feasible and appropriate, giving considerations to cybersecurity risk, international commitments, legal constraints, and other relevant factors.

4. **Accelerate CBER Modernization**

During PDUFA VII, CBER will retire its older IT systems and capabilities, leverage capabilities in other Centers where feasible, and utilize new data management tools and technologies in line with Agency strategic plans and effective use of resources.

In coordination with CDER and CDRH, CBER will accelerate its data and IT modernization in order to leverage or develop state-of the art IT technology to provide cloud-based, agile, and stable integrated platforms, to streamline and improve its ability to perform complex reviews, access, utilize and protect data, and redirect IT spending from maintenance of older IT systems to improving the reviewer experience. Modernization efforts will enable new capabilities such as knowledge management, data and analytic reporting, decision tools, and, workflow and workload management to be developed sooner. CBER will share its experience and new capabilities with other Centers.

b. By the end of Q4 FY 2022, CBER will have established a multi-year modernization roadmap, including concrete implementation phases and milestones with defined success and performance criteria and anticipated costs.

i. Criteria may include, for example, retiring a minimum 25% of CBER legacy systems and capabilities by the end of PDUFA VII; leveraging existing adverse events reporting capabilities for CBER adverse event reporting; transitioning regulatory data and analytics to a new shared environment; using a new electronic review management tool and knowledge management system.

ii. These and other modernization efforts will allow for measurable improved review and internal management of novel and scientifically complex PDUFA biologics, leading to enhanced review efficiency, effectiveness and quality.

iii. Modernization outcomes will facilitate external interactions with developers, manufacturers, and other stakeholders — resulting in faster

information exchange, data analysis, and dissemination of safety information; and better consistency of advice and decisions to guide and foster product development and review.

c. Annually and at key milestones, CBER will share its roadmap, provide updates on its progress including successes, issues, performance metrics, accomplishments and any issues or necessary adjustments to accommodate unexpected events (e.g., contracting, delays outside of CBER control) or reasonable deviations from its modernization roadmap. This information will be shared at regularly scheduled FDA-industry meetings.

d. In order to ensure successful modernization, CBER maintains active management and oversight of its IT and Data projects through a structured system of controls that covers all phases of projects. CBER will not progress to the next phase of implementation for an IT modernization project without successful completion of the previous phase.

e. CBER will scope and plan its IT modernization activities to conclude by the end of FY 2027 with no expectation of continued additional direct costs funding to support the effort beyond PDUFA VII.

5. **Monitor and Modernize ESG**

FDA will continue to ensure the usability and improvement of the ESG.

a. Annually, FDA will provide on the ESG website historic and current metrics on ESG performance in relation to published targets, characterizations and volume of submissions, and standards adoption and conformance.

FDA will advance the ESG cloud-based modernization with an improved architecture that supports greatly expanding data submission bandwidth and storage, while continuing to ensure its stable operation.

a. By the end of FY 2025, FDA will complete ESG transition to the cloud, including set-up and integration of an enterprise Identity and Access Management solution that will streamline applicant access to FDA resources.

b. Annually, FDA will share progress against the implementation project plan.

c. FDA will engage industry to provide feedback and/or participate in pilot testing in advance of implementing significant changes that impact industry's interaction with the enterprise-wide systems.

6. **Leverage Cloud Technology to Progress Regulatory Digital Transformation**

Cloud and cloud-based technology offer significant advantages over traditional on-premise data repositories and analytics. Combined with interoperable information exchange mechanisms, these advantages open a host of new opportunities to explore, promote and implement innovation in the drug development and regulatory review process.

The outcomes of demonstration projects in PDUFA VII will be the building blocks, informing and positioning FDA and regulated industry to take best advantage of third-party hosted capabilities in conjunction with their own infrastructure, as well as investigating the potential for such capabilities to be jointly leveraged by other regulatory authorities and applicants.

a. FDA will engage with external parties to develop and test reusable and portable core capabilities that can be supported both with FDA's environment and in trusted third-party environments. This engagement will be through mechanisms such as, but not limited to, cooperative agreements, contracts, Cooperative Research and Development Agreements (CRADAs) and public-private partnerships.

b. By the end of Q3 FY 2023, FDA will assess challenges or barriers in FDA's adoption of cloud-based technologies in applicant-regulator interactions and within 6 months will publish the findings of this assessment.

c. In FY 2023, FDA, in consultation with industry, will prioritize and initiate the first of at least 3 demonstration projects to explore application of cloud-based technologies to streamline, improve and enable a variety of applicant-regulator interactions.

    i. In support of the use of DHT-derived data in applications, FDA will enhance its capability to effectively receive, aggregate, store, and process large volumes of static or continuously updated DHT-derived data captured as part of a clinical trial.

    ii. Projects will demonstrate applications of cloud technology to applicant-regulator interactions and secure shared environments for specific regulatory activities (e.g., support labeling negotiations between FDA and applicants, develop a standard protocol template to accelerate review and provide usable archive, improve statistical analysis plan between FDA and applicants).

    iii. Projects will develop increasingly rich and flexible technical capabilities that can be leveraged for multiple purposes by regulators and industry, either internally within a regulator's or industry's environment, or through a trusted third-party, thus promoting convergence through common components such as Cloud-hosted Individualized Secure Collaboration Hubs (ISCH) which provide secure and effective environments for various cloud-based collaboration initiatives;

        1) An example might be to utilize an ISCH for applicant-regulator label negotiations; another might be to hold continuously updated DHT-derived data for analysis.

d. Within 6 months of completion of a demonstration project, a summary of outcomes and next steps will be compiled and shared with industry at the regularly scheduled FDA-industry meetings. A description of the project and summary of outcomes will be posted on the FDA website.

e. FDA will engage industry to provide feedback and/or participate in testing in advance of implementing significant changes that impact industry's interaction with the enterprise-wide systems.

    i. FDA will review progress and plans at quarterly meetings with industry.

f. Demonstration projects and associated capabilities development will be completed by the end of FY 2027 with no expectation of additional funding for those activities beyond PDUFA VII.

7. **Provide Bioinformatics IT Support**

CDER and CBER are seeing increasing volume and diversity of bioinformatics and computational biology information and data, such as Next Generation Sequencing, in sponsor-regulator interactions. Bioinformaticists play an essential and expanding role in new drug and biologic application reviews, providing in-depth independent analysis of submitted data to support review decisions in close coordination with clinical and product experts. To be effective entails appropriate IT support.

a. FDA will assess its bioinformatics capabilities, and annually, ensure that IT resources are provided to support bioinformatics activities, including software licensing, cloud-based storage and computing capacity, operations support and maintenance.

b. Outcomes will be shared at regularly scheduled FDA-industry meetings.

B. EXPANDING AND ENHANCING BIOINFORMATICS SUPPORT

Bioinformatics and computational biology are increasingly being used to assess product quality, safety and efficacy and facilitate the development, characterization and manufacture of human drugs and biologics. Recognizing the substantial increase in the volume and diversity of bioinformatics and computational biology information and data, such as Next Generation Sequencing, in regulatory submissions, FDA will develop additional expertise and staff capacity in both CDER and CBER to efficiently review and provide technical and timely feedback on information and accompanying data in submissions and meet performance goals, especially for those submitted early in development. FDA will hire technical expertise necessary to assess the approaches and evaluate data as appropriate, validating the results and/or analytic process using existing tools or through independent analysis when necessary. Staff with specialized expertise in specific product/therapeutic areas will also be developed to facilitate translation of bioinformatic information to subject matter review experts. FDA will also assess and strengthen its computational infrastructure to support and advance its informatics platforms, allowing FDA to remain current with the most recent technology in the field. To facilitate submission and review of bioinformatics and computational biology information, FDA will continue to develop data standards and revise guidance or issue draft guidance on this topic including how to submit, and format submissions, and technical validation criteria. FDA will work globally to advance harmonization of these standards and methodologies.

C. ENHANCING USE OF DIGITAL HEALTH TECHNOLOGIES TO SUPPORT DRUG DEVELOPMENT AND REVIEW

A Digital Health Technology (DHT) in the context of this commitment may be considered as a system that uses computing platforms, connectivity, software, and sensors for healthcare and related uses. These technologies may span a wide range of uses, from applications in general wellness to applications as a medical device to applications generating data that may be used in the evaluation of drug or biologic products.

DHTs can allow for remote data acquisition from patients and clinical trial participants to measure a wide range of activities, behaviors, and functioning in real life settings that can inform important clinical endpoints. DHTs may include wearable, implantable, ingestible, and environmental sensors or software applications on mobile devices, among other approaches. The use of DHTs can support and enable the conduct of decentralized clinical trials (DCTs), the clinical investigations in which some or all trial-related procedures and data acquisition take place at locations remote from the investigator.

While the biomedical field has experienced rapid development and implementation of DHTs, FDA has limited experience evaluating novel DHT-based measurements in human drug development. FDA recognizes the potential for DHTs to provide scientific and practical advantages in supporting the assessment of patients by generating information outside of the traditional clinic visit and needs to build capacity and expertise to advise the biopharmaceutical industry in their development and implementation and to evaluate DHT outputs including the impact of regulatory initiatives (or regulatory science). To support new drug registration, label expansion, and safety monitoring, DHT-based data need to be fit for the intended purpose. Toward these ends, FDA will do the following:

1. By the end of Q2 FY 2023, FDA will establish a DHT framework document guide the use of DHT-derived data in regulatory decision-makings for drugs and biological products. The framework will guide activities such as to:

    a. Define objectives for workshops and demonstration projects;

    b. Develop methodologies for evaluating DHTs proposed as measuring key (primary or important secondary) endpoints or other important measures (e.g., for safety monitoring, or baseline characterization) in clinical trials;

    c. Manage submissions with extensive and continuous data, e.g., in order to develop acceptable approaches to capture adverse events; and

    d. Develop a standardized process for data management and analysis of large datasets from DHTs.

2. By the end of Q2 FY 2023, FDA will establish a committee including members from CDER and CBER to support implementation of the commitments in this section. The establishment of the committee and its purpose will be made public on the FDA website. Responsibilities will include, but not be limited to:

    a. Oversee the design and implementation of the DHT framework;

    b. Promote consistency across centers regarding DHT-based policy, procedure, and analytic tool development;

c. Work with the FDA Digital Health Center of Excellence (DHCoE) to increase consistency across regulatory programs, to incorporate relevant learnings from review of digital tools and devices by CDRH, and to consider cross-center topics;

d. Gather information about the present state of DHTs, including specific challenges in their use; and

e. Engage with external stakeholders on DHT-related issues.

3. By the end of Q2 FY 2023, FDA will convene the first of a series of 5 public meetings or workshops with key stakeholders including patients, biopharmaceutical companies, DHT companies, and academia to gather input into issues related to the use of DHTs in regulatory decision-making. The meetings and workshops will be designed with objectives such as to:

    a. Understand priorities for development of DHTs to support clinical trials, including the potential for DHTs to increase diverse patient populations in clinical trials;

    b. Identify approaches to DHT validation;

    c. Gain understanding of DHT data processing and analysis and inform need for novel analytical techniques; and

    d. Address the regulatory acceptance of safety monitoring tools that utilize artificial intelligence/machine learning-based algorithms for pharmacovigilance purposes, e.g., continuous data streams from DHT.

4. FDA will identify at least 3 issue-focused demonstration projects to inform methodologies for efficient DHT evaluation. These projects may include engagement with researchers from academia, biopharmaceutical industry, patient groups and other stakeholders, and will:

    a. Cover key issues to inform regulatory policy development and regulatory advice. E.g.,. the projects may examine such areas as validation methods, analytic approaches to missing data, the use of multi-channel inputs to characterize an endpoint, evaluation of continuous data vs discrete measurements, use and limitations of use of DHTs in DCTs, and other related efforts.

5. By the end of Q1 FY 2023, FDA will publish draft, revised or final guidance on the use of DHTs in traditional and decentralized clinical trials, addressing the validation of measurements made by DHTs, the development of novel endpoints using DHTs, the use of DHTs as new ways to measure existing endpoints, approaches to using the patients' own DHTs such as cell phones or smart watches, usability considerations for patients, detection of safety signals during continuous data acquisition, and issues related to security and confidentiality of data.

    a. Beginning in FY 2024, FDA will publish additional draft guidances in identified areas of need informed by stakeholder engagement.

i. For example, acceptable approaches to capturing and reporting adverse events in clinical trials using DHTs.

b. FDA will work towards the goal of publishing final guidance within 18 months after the close of the public comment period on the draft guidance. If, after receiving comments on the draft guidance, FDA determines that the guidance requires substantive changes on which further public comments are warranted, FDA will issue a revised draft guidance within those 18 months instead. It then will work towards publishing a final guidance within 18 months after the close of the public comment period on the revised draft guidance.

6. By the end of FY 2023, FDA will publish draft, revised or final guidance on regulatory considerations for Prescription Drug Use-Related Software that includes information about software that is disseminated by a drug applicant for use with a prescription drug or biologic product that may be described in labeling, including prescribing information. This guidance will cover software that is distributed with a drug or integrated as part of a drug- or biologic-led combination product, as well as software that is distributed by an applicant independent of an approved product.

7. FDA will expand its capacity to achieve its stated objectives in this section and to enhance consistency across the human drugs and biologics program (and as appropriate with the medical devices program) with regards to development, use, and review of DHT's and associated endpoints. Through a combination of expanded staff and contract support, FDA will:

    a. Build technical expertise within the human drugs and biologics program to enhance internal knowledge, capabilities for review of IND- and NDA/BLA submissions including DHT derived endpoints, policy, standards and guidance development;

    b. Train FDA staff in evaluation of DHTs;

    c. Develop statistical methodology for the design, analysis, and interpretation of DHT-derived clinical trial endpoints;

    d. Build review capacity and expertise to respond to DHT developers and biopharmaceutical applicants who want to use DHTs; and

    e. Apply a consistent approach to review of DHTs across CDER, CBER, and CDRH as appropriate.

8. FDA will enhance its IT capabilities to support the review of DHT-generated data:

    a. By end of Q2 FY 2023, FDA will enhance its internal systems to support review of DHT-related submissions including capturing key information about clinical trials utilizing DHTs to support tracking the number and rate of change of DHT-related submissions.

    b. In FY 2023, FDA will establish a secure cloud technology to enhance its infrastructure and analytics environment that will enable FDA to effectively

receive, aggregate, store, and process large volumes of data from trials conducted using DHTs.

c. After establishing the cloud environment, FDA will pilot a secure cloud-based mechanism to support submission and review of DHT-generated data sets.

d. FDA will work to enhance, recommend and implement standards that reduce the handling necessary to make data analyzable.

V. IMPROVING FDA PERFORMANCE MANAGEMENT

A. STUDIES WILL INCLUDE:

1. Assessment of the internal activities related to the STAR pilot program as described in Section I.D.4.

2. Assessment of the current practices of FDA and sponsors in communicating through product quality IRs during application review as described in Section I.N.1.c.

3. Evaluation of the resource capacity planning capability as described in Section II.A.2.

4. Assessment of the hiring and retention of staff for the human drug review program in CDER and CBER as described in Section III.B.

5. Assessment of challenges or barriers in FDA's adoption of cloud-based technologies as described in Section IV.A.6.b.

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

A. FDA will include in the annual PDUFA Performance Report information on the Agency's progress in meeting the specific commitments identified in this document as prescribed in statute.

B. FDA will include in the annual PDUFA Financial Report information identified in Section II in this document and as prescribed in statute.

APPENDIX. 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.[14]

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.[15]

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
   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

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

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).

9. "Serious disease or condition," "available therapy," "unmet medical need," and "may demonstrate substantial improvement on clinically significant endpoint(s)" have the meanings given in FDA's Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics (May 2014).