likely explanation is that the President has a talent for bringing out the darker side of people, and this was another example of it.

What we witnessed will drive a deeper wedge between the police and the citizens whose mistrust of them has grown. It will cast doubt on legitimate uses of force.

What troubles me the most about the President's remarks, however, is the way they patronized police officers. He has never held a wounded child in his arms or had to decide whether to punch or shoot a man with a knife. He has never had to race to the scene of a police shooting and choke on his feelings as he hunts for a suspect with precision and restraint. His remarks failed to take police work and its hazards seriously.

When I later served as a precinct commander in the Bronx, a sergeant of mine was suspended because he stood there and did nothing as he watched an officer slam a handcuffed suspect's head into the street. A narcotics detective had been shot during a scuffle with a drug crew, the responding officers were blind with rage, and one exacted revenge. When a video surfaced, the emotions didn't convey. It just looked thuggish, like the cop was a criminal, too. By his own account, it seems the President would also have been inclined to stand there and do nothing. There are thousands of American police chiefs who know what these situations require. They want to protect their officers by leading them in the right direction. We don't need the President joking with them about giving in to their baser instincts.

TRIBUTE TO MARY ALICE McKENZIE

Mr. LEAHY. Mr. President, it is a privilege for each of us to represent our constituents, and it is a great honor to be able to recognize the contributions many of them make to our communities at home. On this occasion, I would like to take this opportunity to recognize Mary Alice McKenzie, a fixture in the Burlington, VT, community. Ms. McKenzie has served as the executive director of the Boys & Girls Club of Burlington since 2007, and during her tenure at the club, she has had a lasting impact on the lives of thousands of Vermont children. The community is grateful for her service.

Ms. McKenzie comes from a business and legal background—a nontraditional path to her current position that provided her with a unique set of skills. Mary Alice began her work at the Boys & Girls Club after serving as the chief executive officer of McKenzie Meats from 1985 to 2000. She then spent several years in the Vermont State college system as general counsel and served with the law firm Paul Frank & Collins before taking over at the Boys & Girls Club of Burlington in 2007.

At the Boys & Girls Club, Mary Alice has focused her efforts on education. When she realized how few club kids were going on to higher education, she enacted the Early Promise program, which targets children at a young age who may need additional academic services and then provides college scholarships to older youth. As of today, the scholarship fund has investments totaling $2.3 million from which to draw. In a short time, the club hopes to be able to help 60 Burlington children achieve their academic goals in high school and beyond.

The Boys & Girls Club plays an important role in the lives of more than 1,000 Burlington children. Aside from the academic services, the club also works to ensure a safe and stable community for its young members. When Ms. McKenzie began hearing reports of suspected drug use occurring in a park across the street from the club, she assembled a task force of local law enforcement officials, social workers, and policymakers to work towards a solution that would ensure the safety of club kids. The Boys & Girls Club expanded activities in the park and eventually took over use of an old storage building which is now an academic center.

Ms. McKenzie has also focused her efforts on children who have experienced trauma. Under her leadership, the club has started a program to help children deal with the issues that stem from trauma at a young age. Their goal is to create stability for children whose home lives may be turbulent due to issues such as homelessness and addiction. These are profoundly difficult situations for youth to handle, and the efforts of the staff at the Boys & Girls Club are surely appreciated.

These efforts have not gone unnoticed. Not only is Ms. McKenzie beloved by members of the club who tell stories of her kindness and generosity, but in 2014, Ms. McKenzie was granted Champlain College's Distinguished Citizen Award for her years of service to the community. This award was well deserved; there are few people who dedicate themselves to service in the way that Mary Alice McKenzie has.

During her tenure at the Boys & Girls Club of Burlington, Mary Alice McKenzie has repeatedly identified significant issues within the community and worked to find creative and lasting solutions. As she concludes her years of service with the club, it is clear that her efforts have paid off. The Boys & Girls Club has more teens moving on to college than ever before, and the club continues to expand, providing an invaluable space for Burlington's youth to spend their free time. I am very grateful for Mary Alice's tireless dedication, and I look forward to seeing what the future of her career brings. Marcelle and I think of her as a dear friend.

CBO ESTIMATE OF H.R. 2430

Mr. ENZI. Mr. President, for the information of my colleagues, the Congressional Budget Office released its estimate of H.R. 2430, the FDA Reauthorization Act of 2017, in July 2017. Information related to this House-passed bill can be found at the Congressional Budget Office's website with the following link: https://www.cbo.gov/system/files/115th-congress-2017-2018/costestimate/hr2430.pdf

FOOD AND DRUG ADMINISTRATION USER FEE REAUTHORIZATION

Mr. ALEXANDER. Mr. President, I ask unanimous consent to have printed in the RECORD a copy of the commitment letters from the Secretary of Health and Human Services to the chairman of the Committee on Health, Education, Labor, and Pensions of the Senate and the chairman of the Committee on Energy and Commerce of the House of Representatives regarding reauthorization of the Biosimilar User Fee Act, Generic Drug User Fee Act, Prescription Drug User Fee Act, and Medical Device User Fee Amendments.

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

DEPARTMENT OF HEALTH & HUMAN SERVICES,
Washington, DC, January 4, 2017.

Hon. LAMAR ALEXANDER,
Chairman, Committee on Health, Education, Labor and Pensions, U.S. Senate, Washington, DC.

DEAR MR. CHAIRMAN: The Generic Drug User Fee Amendments of 2012 (GDUFA) enacted as title III of the Food and Drug Administration Safety and Innovation Act [Pub. L. 112–144], expires at the end of Fiscal Year 2017. With this letter the Administration is providing our recommendations for the reauthorization of GDUFA for the Fiscal Years 2018–2022 (GDUFA II).

Under GDUFA, the revenues generated from fees paid by the generic pharmaceutical industry have been used to expedite the process for the review of generic drugs and to support and augment regulatory science and drug development. The expenditure of these funds is in accordance with the statute and provides resources to meet the performance goals and procedures that were developed by the Food and Drug Administration [FDA] in consultation with representatives of regulated industry. FDA estimates that the fees negotiated in GDUFA II will average approximately $493.6 million per year, adjusted annually for inflation.

Throughout this process, the FDA has solicited input and worked with various stakeholders, including representatives from consumer, patient, academic research, and health provider groups, and negotiated with the regulated industry, to develop reauthorization recommendations for GDUFA that would build upon and enhance the success of the program. In addition, we have complied with the statutory requirements to solicit public comments on our recommendations, and the summary of public comments is posted on the agency web site.

Our recommendations build upon the successes of existing programs and performance goals with step-wise improvements allowing FDA the resources to establish a generic drug review program that can keep up with the ever-expanding generic drug industry. The recommendations will bring all Abbreviated New Drug Applications (ANDAs) under a common review goals scheme which calls for faster review cycles of 10 months for standard ANDAs and eight months for priority ANDAs. Priority status will be reserved for drug shortages, first generics, sole source generics and other public health priorities. The negotiated recommendations provide that FDA will communicate deficiencies to industry throughout rather than at the end of a review cycle, increasing the chances for applicants to remedy deficiencies and obtain approval in fewer cycles. This will allow for improved predictability and transparency and enable industry advanced business planning.

The agreement also establishes a robust Pre-ANDA program for complex products. The program will include meetings with applicants, guidance development and regulatory science enhancements aimed at allowing applicants with complex products to submit more complete applications and FDA to be more prepared for such submissions.

FDA will also make improvements to the facility assessment program in order to increase predictability, transparency and safety. In addition, FDA has committed to accountability and reporting enhancements. FDA will conduct activities to evaluate the financial administration and resource allocations of the GDUFA II program to help identify areas to enhance operational and fiscal efficiency and transparency. FDA will also expand GDUFA program performance reporting to enable the regulated industry, patients and consumer groups, and other stakeholders to better gauge the generic drug program's performance.

Lastly, the agreement would revamp the user fee structure. GDUFA II will be funded at a level commensurate with the volume of ANDA submissions—the primary workload driver of the program. This will allow FDA the resources necessary to meet all of its commitments. In order to maintain a predictable fee base and to more closely align fee responsibility with program costs and fee-paying ability, FDA and industry have agreed to shift the burden more toward annual program fees. To address specific small business concerns, FDA and industry have proposed three distinct small business considerations. We anticipate that the proposed GDUFA II will increase public access to affordable, generic drug products.

The following five enclosures are provided for your consideration: The proposed GDUFA II statutory language; a redline of current law; the GDUFA Reauthorization Performance Goals and Procedures—Fiscal Years 2018 through 2022; the Background for the Proposed Changes for Reauthorization of GDUFA in Fiscal Years 2018 through 2022; and the summary of public comments.

Thank you for the opportunity to present our recommendations to reauthorize this vital program. We would be pleased to brief your staff on the details and want to work closely with Congress in order to reauthorize the program in a timely manner. The Office of Management and Budget has advised that the bill and the enclosed performance goals are in accord with the Administration's program.

Sincerely,

SYLVIA BURWELL,
Secretary.

DEPARTMENT OF HEALTH &
HUMAN SERVICES,
Washington, DC, January 4, 2017.

Hon. PATTY MURRAY,
Ranking Member, Committee on Health, Education, Labor and Pensions, U.S. Senate, Washington, DC.

DEAR SENATOR MURRAY: The Generic Drug User Fee Amendments of 2012 (GDUFA) enacted as title III of the Food and Drug Administration Safety and Innovation Act [Pub. L. 112–144], expires at the end of Fiscal Year 2017. With this letter the Administration is providing our recommendations for the reauthorization of GDUFA for the Fiscal Years 2018–2022 (GDUFA II).

Under GDUFA, the revenues generated from fees paid by the generic pharmaceutical industry have been used to expedite the process for the review of generic drugs and to support and augment regulatory science and drug development. The expenditure of these funds is in accordance with the statute and provides resources to meet the performance goals and procedures that were developed by the Food and Drug Administration [FDA] in consultation with representatives of regulated industry. FDA estimates that the fees negotiated in GDUFA II will average approximately $493.6 million per year, adjusted annually for inflation.

Throughout this process, the FDA has solicited input and worked with various stakeholders, including representatives from consumer, patient, academic research, and health provider groups, and negotiated with the regulated industry, to develop reauthorization recommendations for GDUFA that would build upon and enhance the success of the program. In addition, we have complied with the statutory requirements to solicit public comments on our recommendations, and the summary of public comments is posted on the agency web site.

Our recommendations build upon the successes of existing programs and performance goals with step-wise improvements allowing FDA the resources to establish a generic drug review program that can keep up with the ever-expanding generic drug industry. The recommendations will bring all Abbreviated New Drug Applications (ANDAs) under a common review goals scheme which calls for faster review cycles of 10 months for standard ANDAs and eight months for priority ANDAs. Priority status will be reserved for drug shortages, first generics, sole source generics and other public health priorities. The negotiated recommendations provide that FDA will communicate deficiencies to industry throughout rather than at the end of a review cycle, increasing the chances for applicants to remedy deficiencies and obtain approval in fewer cycles. This will allow for improved predictability and transparency and enable industry advanced business planning.

The agreement also establishes a robust Pre-ANDA program for complex products. The program will include meetings with applicants, guidance development and regulatory science enhancements aimed at allowing applicants with complex products to submit more complete applications and FDA to be more prepared for such submissions.

FDA will also make improvements to the facility assessment program in order to increase predictability, transparency and safety. In addition, FDA has committed to accountability and reporting enhancements. FDA will conduct activities to evaluate the financial administration and resource allocations of the GDUFA II program to help identify areas to enhance operational and fiscal efficiency and transparency. FDA will also expand GDUFA program performance reporting to enable the regulated industry, patients and consumer groups, and other stakeholders to better gauge the generic drug program's performance.

Lastly, the agreement would revamp the user fee structure. GDUFA II will be funded at a level commensurate with the volume of ANDA submissions—the primary workload driver of the program. This will allow FDA the resources necessary to meet all of its commitments. In order to maintain a predictable fee base and to more closely align fee responsibility with program costs and fee-paying ability, FDA and industry have agreed to shift the burden more toward annual program fees. To address specific small business concerns, FDA and industry have proposed three distinct small business considerations. We anticipate that the proposed GDUFA II will increase public access to affordable, generic drug products.

The following five enclosures are provided for your consideration: The proposed GDUFA II statutory language; a redline of current law; the GDUFA Reauthorization Performance Goals and Procedures—Fiscal Years 2018 through 2022; the Background for the Proposed Changes for Reauthorization of GDUFA in Fiscal Years 2018 through 2022; and the summary of public comments.

Thank you for the opportunity to present our recommendations to reauthorize this vital program. We would be pleased to brief your staff on the details and want to work closely with Congress in order to reauthorize the program in a timely manner. The Office of Management and Budget has advised that the bill and the enclosed performance goals are in accord with the Administration's program.

Sincerely,

SYLVIA BURWELL,
Secretary.

DEPARTMENT OF HEALTH &
HUMAN SERVICES,
Washington, DC, January 4, 2017.

Hon. GREG WALDEN,
Chairman, Committee on Energy and Commerce, House of Representatives, Washington, DC.

DEAR MR. CHAIRMAN: The Generic Drug User Fee Amendments of 2012 (GDUFA) enacted as title III of the Food and Drug Administration Safety and Innovation Act [Pub. L. 112–144], expires at the end of Fiscal Year 2017. With this letter the Administration is providing our recommendations for the reauthorization of GDUFA for the Fiscal Years 2018–2022 (GDUFA II).

Under GDUFA, the revenues generated from fees paid by the generic pharmaceutical industry have been used to expedite the process for the review of generic drugs and to support and augment regulatory science and drug development. The expenditure of these funds is in accordance with the statute and provides resources to meet the performance goals and procedures that were developed by the Food and Drug Administration [FDA] in consultation with representatives of regulated industry. FDA estimates that the fees negotiated in GDUFA II will average approximately $493.6 million per year, adjusted annually for inflation.

Throughout this process, the FDA has solicited input and worked with various stakeholders, including representatives from consumer, patient, academic research, and health provider groups, and negotiated with the regulated industry, to develop reauthorization recommendations for GDUFA that would build upon and enhance the success of the program. In addition, we have complied with the statutory requirements to solicit public comments on our recommendations, and the summary of public comments is posted on the agency web site.

Our recommendations build upon the successes of existing programs and performance goals with step-wise improvements allowing FDA the resources to establish a generic drug review program that can keep up with the ever-expanding generic drug industry. The recommendations will bring all Abbreviated New Drug Applications (ANDAs) under a common review goals scheme which calls for faster review cycles of 10 months for standard ANDAs and eight months for priority ANDAs. Priority status will be reserved for drug shortages, first generics, sole source generics and other public health priorities. The negotiated recommendations provide that FDA will communicate deficiencies to industry throughout rather than at the end of a review cycle, increasing the chances for applicants to remedy deficiencies and obtain approval in fewer cycles. This will allow for improved predictability and transparency and enable industry advanced business planning.

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The program will include meetings with applicants, guidance development and regulatory science enhancements aimed at allowing applicants with complex products to submit more complete applications and FDA to be more prepared for such submissions.

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The following five enclosures are provided for your consideration: The proposed GDUFA II statutory language; a redline of current law; the GDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 through 2022; the Background for the Proposed Changes for Reauthorization of GDUFA in Fiscal Years 2018 through 2022; and the summary of public comments.

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Sincerely,

SYLVIA BURWELL,
Secretary.

DEPARTMENT OF HEALTH &
HUMAN SERVICES,
Washington, DC, January 4, 2017.

Hon. FRANK PALLONE,
Ranking Member, Committee on Energy and Commerce, House of Representatives, Washington, DC.

DEAR REPRESENTATIVE PALLONE: The Generic Drug User Fee Amendments of 2012 (GDUFA) enacted as title III of the Food and Drug Administration Safety and Innovation Act [Pub. L. 112–144], expires at the end of Fiscal Year 2017. With this letter the Administration is providing our recommendations for the reauthorization of GDUFA for the Fiscal Years 2018–2022 (GDUFA II).

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Throughout this process, the FDA has solicited input and worked with various stakeholders, including representatives from consumer, patient, academic research, and health provider groups, and negotiated with the regulated industry, to develop reauthorization recommendations for GDUFA that would build upon and enhance the success of the program. In addition, we have complied with the statutory requirements to solicit public comments on our recommendations, and the summary of public comments is posted on the agency web site.

Our recommendations build upon the successes of existing programs and performance goals with step-wise improvements allowing FDA the resources to establish a generic drug review program that can keep up with the ever-expanding generic drug industry. The recommendations will bring all Abbreviated New Drug Applications (ANDAs) under a common review goals scheme which calls for faster review cycles of 10 months for standard ANDAs and eight months for priority ANDAs. Priority status will be reserved for drug shortages, first generics, sole source generics and other public health priorities. The negotiated recommendations provide that FDA will communicate deficiencies to industry throughout rather than at the end of a review cycle, increasing the chances for applicants to remedy deficiencies and obtain approval in fewer cycles. This will allow for improved predictability and transparency and enable industry advanced business planning.

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Thank you for the opportunity to present our recommendations to reauthorize this vital program. We would be pleased to brief your staff on the details and want to work closely with Congress in order to reauthorize the program in a timely manner. The Office of Management and Budget has advised that the bill and the enclosed performance goals are in accord with the Administration's program.

Sincerely,

SYLVIA BURWELL,
Secretary.

Mr. ALEXANDER. Mr. President, I ask unanimous consent to have printed in the RECORD a copy of the commitment letter for the Generic Drug User Fee Act, GDUFA, reauthorization for fiscal years 2018 to 2022, known as GDUFA II.

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

GDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROGRAM ENHANCEMENTS FISCAL YEARS 2018–2022

I. Submission Review Performance Goals
A. Original ANDAs and ANDA Amendments
B. PASs and PAS Amendments
C. Unsolicited ANDA and PAS Amendments
D. DMFs
E. Controlled Correspondence
F. GDUFA I Bridging
II. Original ANDA Review Program Enhancements
A. ANDA Receipt
B. ANDA Review Transparency and Communications Enhancements
C. Review Classification Changes During the Review Cycle
D. ANDA Approval and Tentative Approval
E. Dispute Resolution
F. Other ANDA Review Program Aspirations
III. Pre-ANDA Program and Subsequent Mid-Review-Cycle Meetings for Complex Products
A. Rationale for Pre-ANDA Program, Guidance on Enhanced Pathway for Complex Products
B. Controlled Correspondence
C. Product-Specific Guidance
D. Product Development Meetings
E. Pre-Submission Meetings
F. Inactive Ingredient Database Enhancements
G. Regulatory Science Enhancements
H. Safety Determination Letters
I. Other Pre-ANDA Program Aspirations
IV. DMF Review Program Enhancements
A. Communication of DMF Review Comments
B. Teleconferences to Clarify DMF First Cycle Review Deficiencies
C. DMF First Adequate Letters
D. DMF No Further Comment Letters
E. Guidance on Post-Approval Changes to Type II API DMFs
V. Facilities
A. Guidance on Risk-Based Site Selection Model
B. Outreach to Foreign Regulators on Risk-Based Site Selection Model
C. Export Support and Education of Other Health Authorities
D. Communications to Foreign Regulators
E. Communication Regarding Inspections
F. GDUFA II Facility Compliance Status Database
VI. Enhanced Accountability and Reporting
A. Resource Management Planning and Modernized Time Reporting
B. Financial Transparency and Efficiency

C. Performance Reporting
VII. Definitions

GDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROGRAM ENHANCEMENTS FISCAL YEARS 2018–2022

This document contains the performance goals and program enhancements for the Generic Drug User Fee Act (GDUFA) reauthorization for Fiscal Years (FYs) 2018–2022, known as GDUFA II. It is commonly referred to as the ''goals letter'' or ''commitment letter''. The goals letter represents the product of the Food and Drug Administration's (FDA's) discussions with the regulated industry and public stakeholders, as mandated by Congress. The performance goals and program enhancements specified in this letter apply to aspects of the generic drug review program that are important for facilitating timely access to quality, affordable generic medicines. FDA is committed to meeting the performance goals specified in this letter and to continuous improvement of its performance.

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

GDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2018–2022

The performance goals and procedures of the FDA, as agreed to under the first reauthorization of the generic drug user fee program, are summarized below.

I. SUBMISSION REVIEW PERFORMANCE GOALS

A. Original ANDAs and ANDA Amendments

1. Review and act on 90 percent of standard original Abbreviated New Drug Applications (ANDAs) within 10 months of the date of ANDA submission.

2. Review and act on 90 percent of priority original ANDAs within the applicable review goal.

a. Review and act on priority original ANDAs within 8 months of the date of ANDA submission, if the applicant submits a Pre-Submission Facility Correspondence 2 months prior to the date of ANDA submission and the Pre-Submission Facility Correspondence is found to be complete and accurate and remains unChanged.

b. Review and act on priority original ANDAs within 10 months of the date of ANDA submission if the applicant does not submit a Pre-Submission Facility Correspondence 2 months prior to the date of ANDA submission or facility information changes or is found to be incomplete or inaccurate.

3. Review and act on 90 percent of standard major ANDA amendments within the applicable review goal.

a. Review and act on standard major ANDA amendments within 8 months of the date of amendment submission if preapproval inspection is not required.

b. Review and act on standard major ANDA amendments within 10 months of the date of amendment submission if preapproval inspection is required.

4. Review and act on 90 percent of priority major ANDA amendment submissions within the applicable review goal.

a. Review and act on priority major ANDA amendments within 6 months of the date of amendment submission if preapproval inspection is not required.

b. Review and act on priority major ANDA amendments within 8 months of amendment submission if (i) preapproval inspection is required and (ii) applicant submits a Pre-Submission Facility Correspondence 2 months prior to the date of amendment submission and the Pre-Submission Facility Correspondence is found to be complete and accurate and remains unchanged.

c. Review and act on priority major ANDA amendments within 10 months of amendment submission if (i) preapproval inspection is required and (ii) the applicant does not submit a Pre-Submission Facility Correspondence 2 months prior to amendment submission, or facility information Changes or is found to be incomplete or inaccurate.

5. Review and act on 90 percent of standard and priority minor ANDA amendments within 3 months of the date of amendment submission.

TABLE FOR SECTION I(A)(1) AND (2): ORIGINAL ANDAS

Submission Type	Goal
Standard Original ANDAs	90% within 10 months of submission date.
Priority Original ANDAs	90% within 8 months of submission date if applicant meets requirements under I(A)(2)(a). 90% within 10 months of submission date if applicant does not meet requirements as described under I(A)(2)(b).

TABLE FOR SECTION I(A)(3)–(5): ANDA AMENDMENTS

Submission Type	Goal
Standard Major ANDA Amendments.	90% within 8 months of submission date if preapproval inspection not required. 90% within 10 months of submission date if preapproval inspection required.
Priority Major ANDA Amendments.	90% within 6 months of submission date if preapproval inspection not required. 90% within 8 months of submission date if preapproval inspection required and applicant meets requirements under I(A)(4)(b). 90% within 10 months of submission date if preapproval inspection required and applicant does not meet requirements as described under I(A)(4)(c).
Standard and Priority Minor ANDA Amendments.	90% within 3 months of submission date.

B. PASs and PAS Amendments

1. Review and act on 90 percent of standard Prior Approval Supplements (PASs) within the applicable review goal.

a. Review and act on standard PASs within 6 months of the date of PAS submission if preapproval inspection is not required.

b. Review and act on standard PASs within 10 months of the date of PAS submission if preapproval inspection is required.

2. Review and act on 90 percent of priority PASs within the applicable review goal.

a. Review and act on priority PASs within 4 months of the date of PAS submission if preapproval inspection is not required.

b. Review and act on priority PASs within 8 months of the date of PAS submission if (i) preapproval inspection is required and (ii) the applicant submits a Pre-Submission Facility Correspondence 2 months prior to the date of PAS submission and the Pre-Submission Facility Correspondence is found to be complete and accurate and remains unchanged.

c. Review and act on priority PASs within 10 months of PAS submission if (i) preapproval inspection is required and (ii) the applicant does not submit a Pre-Submission Facility Correspondence 2 months prior to the date of PAS submission, or facility information changes or is found to be incomplete or inaccurate.

3. Review and act on 90 percent of major amendments to standard PASs within the applicable review goal.

a. Review and act on major amendments to standard PASs within 6 months of the date of amendment submission if preapproval inspection is not required.

b. Review and act on major amendments to standard PASs within 10 months of the date of amendment submission if preapproval inspection is required.

4. Review and act on 90 percent of major amendments to priority PASs within the applicable review goal.

a. Review and act on major amendments to priority PASs within 4 months of the date of amendment submission if preapproval inspection is not required.

b. Review and act on major amendments to priority PASs within 8 months of the date of amendment submission if (i) preapproval inspection is required and (ii) the applicant submits a Pre-Submission Facility Correspondence 2 months prior to the date of amendment submission and the Pre-Submission Facility Correspondence is found to be complete and accurate and remains unchanged.

c. Review and act on major amendments to priority PASs within 10 months of amendment submission if (i) preapproval inspection is required and (ii) the applicant does not submit a Pre-Submission Facility Correspondence 2 months prior to the date of amendment submission, or facility information changes or is found to be incomplete or inaccurate.

5. Review and act on 90 percent of minor amendments to standard and priority PASs within 3 months of the date of amendment submission.

TABLE FOR SECTION I(B)(1) AND (2): PASs

Submission Type	Goal
Standard PASs	90% within 6 months of submission date if preapproval inspection not required. 90% within 10 months of submission date if preapproval inspection required.
Priority PASs	90% within 4 months of submission date if preapproval inspection not required. 90% within 8 months of submission date if preapproval inspection required and applicant meets requirements under I(B)(2)(b). 90% within 10 months of submission date if preapproval inspection required and applicant does not meet requirements as described under I(B)(2)(c).

TABLE FOR SECTION I(B)(3)–(5): PAS AMENDMENTS

Submission Type	Goal
Standard PAS Major Amendments.	90% within 6 months of submission date if preapproval inspection not required. 90% within 10 months of submission date if preapproval inspection required.
Priority PAS Amendments	90% within 4 months of submission date if preapproval inspection not required. 90% within 8 months of submission date if preapproval inspection required and applicant meets requirements under I(B)(4)(b). 90% within 10 months of submission date if preapproval inspection required and applicant does not meet requirements as described under I(B)(4)(c).
Standard and Priority Minor PAS Amendments.	90% within 3 months of submission date.

C. Unsolicited ANDA Amendments and PAS Amendments

1. Review and act on unsolicited ANDA amendments and PAS amendments submitted during the review cycle by the later of the goal date for the original submission/solicited amendment or the goal date assigned in accordance with Sections (I)(A)(3), (4) and (5) and (I)(B)(3), (4) and (5), respectively, for the unsolicited amendment.

2. Review and act on unsolicited ANDA amendments and PAS amendments submitted between review cycles by the later of the goal date for the subsequent solicited amendment or the goal date assigned in accordance with Sections (I)(A)(3), (4) and (5) and (I)(B)(3), (4) and (5), respectively, for the unsolicited amendment.

D. DMFs

1. Complete the initial completeness assessment review for 90 percent of Type II Active Pharmaceutical Ingredient (API) Drug Master Files (DMFs) within 60 days of the later of the date of DMF submission or DMF fee payment.

TABLE FOR SECTION I(D): DMFs

Submission Type	Goal
Type II API DMF	90% of initial completeness assessments within 60 days of the later of the date of DMF submission or DMF fee payment.

E. Controlled Correspondence

1. Review and respond to 90 percent of controlled correspondences within the applicable review goal.

a. Review and respond to Standard controlled correspondence within 60 days of the date of submission.

b. Review and respond to Complex controlled correspondence within 120 days of the date of submission.

2. In the case of controlled correspondence that raises an issue that relates to one or more pending citizen petitions, the 60- or 120-day time period starts on the date FDA responds to the petition (if there is only one petition) or last pending petition.

3. FDA will review and respond to 90% of submitter requests to clarify ambiguities in the controlled correspondence response within 14 days of receipt of the request. The response to the submitter's request will provide clarification or advice concerning the ambiguity in the controlled correspondence response.

TABLE FOR SECTION I(E): CONTROLLED CORRESPONDENCE

Submission Type	Goal
Standard Controlled Correspondence.	90% within 60 days of submission date.
Complex Controlled Correspondence.	90% within 120 days of submission date.
FDA will review and respond to 90% of submitter requests to clarify ambiguities in the controlled correspondence request within 14 days of request receipt	

F. GDUFA I Bridging

1. Continue to review and act on ANDAs and ANDA amendments, PASs and PAS amendments and controlled correspondence submitted prior to October 1, 2017 that have been assigned GDUFA I goal dates pursuant to the GDUFA I review metrics applicable to those submissions.

2. Review and act on 90% of ANDAs and ANDA amendments with Target Action Dates (TADs) by the goal date. The TAD for an ANDA or ANDA amendment becomes its GDUFA II goal date. (Attachment A shows how FDA, until September 30, 2017, assigned TADs to ANDA amendments not subject to GDUFA I review goals.)

3. Review and act on 90% of ANDAs and ANDA amendments pending FDA as of October 1, 2017 that were not subject to GDUFA I goal dates and either (a) were not previously assigned TADs or (b) were previously assigned TADs that came due prior to October 1, 2017 but remain pending in the same review cycle as of October 1, 2017, by GDUFA II ANDA and ANDA amendment goal dates that FDA will assign on October 1, 2017. No such goal date shall be later than July 31, 2018.

4. Review and act on amendments received on or after October 1, 2017, to any ANDAs submitted prior to October 1, 2017, pursuant to the amendment review goals set forth in (A)(3)–(5) of this section.

II. ORIGINAL ANDA REVIEW PROGRAM ENHANCEMENTS

A. ANDA Receipt

1. FDA will strive to determine whether to receive ANDAs within 60 days of the date of ANDA submission.

2. To enable FDA to rapidly determine whether to receive an ANDA pursuant to 21 Code of Federal Regulations (CFR) 314.101, and with consideration of final agency guidances that address ANDA receipt determinations, FDA will issue a Manual of Policies and Procedures (MAPP) by October 1, 2017 setting forth procedures for filing reviewers on communication of minor technical deficiencies (e.g., document legibility); and on deficiencies potentially resolved with information in the ANDA at original submission, in order to provide applicants with an opportunity for resolution within 7 calendar days. If such a deficiency is resolved within 7 calendar days, that deficiency will not be a basis for a refuse-to-receive decision.

3. At the time of receipt, FDA will notify the applicant in the acceptance letter whether the ANDA or PAS is subject to priority or standard review

B. ANDA Review Transparency and Communications Enhancements

To promote transparency and communication between FDA and ANDA applicants, FDA will apply the review program enhancements below to the review of all ANDAs. The goal of these program enhancements is to improve predictability and transparency, promote the efficiency and effectiveness of the review process, minimize the number of review cycles necessary for approval, increase the overall rate of approval, and facilitate greater access to generic drug products.

1. FDA will issue the appropriate Information Request(s) (IR(s)) and/or Discipline Review Letter(s) (DRL(s)) from each review discipline as soon as the discipline has completed its review, with the first IR(s) and/or DRL(s) at about the mid-point of the review.

2. Following the IR and/or DRL at about the mid-point of the review, IRs and/or DRLs will, as appropriate, continue from each review discipline on a rolling basis.

3. Neither IRs nor DRLs stop the review clock or add to a GDUFA goal.

4. If an applicant is unable to completely respond within the time frame requested by FDA, including any extensions that may be granted by FDA, then FDA will generally issue a Complete Response Letter (CRL).

5. FDA will continue to issue IRs and/or DRLs late in the review cycle, until it is no longer feasible, within the current review cycle, for applicant to develop and FDA to review a complete response to the IR and/or DRL.

6. FDA should continue to work through the goal date if in FDA's judgment continued work would likely result in an imminent tentative approval that could prevent forfeiture of 180-day exclusivity or in an imminent approval.

7. FDA will strive to act prior to a goal date when the review is done and there are no outstanding issues.

8. If in the ordinary course a Regulatory Project Manager (RPM) learns that a major deficiency is likely forthcoming, the RPM will notify the Authorized Representative that a major deficiency is likely forthcoming. If the Authorized Representative raises concerns or seeks additional information regarding the forthcoming major deficiency, the RPM will encourage the Authorized Representative to review the forthcoming deficiency upon receiving it.

9. If in the ordinary course an RPM learns that FDA is likely to miss the goal date for the submission, the RPM will notify the Authorized Representative of the outstanding discipline(s), the general nature of the delay (when possible), and the estimated timeframe for receiving the response.

10. The Authorized Representative may periodically request a Review Status Update. In response to the Authorized Representative's request, the RPM will timely provide a Review Status Update.

11. FDA will include in the CRL its basis for classifying a responding amendment Major.

12. Applicants may opt for a post-CRL teleconference to seek clarification concerning deficiencies identified in a CRL. FDA will grant appropriate requests for teleconferences requested by applicants upon receiving first cycle major complete response letters. FDA will also grant appropriate requests for teleconferences requested by applicants upon receiving subsequent major complete response letters or minor complete response letters. FDA will provide a scheduled date for 90 percent of post-CRL teleconferences within 10 days of the request for a teleconference, and conduct 90 percent of such post-CRL teleconferences held on the FDA-proposed date, within 30 days of receipt of the written request.

C. Review Classification Changes During the Review Cycle

1. If during a review cycle of an ANDA or PAS, the review classification of the ANDA or PAS changes from Standard to Priority, FDA will notify the applicant within 14 days of the date of the change.

2. If a previous ANDA or ANDA amendment was subject to priority review, but a subsequent ANDA amendment is subject to standard review, FDA will notify applicant within 14 days of the date of receipt of the solicited amendment.

3. A request for a change may occur at any time during the review.

4. Once an ANDA or PAS submission is classified as being subject to priority review, the application will retain such priority review classification status until FDA takes an action on the submission.

5. FDA will include an explanation of the reasons for any denial of a review status reclassification request.

6. If an applicant requests a teleconference as part of its request to reclassify a major amendment or standard review status, FDA will schedule and conduct the teleconference and decide 90% of such reclassification requests within 30 days of the date of FDA's receipt of the request for a teleconference. This goal only applies when applicant accepts the first scheduled teleconference date offered by FDA.

D. ANDA Approval and Tentative Approval

If applicants submit and maintain ANDAs consistent with the statutory requirements for approval under 505(j); respond to IRs and DRLs completely and within the time frames requested by FDA and timely submit all required information under 21 CFR parts 314 and 210, including information concerning notice (21 CFR 314.95), litigation status (21 CFR 314.107), and commercial marketing (21 CFR 314.107); then FDA will strive to approve approvable ANDAs in the first review cycle; to approve potential first generics on the earliest lawful ANDA approval date, if known to FDA; and to tentatively approve first to file Paragraph IV ANDAs so as to avoid forfeiture of 180-day exclusivity.

E. Dispute Resolution

1. An applicant may pursue a request for reconsideration within the review discipline at the Division level or original signatory authority, as needed.

2. The Office of Generic Drugs (OGD) Office of Regulatory Operations Associate Director will track each request for Division level reconsideration through resolution.

3. Following resolution of a request for reconsideration, an applicant may pursue formal dispute resolution above the Division level, pursuant to procedures set forth in the September 2015 Guidance, Formal Dispute Resolution: Appeals Above the Division Level.

4. FDA will respond to appeals above the Division level within 30 calendar days of the Center for Drug Evaluation and Research's (CDER's) receipt of the written appeal pursuant to the applicable goal.

a. In FY 2018, the goal is 70 percent.

b. In FY 2019, the goal is 80 percent.

c. In FY 2020, 2021, and 2022 the goal is 90 percent.

5. CDER's Formal Dispute Resolution Project Manager (or designee) will track each formal appeal above the Division level through resolution

F. Other ANDA Review Program Aspirations

1. FDA aspires to continually improve the efficiency of the ANDA review program.

2. The absence of a GDUFA II commitment for a specific program function does not imply that the program function is not important. For example, other program functions include determinations whether listed drugs were voluntarily withdrawn from sale for reasons of safety or effectiveness and ANDA proprietary name reviews.

III. PRE-ANDA PROGRAM AND SUBSEQUENT MID-REVIEW-CYCLE MEETINGS FOR COMPLEX PRODUCTS

A. Rationale for Pre-ANDA Program, Guidance on Enhanced Pathway for Complex Products

The goal of the pre-ANDA program is to clarify regulatory expectations for prospective applicants early in product development, assist applicants to develop more complete submissions, promote a more efficient and effective ANDA review process, and reduce the number of review cycles required to obtain ANDA approval, particularly for Complex Products.

1. FDA will issue guidance describing an enhanced pathway for Complex Products, including policies and procedures for Product Development Meetings, pre-submission meetings, and mid-review cycle meetings. An ANDA applicant who was granted a Product Development Meeting has the option of a pre-submission meeting with FDA and also the option of a mid-review-cycle meeting with FDA, subject to policies and procedures to be set forth in the guidance.

B. Controlled Correspondence

1. FDA will review and respond to standard controlled correspondence and to complex controlled correspondence with meaningful responses that can more consistently inform drug development and/or regulatory decision making pursuant to the applicable metric goals.

C. Product-Specific Guidance

1. FDA will issue product-specific guidance identifying the methodology for developing drugs and generating evidence needed to support ANDA approval, for 90 percent of new chemical entity New Drug Applications that are approved on or after October 1, 2017, at least 2 years prior to the earliest lawful ANDA filing date.

2. This goal shall not apply to Complex Products. FDA will strive to issue guidance for a Complex Product as soon as scientific recommendations are available.

3. FDA will continue to develop and issue product-specific guidance based on requests from industry and public health priorities as set forth in the CDER Prioritization MAPP.

4. Industry may request that FDA develop product-specific guidance via email to genericdrugs@fda.hhs.gov.

D. Product Development Meetings

1. FDA will grant a prospective applicant a Product Development Meeting if, in FDA's judgment:

a. The requested Product Development Meeting concerns:

i. Development of a Complex Product for which FDA has not issued product-specific guidance or

ii. An alternative equivalence evaluation (i.e., change in study type, such as in vitro to clinical) for a Complex Product for which FDA has issued product-specific guidance,

b. The prospective applicant submits a complete meeting package, including a data package and specific proposals,

c. A controlled correspondence response would not adequately address the prospective applicant's questions, and

d. A Product Development Meeting would significantly improve ANDA review efficiency.

2. Dependent on available resources, FDA may grant a prospective applicant a Product Development Meeting concerning Complex Product development issues other than those described in Section III(D)(1)(a) above if, in FDA's judgment:

a. The prospective applicant submits a complete meeting package, including a data package and specific proposals,

b. A controlled correspondence response would not adequately address the prospective applicant's questions, and

c. A Product Development Meeting would significantly improve ANDA review efficiency.

3. FDA will grant or deny 90% of Product Development Meeting requests within the applicable goal.

a. In FYs 2018 and 2019, the goal is 30 days from receipt of the request.

b. In FYs 2020, 2021 and 2022, the goal is 14 days from receipt of the request.

4. FDA will conduct Product Development Meetings granted pursuant to the applicable goal.

a. In FY 2018, FDA will conduct 60 percent of such meetings within 120 days of granting them.

b. In FY2019, FDA will conduct 70 percent of such meetings within 120 days of granting them.

c. In FY2020, FDA will conduct 80 percent of such meetings within 120 days of granting them.

d. In FYs 2021 and 2022, FDA will conduct 90 percent of such meetings within 120 days of granting them.

5. FDA can meet the Product Development Meeting Goal by either conducting a meeting or providing a meaningful written response that will inform drug development and/or regulatory decision making to the prospective applicant, within the applicable goal date.

6. Unless FDA is providing a written response to satisfy the Product Development Meeting goal, FDA will provide preliminary written comments before each Product Development Meeting (and aspire to provide the written comments 5 calendar days before the meeting), and will provide meeting minutes within 30 calendar days following the meeting.

E. Pre-Submission Meetings

1. Prospective applicants may request and FDA will conduct pre-submission meetings, subject to Section III(A)(1). An applicant's decision not to request a pre-submission meeting will not prejudice the receipt or review of an ANDA.

2. FDA will grant or deny 90% of pre-submission meeting requests within the applicable goal.

a. In FYs 2018 and 2019, the goal is 30 days.

b. In FYs 2020, 2021, and 2022, the goal is 14 days.

3. If an applicant did not have a Product Development Meeting, FDA may grant a pre-submission meeting if in FDA's judgment the pre-submission meeting would improve review efficiency.

4. FDA will conduct pre-submission meetings granted pursuant to the applicable goal.

a. In FY 2018, FDA will conduct 60 percent of such meetings within 120 days of granting them.

b. In FY 2019, FDA will conduct 70 percent of such meetings within 120 days of granting them.

c. In FY 2020, FDA will conduct 80 percent of such meetings within 120 days of granting them.

d. In FYs 2021 and 2022, FDA will conduct 90 percent of such meetings within 120 days of granting them.

5. If appropriate to the purpose of the meeting, FDA will provide preliminary written comments 5 calendar days before each meeting, and meeting minutes within 30 calendar days of the meeting.

F. Mid-Review-Cycle Meetings for Complex Products

As set forth in guidance issued pursuant to Section III(A)(1), the Project Manager and other appropriate members of the FDA review team will call the applicant 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-review-cycle meeting. The Project Manager will coordinate the specific date and time of the telephone call with the applicant.

G. Inactive Ingredient Database Enhancements

1. By October 1, 2020, FDA will complete enhancements to the Inactive Ingredient Database so users can perform electronic queries to obtain accurate Maximum Daily Intake and Maximum Daily Exposure information for each route of administration for which data is available.

2. FDA will update the Inactive Ingredient Database on an ongoing basis, and post quarterly notice of updates made. Such notices will include each change made and, for each change, the information replaced.

H. Regulatory Science Enhancements

FDA will conduct internal and external research to support fulfilment of submission review and pre-ANDA commitments set forth in Sections I and III, respectively.

1. Annually, FDA will conduct a public workshop to solicit input from industry and stakeholders for inclusion in an annual list of GDUFA II Regulatory Science initiatives. Interested parties may propose regulatory science initiatives via email to genericdrugs@fda.hhs.gov. After considering Industry and stakeholder input, FDA will post the list on FDA's website.

2. If Industry forms a GDUFA II regulatory science working group, then upon request of the working group to the Director of the Office of Research and Standards in the Office of Generic Drugs, FDA will meet with the working group twice yearly to discuss current and emerging challenges and concerns. FDA will post minutes of these meetings on its website.

3. Annually, FDA will report on its website the extent to which GDUFA regulatory science-funded projects support the development of generic drug products, the generation of evidence needed to support efficient review and timely approval of ANDAs, and the evaluation of generic drug equivalence.

I. Safety Determination Letters

1. FDA will issue 90% of safety determination letters within 60 days of the date of submission of disclosure authorization.

J. Other Pre-ANDA Program Aspirations

1. FDA aspires to continually improve the effectiveness of its pre-ANDA activity.

2. The absence of a GDUFA II commitment for a specific program function does not imply that the program function is not important. For example, notwithstanding the absence of a GDUFA II commitment, FDA aspires to respond to Suitability Petitions in a more timely and predictable manner.

IV. DMF REVIEW PROGRAM ENHANCEMENTS

A. Communication of DMF Review Comments

1. FDA will ensure that DMF review comments submitted to the DMF holder are issued at least in parallel with the issuance of review comments relating to the DMF for

the ANDA. This commitment applies to comments to the applicant issued in any ANDA CRL and comments issued in the first IR letter by the drug product review discipline.

B. Teleconferences to Clarify DMF First Cycle Review Deficiencies

1. FDA will grant and conduct teleconferences when requested to clarify deficiencies in first cycle DMF deficiency letters.

2. DMF holders must request such teleconferences in writing within 20 business days of issuance of the first cycle DMF deficiency letter, identifying specific issues to be addressed. FDA may initially provide a written response to the request for clarification, but if the DMF holder indicates that a teleconference is still desired, FDA will schedule the teleconference.

3. FDA will strive to grant such teleconferences within 30 days, giving priority to DMFs based on the priority of the referencing ANDA.

4. In lieu of a teleconference, the DMF holder may submit a request for an email exchange between FDA and the DMF holder. The request must identify specific issues to be addressed. After FDA responds to the request, the DMF holder may submit, and FDA will respond to, one follow up email to obtain additional clarification.

C. DMF First Adequate Letters

1. Once a DMF has undergone a full scientific review and has no open issues related to the review of the referencing ANDA, FDA will issue a First Adequate Letter.

D. DMF No Further Comment Letters

1. Once a DMF has undergone a complete review and the ANDA referencing the DMF has been approved or tentatively approved, FDA will issue a no further comment letter.

E. Guidance on Post-Approval Changes to Type II API DMFs.

1. By October 1, 2018, FDA will issue a guidance regarding post-approval changes to a Type II API DMF and submission mechanisms for ANDA applicants who reference the Type II API DMF.

V. FACILITIES

A. Guidance on Risk-Based Site Selection Model—Issue a guidance explaining the Agency's risk-based site surveillance model for human pharmaceutical manufacturing establishments, including a discussion of the risk factors incorporated in the model and how the model is used to help determine which establishments are scheduled to receive a surveillance inspection each year.

B. Outreach to Foreign Regulators on Risk-Based Site Selection Model—Undertake outreach activities to better inform other pharmaceutical regulators of FDA's risk-based surveillance model.

C. Export Support and Education of Other Health Authorities—Support the export of safe and effective pharmaceutical products by the U.S.-based pharmaceutical industry, including but not limited to timely updates to FDA's Facility Compliance Status Database as described below, and educating other health authorities regarding FDA's surveillance inspection program and the meaning of inspection classifications.

D. Communications to Foreign Regulators—Upon receipt of a written or email request by an establishment physically located in the U.S. that has been included as part of a marketing application submitted to a foreign regulator, issue within 30 days of the date of receipt of the request a written communication to that foreign regulator conveying the current compliance status for the establishment.

E. Communication Regarding Inspections

1. By May 31, 2018, when FDA conducts an application-related inspection of a facility or site named in the ANDA, PAS, or associated Type II DMF and identifies outstanding issues that could prevent approval of an ANDA or PAS, the applicant will be notified that issues exist through an IR, DRL or CRL pursuant to Section II(B)) above.

2. By October 1, 2018, FDA agrees to communicate to the facility owner final inspection classifications that do not negatively impact approvability of any pending application within 90 days of the end of the inspection. FDA agrees to ongoing periodic engagement with industry stakeholders to provide updates on agency activities and seek stakeholder feedback.

F. GDUFA II Facility Compliance Status Database—By January 1, 2019, FDA will update its existing, publicly available database that describes the compliance status of GDUFA self-ID facilities and sites. Compliance status is based on the most recent inspection or related FDA action for facilities involved in any manufacturing activities subject to Current Good Manufacturing Practices (CGMP) inspection and for sites involved in the conduct or analysis of bioanalytical or clinical bioequivalence/bioavailability studies conducted to support an ANDA. The database will be updated every 30 days and will reflect FDA's final assessment of the facility or site following an FDA inspection and review of the inspected entity's timely response to any documented observations. The public website containing the database will also include an explanation of terms used to describe the compliance status of facilities and sites.

VI. ENHANCED ACCOUNTABILITY AND REPORTING

FDA will build internal capacity to enable improved productivity and performance through regular assessment of progress towards GDUFA goals, consistent methodologies for and timely reporting of GDUFA metrics, and transparent and efficient administration; allocation and reporting of user fee resources.

A. Resource Management Planning and Modernized Time Reporting

FDA is committed to enhancing management of the GDUFA program in GDUFA II.

1. FDA will conduct activities to develop a resource management planning function and modernized time reporting approach in GDUFA II. FDA will staff a planning team responsible for these activities and for publishing a GDUFA program resource management planning and modernized time reporting implementation plan no later than fourth quarter FY 2018.

2. FDA will obtain through a contract with an independent third party an evaluation of options and recommendations for a new methodology to accurately assess changes in the resource needs of the human generic drug review program and how to monitor and report on those needs moving forward. The report will be published no later than the end of FY 2020 for public comment. Upon review of the report and comments, FDA will implement robust methodologies for assessing resource needs of the program and tracking resource utilization across the program elements.

B. Financial Transparency and Efficiency

FDA is committed to ensuring GDUFA user fee resources are administered, allocated, and reported in an efficient and transparent manner. FDA will conduct activities to evaluate the financial administration of the GDUFA program to help identify areas to enhance operational and fiscal efficiency. FDA will also conduct activities to enhance transparency of how GDUFA program resources are used.

1. FDA will contract with an independent third party to evaluate and report on how the GDUFA program is resourced and how those resources are utilized, and recommend improvements to the process.

2. FDA will use the results of that evaluation to create an ongoing financial reporting mechanism to enhance the transparency of GDUFA program resource utilization.

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

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

C. Performance Reporting

1. FDA will publish the following monthly metrics on its website, using a consistent, publicly disclosed reporting methodology:

a. Number of ANDAs and ANDA amendments, DMFs, Changes Being Effected (CBEs) and PASs submitted in the reporting month delineated by type of submission,

b. Number each of ANDAs and PASs FDA refused for receipt in the reporting month,

c. Number of actions taken in the reporting month delineated by the type of action.

For purposes of the metrics, actions shall include final approvals, tentative approvals, complete response letters, information requests, and discipline review letters (or other such nomenclature as FDA determines to reflect the concepts of an information request or complete response letter), and

d. Number of first cycle approvals and tentative approvals in the reporting month.

2. FDA will publish the following quarterly metrics on its website, using a consistent, publicly disclosed reporting methodology:

a. Number of ANDAs and PASs withdrawn in each reporting month,

b. Number of ANDAs awaiting applicant action, and

c. Number of ANDAs awaiting FDA action.

d. Mean and median approval and tentative approval times for the quarterly action cohort.

3. FDA will publish the following metrics annually as part of the GDUFA Performance Report:

a. Mean and median approval and tentative approval times by FY receipt cohort,

b. Mean and median ANDA approval times, including separate reporting of mean and median times for first cycle approvals,

c. Mean and median number of ANDA review cycles to approval and tentative approval by FY receipt cohort,

d. Number of GDUFA related teleconferences requested, granted, denied and conducted, broken down by type of teleconference,

e. Number of applications received, refused to receive, and average time to receipt decision,

f. Number of product development, pre-submission and mid-review cycle meetings requested, granted, denied and conducted, by face to face or in writing,

g. Number of inspections conducted by domestic or foreign establishment location and inspection type (Pre-Approval Inspection (PAI), Good Manufacturing Practices (GMP), Bioequivalence (BE) clinical and BE analytical) and facility type (Finished Dosage Form (FDF), API, etc.),

h. Median time from beginning of inspection to 483 issuance,

i. Median time from 483 issuance to Warning Letter, Import Alert and Regulatory Meeting for inspections with final classification of Official Action Indicated (OAI) (or equivalent),

j. Median time from date of Warning Letter, Import Alert and Regulatory Meeting to resolution of the OAI status (or equivalent),

k. Number of ANDAs accepted for standard review and priority review,

l. Number of suitability petitions pending a substantive response for more than 270 days from the date of receipt,

m. Number of petitions to determine whether a listed drug has been voluntarily withdrawn from sale for reasons of safety or effectiveness pending a substantive response for more than 270 days from the date of receipt,

n. Percentage of ANDA proprietary name requests reviewed within 180 days of receipt,

o. Number of DMF First Adequate Letters issued, and

p. Number of email exchanges requested and conducted in lieu of teleconferences to clarify deficiencies in first cycle DMF deficiency letters.

VII. DEFINITIONS

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

B. Ambiguity in the controlled correspondence response—means the controlled correspondence response or a critical portion of it, in FDA's judgment, merits further clarification.

C. Appropriate, with respect to a request for a post-CRL teleconference—means a complete and clear request for a teleconference where the applicant's goal is to gain an understanding of specific deficiencies and expectations for resolution.

D. Authorized Representative—means the authorized point of contact identified in applicant's letter of authorization or Form 356h. An Authorized Representative may designate an alternate to serve in the Authorized Representative's absence.

E. Change, with respect to facility information—means a change to information in the Pre-Submission Facilities Correspondence that causes FDA to re-evaluate its facility assessment (i.e., assess the impact of the change on its previous recommendation), such as a change in facility (as described by address, FDA Establishment Identification (FEI) number, or Data Universal Numbering System (DUNS) number), change in operation(s) performed by a facility, addition of a new facility, withdrawal of a facility used to generate data to meet application requirements or intended for commercial production, or a change in inspection readiness (i.e., a facility is no longer ready for inspection).

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

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

H. Complex controlled correspondence—means:

1. Controlled correspondence involving evaluation of clinical content,

2. Bioequivalence protocols for Reference Listed Drugs with Risk Evaluation and Mitigation Strategies (REMS) Elements To Assure Safe Use (ETASU), or

3. Requested evaluations of alternative bioequivalence approaches within the same study type (e.g., pharmacokinetic, in vitro, clinical).

I. Complex Product—generally includes:

1. Products with complex active ingredients (e.g., peptides, polymeric compounds, complex mixtures of APIs, naturally sourced ingredients); complex formulations (e.g., liposomes, colloids); complex routes of delivery (e.g., locally acting drugs such as dermatological products and complex ophthalmological products and otic dosage forms that are formulated as suspensions, emulsions or gels) or complex dosage forms (e.g., transdermals, metered dose inhalers, extended release injectables)

2. Complex drug-device combination products (e.g., auto injectors, metered dose inhalers); and

3. Other products where complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement.

J. Days—unless otherwise specified, means calendar days.

K. Discipline review letter (DRL)—means a letter used to convey preliminary thoughts on possible deficiencies found by a discipline reviewer and/or review team for its portion of the pending application at the conclusion of the discipline review.

L. Earliest lawful ANDA approval date—the first date on which no patent or exclusivity prevents full approval of an ANDA

M. First adequate letter—a communication from FDA to DMF holder indicating that the DMF has no open issues related to the review of the referencing ANDA. Issued only at the conclusion of the first DMF review cycle that determines the DMF does not have any open issues.

N. First generic—any received ANDA (1) that is a first-to-file ANDA eligible for 180-day exclusivity or for which there are no blocking patents or exclusivities and (2) for which there is no previously approved ANDA for the drug product.

O. Information Request (IR)—means a letter that is sent to an applicant during a review to request further information or clarification that is needed or would be helpful to allow completion of the discipline review.

P. Major amendment—means a major amendment as described in CDER's December 2001 Guidance for Industry: Major, Minor and Telephone Amendments to Abbreviated New Drug Applications.

Q. Mid-review-cycle meeting—after the last key discipline has issued its IR and/or DRL, for ANDAs that were the subject of prior Product Development Meetings or pre-submission meetings, CDER will schedule a teleconference meeting with the applicant to discuss current concerns with the application and next steps.

R. Minor amendment—means a minor amendment as described in CDER's December 2001 Guidance for Industry: Major, Minor and Telephone Amendments to Abbreviated New Drug Applications.

S. Complete and accurate Pre-Submission Facility Correspondence—lists all of the following:

1. All facilities involved in manufacturing processes and testing for the ANDA and corresponding Type II API DMF as required by 21 CFR 314.50(d)(1)(i) and (iii). For each manufacturing or testing facility, the correspondence includes facility name, operation(s) performed, facility contact name, address, FEI number (if a required registrant or one has been assigned), DUNS number, registration information (for required registrants), a confirmation that the facility is ready for inspection, a description of the manufacturing process, and a certification by the applicant that any Type II DMF has similarly complete and accurate facility information as required by 21 CFR 314.50(d)(1)(i), including complete facility information (i.e., facility name, operation, facility contact name, address, FEI number and DUNS number). Facility information that is included in a corresponding Type II DMF is not required to be duplicated in the Pre-Submission Facility Correspondence for the ANDA.

2. All sites or organizations involved in bioequivalence and clinical studies used to support the ANDA submission as described in 21 CFR 314.94(a)(7). This information is provided using a standardized electronic format and includes unique identifiers that are current and accurate, including site or organization name, address and website; and study information including a listing of study names, dates of conduct and main investigators.

T. Pre-submission meeting—means a meeting in which an applicant has an opportunity to discuss and explain the format and content of an ANDA to be submitted. Although the proposed content of the ANDA will be discussed, pre-submission meetings will not include substantive review of summary data or full study reports.

U. Priority—means submissions affirmatively identified as eligible for expedited review pursuant to CDER's Manual of Policy and Procedures (MAPP) 5240.3, Prioritization of the Review of Original ANDAs, Amendments and Supplements, as revised (the CDER Prioritization MAPP).

V. Product Development Meeting—means a meeting involving a scientific exchange to discuss specific issues (e.g., a proposed study design, alternative approach or additional study expectations) or questions, in which FDA will provide targeted advice regarding an ongoing ANDA development program.

W. Review Status Update—means a response from the RPM to the Authorized Representative to update the Authorized Representative concerning, at a minimum, the categorical status of relevant review disciplines with respect to the submission at that time. The RPM will advise the Authorized Representative that the update is preliminary only, based on the RPM's interpretation of the submission, and subject to change at any time.

X. Safety determination letter—a letter from FDA stating that a bioequivalence study protocol contains safety protections comparable to applicable REMS for the Reference Listed Drug.

Y. Standard—means submissions not affirmatively identified as eligible for expedited review pursuant to the CDER Prioritization MAPP.

Z. Standard controlled correspondence—means controlled correspondence

1. as described in CDER's September 2015 Guidance for Industry, Controlled Correspondence Related to Generic Drug Development, or

2. concerning post-approval submission requirements that are not covered by CDER post-approval changes guidance and are not specific to an ANDA.

AA. Target Action Date (TAD)—Under GDUFA I, FDA's aspirational deadline for action on a pre-GDUFA I Year 3 original ANDA and/or a complete response amendment or equivalent IR to an original ANDA.

GDUFA I TADs become GDUFA II goal dates on enactment of GDUFA II.

BB. Teleconference—means a verbal communication by telephone, and not a written response, unless otherwise agreed to by the applicant.

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

GDUFA II COMMITMENT LETTER, ATTACHMENT A

Category	Pre-cohort Year 3 ANDAs	Pre-cohort Year 3 ANDAs (expedited status)
Major Amendment (Complete Response Letter)	10 months	7 months
Minor Amendment (Complete Response Letter)	5 months	3 months
Easily Correctable Deficiency	3 months.	
Information Request	3 months.	

Mr. ALEXANDER. Mr. President, I ask unanimous consent to have printed in the RECORD a copy of the commitment letter for the Medical Device User Fee Amendments of 2017.

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

MDUFA PERFORMANCE GOALS AND PROCEDURES, FISCAL YEARS 2018 THROUGH 2022

GENERAL

The performance goals and procedures agreed to by the Center for Devices and Radiological Health (CDRH) and the Center for Biologics Evaluation and Research (CBER) of the United States Food and Drug Administration (''FDA'' or ''the Agency'') for the medical device user fee program in the Medical Device User Fee Amendments of 2017, are summarized below.

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

I. SHARED OUTCOME GOALS

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

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

A. PMA

FDA will report on an annual basis the average Total Time to Decision as defined in Section VII.H for the three most recent closed receipt cohorts.

For Original PMA and Panel Track Supplement submissions received in Fiscal Years 2016 through 2018, the average Total Time to Decision goal for FDA and industry is 320 calendar days.

For Original PMA and Panel Track Supplement submissions received in Fiscal Years 2017 through 2019, the average Total Time to Decision goal for FDA and industry is 315 calendar days.

For Original PMA and Panel Track Supplement submissions received in Fiscal Years 2018 through 2020, the average Total Time to Decision goal for FDA and industry is 310 calendar days.

For Original PMA and Panel Track Supplement submissions received in Fiscal Years 2019 through 2021, the average Total Time to Decision goal for FDA and industry is 300 calendar days.

For Original PMA and Panel Track Supplement submissions received in Fiscal Years 2020 through 2022, the average Total Time to Decision goal for FDA and industry is 290 calendar days.

B. 510(k)

FDA will report on an annual basis the average Total Time to Decision as defined in Section VII.H for the most recent closed receipt cohort.

For 510(k) submissions received beginning in Fiscal Year 2018, the average Total Time to Decision goal for FDA and industry is 124 calendar days.

For 510(k) submissions received beginning in Fiscal Year 2019, the average Total Time to Decision goal for FDA and industry is 120 calendar days.

For 510(k) submissions received beginning in Fiscal Year 2020, the average Total Time to Decision goal for FDA and industry is 116 calendar days.

For 510(k) submissions received beginning in Fiscal Year 2021, the average Total Time to Decision goal for FDA and industry is 112 calendar days.

For 510(k) submissions received beginning in Fiscal Year 2022, the average Total Time to Decision goal for FDA and industry is 108 calendar days.

II. REVIEW PERFORMANCE GOALS—FISCAL YEARS 2018 THROUGH 2022 AS APPLIED TO RECEIPT COHORTS

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

A. Pre-Submissions

FDA will continue the Pre-Submission program as described in the Guidance on ''Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with FDA Staff'' with process improvements and performance goals as noted in this section.

For all Pre-Submissions in which the applicant requests a meeting or teleconference, the applicant will provide a minimum of three proposed meeting dates in the initial submission.

Within 15 calendar days of receipt of a Pre-Submission, FDA will communicate with the applicant regarding whether the application has been accepted and, if applicable, regarding scheduling of the meeting or teleconference. Acceptance will be determined based on the definition of pre-submission in Section VII.F below and an acceptance checklist in published guidance. This communication consists of a fax, email, or other written communication that a) identifies the reviewer assigned to the submission, b) acknowledges acceptance/rejection of the submission, and c) if the submission included a request for a meeting or teleconference and is accepted, either confirms one of the applicant's requested meeting dates or provides two alternative dates prior to day 75 from receipt of accepted submission. A determination that the request does not qualify as a Pre-Submission will require the concurrence of the branch chief and the reason for this determination will be provided to the applicant in the above written communication. FDA intends to reach agreement with the applicant regarding a meeting date within 30 days from receipt of accepted submission. For all requests for meetings or teleconferences that do not have such a meeting or teleconference scheduled by 30 days from receipt of an accepted submission, an FDA manager will contact the applicant to resolve scheduling issues by the 40th day.

FDA will provide written feedback that addresses the issues raised in the pre-submission request within 70 calendar days of receipt date or five calendar days prior to a scheduled meeting, whichever comes sooner, for at least 1,530 Pre-Submissions received in FY 2018, at least 1,645 Pre-Submissions received in FY 2019, at least 1,765 Pre-Submissions received in FY 2020, at least 1,880 Pre-Submissions received in FY 2021, and at least 1,950 Pre-Submissions received in FY 2022. FDA will provide such timely written feedback for additional Pre-Submissions as resources permit, but not to the detriment of meeting the quantitative review timelines and statutory obligations. Written feedback will be provided to the applicant by email or fax and will include: written responses to the applicant's questions; FDA's suggestions for additional topics for the meeting or teleconference, if applicable; or, a combination of both. If all of the applicant's questions are addressed through written responses to the applicant's satisfaction, FDA and the applicant can agree that a meeting or teleconference is no longer necessary, and the written responses provided by email or fax will be considered the final written feedback to the Pre-Submission.

Meetings and teleconferences related to Pre-Submission will normally be limited to 1 hour unless the applicant justifies in writing the need for additional time. FDA may extend the time for such meetings and/or teleconferences.

Applicants will be responsible for developing draft minutes for a Pre-Submission meeting or teleconference, and provide the draft minutes to FDA within 15 calendar days of the meeting. At the beginning and end of each meeting, the applicant will affirmatively state that they will draft minutes and provide them to FDA within 15 calendar days. The minutes will summarize the meeting discussions and include agreements and any action items. FDA will provide any edits to the draft minutes to the applicant via email within a timely manner. These minutes will become final 15 calendar days after the applicant receives FDA's edits, unless the applicant indicates that there is a

disagreement with how a significant issue or action item has been documented. In this case, within a timely manner, the applicant and FDA will conduct a teleconference to discuss that issue with FDA. At the conclusion of that teleconference, within 15 days FDA will finalize the minutes either to reflect the resolution of the issue or note that this issue remains a point of disagreement.

FDA intends that feedback the Agency provides in a Pre-Submission will not change, provided the information submitted in a future IDE or marketing application is consistent with that provided in the Pre-Submission and documented in the Pre-Submission, and that the data and other information in the future submission do not raise any important new issues materially affecting safety or effectiveness. The minutes described above will serve as the record of the Agency's Pre-Submission feedback. Modifications to FDA's feedback will be limited to situations in which FDA concludes that the feedback does not adequately address important new issues materially relevant to a determination of safety and/or effectiveness or substantial equivalence. Such a determination will be supported by the appropriate management concurrence consistent with applicable guidance and SOPs.

By October 1, 2018, the Agency will update the Guidance on ''Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with FDA Staff'' to include: additional information to assist applicants in determining the need for a Pre-Submission, an enhanced Pre-Submission acceptance checklist, examples of frequently asked Pre-Submission questions that lend themselves to productive Pre-Submission interactions, and edits to reflect the revised process outlined above. FDA will provide an opportunity for the public to comment on the updated guidance. No later than 12 months after the close of the public comment period, the Agency will issue a final guidance. FDA will implement this guidance once final.

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

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

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

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

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

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

If the application is filed, FDA will communicate with the applicant through a Substantive Interaction within 90 calendar days of the filing date of the application for 95% of submissions.

When FDA issues a major deficiency letter, that letter will be based upon a complete review of the application and will include all deficiencies. All deficiency letters will include a statement of the basis for the deficiencies (e.g., a specific reference to applicable section of a rule, final guidance, recognized standard unless the entire or most of document is applicable). In the instance when the deficiency cannot be traced in the manner above and relates to a scientific or regulatory issue pertinent to the determination, FDA will cite the specific scientific issue and the information to support its position. All deficiency letters will undergo supervisory review prior to issuance to ensure the deficiencies cited are relevant to a determination of safety and effectiveness. Any subsequent deficiencies will be limited to issues raised by the information provided by the applicant in its response, unless FDA concludes that the initial deficiencies identified do not adequately address important new issues materially relevant to a determination of safety or effectiveness. Such a determination will be supported by the appropriate management concurrence consistent with applicable guidance and SOPs. Issues related to post-approval studies, if applicable, and revisions to draft labeling will typically be addressed through interactive review once major deficiencies have been adequately addressed.

For submissions that do not require Advisory Committee input, FDA will issue a MDUFA decision within 180 FDA Days for 90% of submissions.

For submissions that require Advisory Committee input, FDA will issue a MDUFA decision within 320 FDA Days from receipt of the accepted submission for 90% of submissions. FDA will issue a MDUFA decision within 60 days of the Advisory Committee recommendation, as resources permit, but not to the detriment of meeting the quantitative review timelines and statutory obligations. The Office Director shall review each request for Advisory Committee input for appropriateness and need for this input.

If in any one fiscal year, the number of submissions that require Advisory Committee input is less than 10, then it is acceptable to combine such submissions with the submissions for the following year(s) in order to form a cohort of 10 or more submissions, upon which the combined years' submissions will be subject to the performance goal. If the number of submissions that require Advisory Committee input is less than 10 for FY 2022, it is acceptable to combine such submissions in the prior year to form a cohort of 10 or more submissions: in such cases, FDA will be held to the FY2022 performance goal for the combined years' submissions.

To facilitate an efficient review prior to the Substantive Interaction, and to incentivize submission of a complete application, submission of an unsolicited major amendment prior to the Substantive Interaction extends the FDA Day review clock by the number of FDA Days that have elapsed. Submission of an unsolicited major amendment after the Substantive Interaction extends the FDA Day goal by the number of FDA Days equal to 75% of the difference between the filing date and the date of receipt of the amendment. Requests from FDA that a submission be made will not be considered unsolicited.

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

For PMA submissions that receive a MDUFA decision of Approvable, FDA will issue a decision within 60 days of the sponsor's response to the Approvable letter, as resources permit, but not to the detriment of meeting the quantitative review timelines and statutory obligations.

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

C. 180-Day PMA Supplements

FDA will communicate with the applicant through a Substantive Interaction within 90 calendar days of receipt of 95% of submissions.

FDA will issue a MDUFA decision within 180 FDA Days for 95% of submissions.

D. Real-Time PMA Supplements

FDA will issue a MDUFA decision within 90 FDA Days for 95% of submissions.

E. De Novo Submissions

FDA will issue draft and final guidance that includes a submission checklist to facilitate a more efficient and timely review process.

Deficiencies identified will be based upon a complete review of the submission and will include all deficiencies. All deficiency letters will include a statement of the basis for the deficiencies (e.g., a specific reference to applicable section of a rule, final guidance, recognized standard unless the entire or most of document is applicable). In the instance when the deficiency cannot be traced in the manner above and relates to a scientific or regulatory issue pertinent to the determination, FDA will cite the specific scientific issue and the information to support its position. All deficiency letters will undergo supervisory review prior to issuance to ensure the deficiencies cited are relevant to a classification determination. Any subsequent deficiencies will be limited to issues raised by the information provided by the applicant in its response, unless FDA concludes that the initial deficiencies identified do not adequately address important new issues materially relevant to a classification determination. Such a determination will be supported by the appropriate management concurrence consistent with applicable guidance and SOPs. Issues related to revisions to draft labeling will typically be addressed through interactive review once major deficiencies have been adequately addressed.

FDA will issue a MDUFA decision within 150 FDA days of receipt of the submission for: 50% of *de novo* requests received in FY 2018; 55% of *de novo* requests received in FY 2019; 60% of *de novo* requests received in FY 2020; 65% of *de novo* requests received in FY 2021 and 70% of *de novo* requests received in FY 2022. At Industry's request and as resources permit, but not to the detriment of meeting the quantitative review timelines, if a final decision has not been rendered within 180 FDA days, FDA will discuss with the applicant all outstanding issues with the submission preventing FDA from reaching a decision. This discussion will reflect appropriate management input and approval, and will include action items for FDA and/or the applicant, as appropriate, with an estimated date of completion for each party to complete their respective tasks.

F. 510(k) Submissions

FDA will communicate with the applicant regarding whether the submission has been

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

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

FDA will communicate with the applicant through a Substantive Interaction within 60 calendar days of receipt of the submission for 95% of submissions.

Deficiencies identified in a Substantive Interaction, such as a telephone/email hold or Additional Information Letter, will be based upon a complete review of the submission and will include all deficiencies. All deficiency letters will include a statement of the basis for the deficiencies (e.g., a specific reference to applicable section of a rule, final guidance, recognized standard unless the entire or most of document is applicable). In the instance when the deficiency cannot be traced in the manner above and relates to a scientific or regulatory issue pertinent to the determination, FDA will cite the specific scientific issue and the information to support its position. All deficiency letters will undergo supervisory review prior to issuance to ensure the deficiencies cited are relevant to a determination of substantial equivalence. Any subsequent deficiencies will be limited to issues raised by the information provided by the applicant in its response, unless FDA concludes that the initial deficiencies identified do not adequately address important new issues materially relevant to a determination of substantial equivalence. Such a determination will be supported by the appropriate management concurrence consistent with applicable guidance and SOPs.

FDA will issue a MDUFA decision for 95% of 510(k) submissions within 90 FDA Days. For all 510(k) submissions that do not reach a MDUFA decision within 100 FDA Days, FDA will provide written feedback to the applicant to be discussed in a meeting or teleconference, including all outstanding issues with the application preventing FDA from reaching a decision. The information provided will reflect appropriate management input and approval, and will include action items for FDA and/or the applicant, as appropriate, with an estimated date of completion for each party to complete their respective tasks. Issues should be resolved through interactive review. If all of the outstanding issues are adequately presented through written correspondence, FDA and the applicant can agree that a meeting or teleconference is not necessary.

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

G. CLIA Waiver by Application

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

Industry will inform FDA that it plans to submit a dual submission (510(k) and CLIA Waiver application) during the Pre-Submission process. FDA will issue a decision for 90% of dual submission applications within 180 FDA days.

For ''CLIA Waiver by application'' submissions FDA will issue a MDUFA decision for 90% of the applications that do not require Advisory Committee input within 150 FDA days.

For ''CLIA Waiver by application'' submissions FDA will issue a MDUFA decision for 90% of the applications that require Advisory Committee input within 320 FDA days.

If in any one fiscal year, the number of submissions in any CLIA Waiver by Application category is less than 10, then it is acceptable to combine such submissions with the submissions for the following year(s) in order to form a cohort of 10 or more submissions, upon which the combined years' submissions will be subject to the performance goal.

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

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

In addition, FDA will:

1. Hold CLIA Waiver Vendor Days, with the first to occur before the end of FY2018.

2. Permit discussion of both 510(k) and CLIA waiver process in Pre-Submissions.

3. Specifically permit discussion of appropriate reference/comparator for both 510(k) and CLIA waiver submissions in Pre-Submissions.

4. Provide a status report on completion and issuance of revisions to Section V of the Guidance on ''Recommendations for CLIA Waiver Applications'' to include appropriate use of comparable performance between a waived user and moderately complex laboratory user to demonstrate accuracy.

H. Original Biologics Licensing Applications (BLAs)

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

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

I. BLA Efficacy Supplements

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

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

J. Original BLA and BLA Efficacy Supplement Resubmissions

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

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

K. BLA Manufacturing Supplements Requiring Prior Approval

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

III. INFRASTRUCTURE

A. Quality Management

The Agency will establish a dedicated Quality Management (QM) Unit that reports directly to the CDRH Director or Deputy Director and establish a quality management framework for the premarket submission process in CDRH. The Framework will include infrastructure, senior management responsibility, resource management, lifecycle management, and quality management system evaluation.

At least once per year, the Agency will discuss with industry the specific areas it intends to incorporate in its ongoing audit plan. FDA will identify, with industry input, areas to audit, which will include the effectiveness of CDRH's Corrective and Preventive Action (CAPA) process. FDA will expand the scope of its annual audits as it implements and builds up its auditing capability. As part of these ongoing audits, high-performing premarket review processes utilized in one division will be identified and shared accordingly with other divisions to improve efficiencies and effectiveness. At a minimum, FDA audits in the following areas will be completed by the end of FY 2020: Deficiency Letters and Pre-Submissions. Additional audits in the following areas will be completed by the end of FY 2022: Submission Issue Meetings, Interactive Review, Withdrawals and Special 510(k) conversions.

The effectiveness of the QM framework will be evaluated in Phase 2 of the Independent Assessment (see Section V).

B. Scientific and Regulatory Review Capacity

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

To ensure such additional positions are filled by qualified experts, the Agency will apply user fee revenues to recruitment and hiring. The Agency will apply user fee revenues to retain high-performing supervisors in the premarket review program.

CDRH intends to enter into an Inter-Agency Agreement (IAA) with the Office of Personnel Management (OPM) to provide supplemental recruitment and staffing support throughout MDUFA IV to augment existing FDA Human Resources services.

C. IT Infrastructure for Submission Management

FDA will enhance IT infrastructure that will allow FDA to perform quality management audits and review consistency.

FDA will implement a new information management system that provides an industry dashboard that displays near real-time submission status.

FDA will develop electronic submission templates that will serve as guided submission preparation tools for industry to improve submission consistency and enhance efficiency in the review process. By FY 2020, the Agency will issue a draft guidance document on the use of the electronic submission templates. FDA will provide an opportunity for public comment on the guidance. No later than 12 months after the close of the public comment period, the Agency will issue a final guidance. FDA will implement the guidance once final. In addition, the Agency will update the Guidance ''eCopy Program for Medical Device Submissions'' to reflect the respective changes to the technical standards and specifications.

FDA will link pre-submissions with subsequent premarket submissions when identified by the applicant.

D. Training

FDA will continue to improve training for new and existing reviewers under this agreement. FDA will achieve Kirkpatrick Level 3 for curriculum-based premarket training through assessment of work performance behavior change and evaluate the effectiveness of the impact of curriculum-based premarket training activities on relevant premarket program metrics and goals (Kirkpatrick Level 4) by the end of FY 2020. FDA training efforts will also be closely coordinated with the Quality Management Unit described in item III.A above to provide more targeted and personalized training to staff.

E. Time Reporting

FDA will implement complete time reporting by the end of MDUFA IV such that data from time reporting can be used to conduct workload analysis and capacity planning.

F. Fee Setting, Fee Collections, and Workload

FDA will seek authority to eliminate the fifth-year offset provision and to maintain and use any and all fee collections, including collections over the statutory total revenue targets.

If the collections are in excess of the resources needed to meet performance goals given the workload, or in excess of inflation-adjusted statutory revenue targets, FDA and industry will work together to assess how best to utilize those resources to improve performance on submission types with performance goals and/or quality management programs, using, as input for the discussion: workload information, performance objectives and ongoing reported performance.

IV. PROCESS IMPROVEMENTS

A. Interactive Review

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

B. Deficiency Letters

By October 1, 2017, the Agency will publish a level 2 update to the final guidance ''Suggested Format for Developing and Responding to Deficiencies in Accordance with the Least Burdensome Provisions of FDAMA; Final Guidance for Industry and FDA Staff'' to reflect the following:

All deficiency letters will include a statement of the basis for the deficiencies (e.g., a specific reference to applicable section of a rule, final guidance, recognized standard unless the entire or most of document is applicable). In the instance when the deficiency cannot be traced in the manner above and relates to a scientific or regulatory issue pertinent to the determination, FDA will cite the specific scientific issue and the information to support its position. All deficiency letters will undergo supervisory review prior to issuance to ensure the deficiencies cited are relevant to a marketing authorization decision (e.g., 510(k) clearance, PMA approval, and de novo classification). Any additional best practices identified by quality audits and/or the Independent Assessment will be incorporated in updates to the guidance, as appropriate.

FDA will train staff and managers on this process improvement and the updated guidance.

C. Device Accessories

FDA and Industry will explore additional mechanisms for a streamlined, resource minimal pathway to reclassify accessories previously classified as class III devices as a part of a PMA review if they meet the requirements of a low or moderate risk device.

D. Enhanced Use of Consensus Standards

FDA will establish an Accreditation Scheme for Conformity Assessment (ASCA) Program using FDA-recognized consensus standards. FDA will define the 'scheme' and oversee the Conformity Assessment (CA) model and ensure that there is appropriate interaction with parties that serve as Accrediting Bodies (ABs) to accredit test laboratories (TLs). When a device type using the 'scheme' is evaluated according to a specific recognized standard by an accredited TL, FDA intends to rely on the results from the accredited TL for the purpose of premarket review (i.e., generally accept a determination that a device conforms with the standard) without the need to address further questions related to standards conformance. Assuming that it meets established criteria as outlined in the ASCA program, a device company's internal TL will be eligible to participate in the ASCA program. FDA will not review reports from accredited TLs except as part of a periodic quality audit or if FDA becomes aware of new information materially relevant to safety and/or effectiveness.

Specific actions that FDA will undertake include the following:

1. Conduct a Public Workshop by the end of FY 2018 to discuss objectives for the establishment of ABs and TLs. Discussion would include areas (specific FDA-recognized consensus standards) where the ASCA Program can be piloted to maximize initial impact of existing CA activities and potential new areas.

2. Hold educational sessions with stakeholders by the end of FY 2018 about the purpose of the ASCA Program

3. Develop and initiate the pilot of the ASCA program with stakeholder input by the end of FY 2020.

a. FDA intends to pilot inclusion of recognized standards of public health significance where specific pass/fail criteria are part of the standard

4. Develop an internal IT system to track CA activities of the ASCA Program

5. Establish a process for accreditation of ABs and TLs. FDA will issue draft guidance by the end of FY 2019 and issue final guidance within 12 months post initiation of the pilot.

a. In limited circumstances, the FDA may directly accredit third-party TLs. For example, FDA could directly accredit third party TLs, if FDA has not identified and recognized an AB within 2 years after establishing the tenets of the ASCA program.

6. Establish a process for reaccreditation and the suspension or withdrawal of accreditation of poor performing ABs and TLs. FDA will issue draft guidance by the end of FY 2019 and final guidance within 12 months post initiation of the pilot.

7. Establish a publicly-accessible website listing TLs accredited by ASCA and the FDA-recognized consensus standard(s) for which they are accredited

8. FDA, in consultation with stakeholders, will identify appropriate recognized consensus standards for consideration as part of the pilot as the specific focus for ASCA.

a. By the end of FY 2022: FDA will have piloted, and provided a report on the viability of, an ASCA program which utilizes the schema identified in guidance to include utilization of 5 appropriate cross-cutting/horizontal and/or device-specific areas, at least one of which will be device-specific.

b. Standards included as part of the ASCA Program will need to have well established endpoints/acceptance criteria built into the standard to allow effective tracking of TL competence.

FDA will provide an annual report on the progress of the ASCA program.

FDA will work with stakeholders for further input on programmatic improvements and/or consideration for expansion.

E. Third Party Review

The Agency will take the following actions to improve the Third Party Review program with a goal of eliminating routine re-review by FDA of Third Party reviews:

1. Strengthen the process for accreditation of Third Parties.

a. Provide training for Third Parties seeking accreditation by FDA. This training shall include the opportunity for Third Parties to have access to redacted review memos and other information as appropriate.

b. When FDA's expectations for a particular device type change, FDA will have in place a process to convey this information to the Third Parties and to industry.

2. By the end of FY 2018, establish a plan for eliminating routine re-review by FDA of Third Party reviews and implement plan within 12 months.

3. Implement a program to audit reviews conducted by accredited Third Parties.

a. Provide tailored re-training to accredited Third Parties based on the results of audits.

4. By the end of FY 2018, issue draft guidance outlining criteria for reaccreditation of 3rd Parties and the suspension or withdrawal of accreditation of a Third Party. FDA will issue final guidance within 12 months of the conclusion of the public comment period.

5. Publish performance of individual accredited Third Parties with at least five completed submissions on the web (e.g., rate of NSE, average number of holds, average time to SE).

6. Require the independent assessment of the Third Party Review Program to evaluate efficiency including the circumstances when FDA re-reviews were conducted; and to suggest process improvements.

The Agency will seek greater authority to tailor the program. Specifically, FDA intends to expand the scope of the program to some product codes that require clinical data and to remove product codes from eligibility when appropriate, such as if/when safety signals arise.

As resources permit, FDA will identify pilot device areas to be the specific focus of an effort where FDA would work with willing industry partners to ensure that information allowing for high quality Third Party reviews could be made available to provide a proof of concept in certain device areas and enable the development of a broader successful program.

F. Patient Engagement & the Science of Patient Input

The Agency will take the following actions to advance patient input and involvement in the regulatory process. Where appropriate, the Agency will leverage public private partnerships (PPPs) to advance these actions.

1. Develop clinical, statistical, and other scientific expertise and staff capacity to respond to submissions containing applicant-

proposed use of publicly available and validated, voluntary patient preference information (PPI) or voluntary patient reported outcomes (PROs). These staff will provide submission review and early consultation/advice to industry during study planning.

2. By the end of FY 2020, hold one or more public meetings to discuss the topics below and publish the findings and next steps.

a. Discuss approaches for incorporating PPI and PRO as evidence in device submissions, as well as other ways of advancing patient engagement;

b. Discuss ways to use patient input to inform clinical study design and conduct, with a goal of reducing barriers to patient participation and facilitating recruitment and retention;

c. Public meetings should include specific examples and case histories for PPIs and PROs to ensure clarity and understanding by workshop attendees; and

d. Identify priority areas where decisions are preference-sensitive and PPI data can inform regulatory decision-making, in order to advance design and conduct of patient preference studies in high impact areas. Publish the priority areas in the Federal Register for public comment following the public meeting.

3. FDA will undertake several activities to improve the regulatory predictability and impact of PROs, including:

a. Clarify to device review divisions that use of PROs is voluntary and may be one potential way of demonstrating safety or effectiveness (or elements of either or both, such as in a composite endpoint). Consistent with least burdensome principles, applicants may use alternative approaches.

b. Modify the guidance to outline a flexible framework for PRO validation evidentiary thresholds. These thresholds may vary depending on the particular regulatory use of the PRO.

c. Work on developing a model for ''bridging studies'' to make efficient use of existing validated PROs which may be improved, or adapted to other subpopulations or other regulatory uses in a more streamlined and expeditious manner than creating novel PROs.

4. The existing dispute resolution process should be used in the event of disagreement between the applicant and the Agency on the need for PPI or PRO.

G. Emerging Diagnostics

FDA will work with industry to continue the pilot for emerging diagnostics started under MDUFA III.

H. Real World Evidence (RWE)

1. The Agency will use user fee revenue to support the National Evaluation System for health Technology (NEST) by providing funding for the NEST Coordinating Center and hiring FDA staff with expertise in the use of RWE. The NEST governing board will include no fewer than 4 representatives of the trade associations that participated in the MDUFA IV negotiations (AdvaMed, MDMA, MITA, and ACLA), with each association appointing an individual to serve. Industry representation on the NEST governing board will make up at least 25% of the governing board membership. The representative from each trade association may be part of the staff of the association or appointed from a member company. If any of the trade associations elects not to participate on the NEST governing board or for any additional seats allocated to Industry, the participating trade associations will determine how to fill any vacant Industry positions. The governing board also will include, but not be limited to, representation from patient organizations. By the end of FY2019, NEST will implement pilots for at least two product codes (and related product codes), one of which will cover devices approved through the PMA process and the other of which will cover devices cleared through the 510(k) process. The NEST Coordinating Center will seek ways in which to make NEST financially self-sustaining so as not to rely on MDUFA user fees in the long term unless FDA and Industry determine continued user fee support is warranted and provides a sufficient return on investment.

2. FDA will contract with an organization to serve as the NEST Coordinating Center to facilitate use of real world evidence to support premarket activities. The contract will specify actions the Coordinating Center will take to advance the use of RWE, including:

a. Establish a framework to fund pilot projects to determine the usability of RWE for:

i. Expanded indications for use

ii. New clearances/approvals

iii. Improved malfunction reporting

b. No later than October 1, 2020, the Coordinating Center will hold a public meeting to review and evaluate the progress and outcomes (as of the date of the public meeting) of the pilots described in (H)(1) above.

c. The pilots will take place over a period of three years, including data analysis and the Coordinating Center will issue a publicly available report of the results.

d. The pilots will include devices not currently subject to a registry.

e. At the conclusion of the pilots, an independent third-party will conduct an assessment to evaluate the strengths, limitations, and appropriate use of RWE for informing premarket decision-making for multiple device types.

f. If warranted based on the results of the pilot(s) described in (H)(1) above, FDA will revise its guidance on the use of RWE to reflect what has been learned from the pilots as to how RWE can be used to support:

i. Expanded indications for use; and

ii. New clearances/approvals.

If supported by the pilot(s) described in (H)(1) above, the guidance will include discussion of how devices not currently subject to a registry can benefit from RWE.

3. The Agency will establish criteria for streamlining MDR requirements.

a. For most, if not all, device procodes, FDA will permit manufacturers of such devices in those procodes to report malfunctions on a quarterly basis and in a summary MDR format. FDA will publish the list of eligible device procodes within 12 months of receiving a proposed list from Industry. The list will include, among other device procodes, Class II implantable and Class III devices, as appropriate, and will reflect FDA's consideration of Industry's proposed list.

b. FDA may determine that devices under a new procode in existence for less than 2 years are not eligible for reporting of malfunctions on a quarterly basis and in a summary format.

c. If a new type of malfunction occurs that the manufacturer has not previously reported to FDA, the manufacturer must submit an individual report. The manufacturer will notify FDA when the issue has been resolved, using current requirements per 21 C.F.R. 803, 806.

d. FDA will maintain on its website the list of eligible device procodes for which manufacturers are permitted to report malfunctions on a quarterly basis and in a summary MDR format.

e. FDA will establish a mechanism at the time it publishes the list of eligible devices under 3(a) that permits stakeholders to request device procodes be added to the list.

f. Nothing in this section precludes the Agency from requiring individual malfunction reports from a specific manufacturer and/or for a specific device if necessary to protect public health. In these situations, FDA will notify the manufacturer they are not eligible for quarterly summary MDR reporting and provide an explanation for that decision and the steps necessary to return to eligibility for quarterly summary MDR reporting.

4. FDA will not require postmarket surveillance studies (i.e., 522 Studies) for devices for which registries and/or other real world data (RWD) sources exist if FDA has access to the information/data in the RWD source and has determined that the information/data in the RWD source is sufficient to take the place of a postmarket surveillance study.

I. Digital Health

The Agency will build expertise and streamline and align FDA review processes with software lifecycles for Software as a Medical Device (SaMD) and software inside of medical devices (SiMD). Specifically, the Agency will:

1. Establish a central digital health unit within CDRH's Office of the Center Director to ensure proper coordination and consistency across the Agency. The Agency will not reorganize staff such that existing review staff would be reassigned to the central digital health unit, while retaining and not disrupting the existing digital health talent within the reviewing divisions who have established, long-term therapeutic and device expertise. The digital health unit will perform, at a minimum, the following tasks:

a. Develop software and digital health technical expertise (''Technical Experts'') to provide assistance for premarket submissions that include SaMD, SiMD, interoperable devices, or otherwise incorporate novel digital health technologies.

b. Utilize Technical Experts as appropriate or when requested by the manufacturer for submissions that include SaMD, SiMD, interoperable devices, or otherwise incorporate novel digital health technologies; and

c. Incorporate appropriate metrics for digital health improvements to monitor, track, analyze and report the results of digital health premarket review timelines.

2. Publish final guidance addressing when to submit a 510(k) for a software modification to an existing device within 18 months of the close of the comment period.

3. Explore opportunities to establish premarket approval/clearance pathways tailored to SaMD, SiMD, and novel digital health technologies that take into account real world evidence while incorporating principles established through international harmonization. To accomplish this task, the Agency will:

a. Engage with stakeholders, including industry, through roundtables, informal meetings, and teleconferences;

b. Hold a public workshop; and

c. Revise existing and/or publish new relevant guidance documents, including publishing a draft revised version of the ''Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices'' (issued in 2005) by the end of FY2019, and within 12 months of the close of the comment period, publish the final revised version. The Agency will incorporate applicable concepts from its Guidance for ''Off-The-Shelf Software Used in Medical Devices.''

4. Participate in international harmonization efforts related to digital health, including work on developing SaMD and other digital health convergence efforts through the International Medical Device Regulators Forum (IMDRF).

J. Guidance Document Development

FDA will apply user fee revenues to ensure timely completion of Draft Guidance documents. The Agency will strive to finalize, withdraw, reopen the comment period, or issue a new draft guidance for 80% of draft guidance documents within 3 years of the close of the comment periods as resources permit. The Agency will strive to finalize, withdraw, reopen the comment period, or issue a new draft guidance for 100% of draft guidance documents within 5 years of the close of the comment periods as resources permit. The Agency will continue to develop guidance documents and improve the development process as resources permit, but not to the detriment of meeting quantitative review timelines and statutory obligations.

K. Total Product Life Cycle (TPLC)

The establishment of CDRH's Office of In Vitro Diagnostic Device Evaluation and Safety (now the Office of In Vitro Diagnostics and Radiological Health (OIR)) has led to improved consistency and predictability due to the enhanced integration of premarket, postmarket, and compliance-related activities and staff and improved information sharing among staff. In addition, the successful development and evaluation of medical devices depends on the integration of clinical with scientific and engineering disciplines. CDRH will explore transitioning to a similar TPLC model building in the other device areas based on the lessons learned from its experience with OIR and taking into account the Center's mission, vision, strategic priorities, and development of a patient-centric benefit-risk framework for regulatory and non-regulatory decision making across the TPLC. Because an essential element for the success of the Center's benefit-risk decision making framework and approach to device regulation (particularly emerging and innovative technologies) is the incorporation of the clinical context and the impact of a decision on patient health and quality of life, CDRH will take steps to increase and enhance the integration of its clinicians into its TPLC activities, amongst themselves, and with the Center's scientists and engineers. Building on the success of considering and incorporating additional expertise and viewpoints into our decision-making, such as through the use of the Network of Experts and the leveraging of patient perspectives, CDRH will also explore ways in which to better learn from and leverage the expertise of clinicians in other parts of the agency and outside of the agency to inform its decision making, enhance consistency, and assure a more holistic clinical perspective. Clinicians involved in device-related activities will have appropriate training on and make recommendations consistent with applicable device statutory provisions, regulations, guidances, and this Commitment Letter. In addition, CDRH will provide managerial oversight of clinician recommendations and device submission decisions, except for those devices subject to CBER oversight.

V. INDEPENDENT ASSESSMENT OF REVIEW PROCESS MANAGEMENT

FDA and the industry will participate in a comprehensive assessment of the process for the review of device applications. The assessment will include consultation with both FDA and industry. The assessment shall be conducted in two phases under contract to FDA by a private, independent consulting firm capable of performing the technical analysis, management assessment, and program evaluation tasks required to address the assessment scope described below within the budget provided under this user fee agreement.

PHASE 1

During the first phase, the contractor will complete an evaluation of FDA's implementation of the corrective action plan developed in response to recommendations from the MDUFA III independent assessment.

For Phase 1, FDA will award the contract by the end of CY2017. The contractor will evaluate the implementation of MDUFA III recommendations and publish a written assessment within 1 year of contract award.

PHASE 2

During the second phase, the contractor will:

1. Evaluate FDA's premarket review program to identify efficiencies that should be realized as a result of the process improvements and investments under MDUFA III and IV;

2. Evaluate premarket review program infrastructure and allocation of FTEs;

3. Assess the alignment of resource needs with the training and expertise of hires;

4. Identify and share best practices across branches in ODE and OIR;

5. Assess the effectiveness of programs targeted for improvement under this agreement, including the:

a. Quality Management program,

b. Proportion of deficiencies in which FDA references the basis for the deficiency determination,

c. Pre-Submission program (assess whether (a) CDRH is providing guidance specific to the questions being asked; (b) CDRH is using Pre-Submissions appropriately; and (c) CDRH and Industry are adhering to the procedural aspects as set forth in this agreement),

d. Third Party Review program (assess efficiency of program and suggest process improvements),

e. Digital Health program,

f. Patient Engagement program, and

g. Real World Evidence program;

6. Analyze conversions of Special 510(k)s to Traditional 510(k)s; and

7. Assess other key areas identified by FDA and industry as resources permit.

For Phase 2 of the independent assessment, FDA will award the contract no later than 3/31/2020. However, the contractor would not begin the audit of deficiency letters and Pre-Submissions before 10/1/2020. The contractor will publish comprehensive findings and recommendations within 1 year. For all recommendations the contractor will provide an estimate of additional resources needed or efficiencies gained, as applicable.

FDA will incorporate findings and recommendations, as appropriate, into its management of the premarket review program. FDA will analyze the recommendations for improvement opportunities identified in the assessment and, as appropriate, develop and implement a corrective action plan, and assure its effectiveness.

VI. PERFORMANCE REPORTS

The Agency will report its progress toward meeting the goals described in this letter, as follows. If, throughout the course of MDUFA IV, the Agency and Industry agree that a different format or different metrics would be more useful, the reporting will be modified accordingly as per the agreement of both FDA and Industry.

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

1.1. For 510(k) submissions that do not go through a 3rd party, reporting will include:

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

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

iii. Average number of review cycles.

iv. Rate of submissions not accepted for review

1.2. For PMA submissions, reporting will include:

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

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

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

1.3. For de novo requests, reporting will include:

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

ii. Average number of review cycles.

iii. Rate of submissions not accepted for review, upon final guidance

1.4. For Pre-Submissions, reporting will include:

i. Number of all qualified Pre-Submissions received

ii. Rate of submissions not accepted for review, upon final guidance

iii. Average and quintiles of the number of calendar days from submission to written feedback

iv. Number of Pre-Submissions that require a meeting

v. Percent of submissions with meetings for which industry provided minutes within 15 days

1.5. For IDE applications, reporting will include:

i. Number of original IDEs received

ii. Average number of amendments prior to approval or conditional approval of the IDE

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

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

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

2.3. Rate of Not Approvable decisions for PMA submissions

2.4. Rate of Denial decisions for de novo requests

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

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

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

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

2.9. Agency level summary of fee collections

2.10. Independent assessment implementation plan status

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

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

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

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

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

3.3. The number of Premarket Report Submissions received

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

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

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

i. Number of submissions reviewed by a Third Party

ii. Number of Special Submissions

iii. Number of Traditional Submissions

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

v. Number of Abbreviated Submissions

3.7. For 510(k) submissions that go through a 3rd party, reporting will include:

i. Time from FDA receipt of third party report to FDA decision at the 90% percentile

ii. Once 3rd party program enhancements have been implemented, resources saved as a result of enhancements to the 3rd party review program.

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

i. Original PMAs

ii. Priority PMAs

iii. Premarket Reports

iv. Panel-Track PMA Supplement

v. PMA Modules

vi. 180-Day PMA Supplements

vii. Real-Time PMA Supplements

viii. Number of submissions FDA classifies as unsolicited major, solicited major, and minor amendments

3.9. For De Novo requests, reporting will include:

i. Number of submissions received

ii. Average and number of days to Accept/Refuse to Accept, upon final guidance

3.10. For CLIA waiver applications, reporting will include:

i. Number of CLIA waiver applications received

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

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

3.11. Report on the ASCA program

3.12. Data regarding the reduction in reviewer to manager ratio.

3.13. Report on implementation of deficiency performance improvements.

3.14. Report on quality management program

3.15. Summary of quality system audits

FDA will report annual and quarterly data on performance within goals for 510(k), de novo, and PMA MDUFA decisions for devices identified as LDTs by the submitter compared to all non-LDT IVD devices. The following elements will be reported:

Number and percentage of LDT 510(k)s and non-LDT IVD 510(k)s completed within 90 FDA days

Number and percentage of LDT de novos and non-LDT IVD de novos completed within 150 FDA days

Number and percentage of LDT PMAs and non-LDT IVD PMAs completed within 180 FDA days

FDA commits to treat LDTs no less favorably than other devices to which MDUFA performance goals apply.

On an annual basis, FDA and Industry will discuss the return on investment, which may include process improvements, improved performance, and other enhancements, under MDUFA IV.

VII. DEFINITIONS AND EXPLANATIONS OF TERMS

A. Applicant

Applicant means a person who makes any of the following submissions to FDA:

an application for premarket approval under section 515 of the Federal Food, Drug, and Cosmetic Act (FDCA);

a premarket notification under section 510(k) of the FDCA;

an application for investigational device exemption under section 520(g) of the FDCA;

a Pre-Submission;

a de novo request (evaluation of automatic class III designation) under section 513(f)(2) of the FDCA;

a CLIA Waiver by application.

B. Electronic Copy (e-Copy)

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

C. Electronic submission template

An electronic submission template, or eSubmission template, is a guided submission preparation tool for industry. Similar to an online form, the eSubmission template walks industry through the relevant contents and components for the respective premarket submission type and device in order to facilitate submission preparation and enhance consistency, quality, and efficiency in the premarket review process.

D. FDA Days

FDA Days are those calendar days when a submission is considered to be under review at the Agency for submissions that have been accepted (510(k) or de novo classification request), filed (PMA) or submitted (CLIA Waiver by application). FDA Days begin on the date of receipt of the submission or of the amendment to the submission that enables the submission to be accepted (510(k)) or filed (PMA).

E. MDUFA Decisions

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

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

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

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

De Novo Requests: Decisions for De Novo requests are grant, withdrawal, and decline.

CLIA Waiver by Application Submissions: Decisions for CLIA Waiver by Application Submissions are Approval, Withdrawal, and Denial.

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

F. Pre-Submission

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

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

The following forms of FDA feedback to applicants are not considered Pre-Submissions.

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

General information requests initiated through the Division of Industry and Consumer Education (DICE).

General questions regarding FDA policy or procedures.

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

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

Phone calls or email messages to reviewers that can be readily answered based on a reviewer's experience and knowledge and do not require the involvement of a broader number of FDA staff beyond the routine involvement of the reviewer's supervisor and more experienced mentors.

G. Substantive Interaction

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

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

Minor issues may still be included in an Additional Information or Major Deficiency letter where related to the resolution of the

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

H. Total Time to Decision

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

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

The average Total Time to Decision for PMA applications is calculated as the three-year rolling average of the annual Total Times to Decision for applications (for example, for FY2018, the average Total Time to Decision for PMA applications would be the average of FY2016 through FY2018) within a closed cohort, excluding the highest 5% and the lowest 5% of values. A cohort is closed when 95% of the applications have reached a decision.

I. Accreditation Scheme for Conformity Assessment

Conformity Assessment is the demonstration that specified requirements relating to a product, process, system, person or body are fulfilled.

Accreditation is the formal recognition by an independent body, generally known as an accreditation body, that an organization is competent to carry out specific conformity assessment activities. Accreditation is not obligatory but it adds another level of confidence, as 'accredited' means the organization has been independently checked to make sure it operates according to international standards.

A conformity assessment scheme is a system for assessing the conformity of specified objects (e.g., medical devices or management processes) to one or more consensus standards. The system specifies the applicable standards as well as the rules, procedures, and management requirements for carrying out the conformity assessment to meet a regulatory need. Informally, such a scheme may be referred to as an accreditation scheme.

Testing laboratory is an organization that possesses the necessary technical competence and capabilities to conduct testing to making a determination that one or more characteristics of an object are in conformance with a set of predefined requirements.

J. BLA-related Definitions

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

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

(a) Final printed labeling

(b) Draft labeling

(c) Safety updates submitted in the same format, including tabulations, as the original safety submission with new data and changes highlighted (except when large amounts of new information including important new adverse experiences not previously reported with the product are presented in the resubmission)

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

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

(f) Assay validation data

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

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

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

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

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

Mr. ALEXANDER. Mr. President, I ask unanimous consent to have printed in the RECORD a copy of the commitment letter for the Prescription Drug User Fee Act, PDUFA, reauthorization for fiscal years 2018 to 2022, known as PDUFA VI.

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

PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2018 THROUGH 2022

PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2018 THROUGH 2022

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

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

I. ENSURING THE EFFECTIVENESS OF THE HUMAN DRUG REVIEW PROGRAM

A. Review Performance Goals

1. NDA/BLA Submissions and Resubmissions

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

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

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

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

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

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

2. Original Efficacy Supplements

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

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

3. Resubmitted Efficacy Supplements

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

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

4. Original Manufacturing Supplements

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

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

5. Review Performance Goal Extensions

a. Major Amendments

i. A major amendment to an original application, efficacy supplement, or resubmission of any of these applications, submitted at any time during the review cycle, may extend the goal date by three months.

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

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

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

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

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

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

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

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

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

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

TABLE 1.—ORIGINAL AND RESUBMITTED APPLICATIONS AND SUPPLEMENTS

Submission Cohort	Standard	Priority
NME NDAs and original BLAs	90% in 10 months of the 60 day filing date	90% in 6 months of the 60 day filing date
Non NME NDAs	90% in 10 months of the receipt date	90% in 6 months of the receipt date
Class 1 Resubmissions	90% in 2 months of the receipt date	90% in 2 months of the receipt date
Class 2 Resubmissions	90% in 6 months of the receipt date	90% in 6 months of the receipt date
Original Efficacy Supplements	90% in 10 months of the receipt date	90% in 6 months of the receipt date
Class 1 Resubmitted Efficacy Supplements	90% in 2 months of the receipt date	90% in 2 months of the receipt date
Class 2 Resubmitted Efficacy Supplements	90% in 6 months of the receipt date	90% in 6 months of the receipt date

TABLE 2

	Prior Approval	All Other
Manufacturing Supplements	90% in 4 months of the receipt date	90% in 6 months of the receipt date

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

To promote transparency and communication between the FDA review team and the applicant, FDA will apply the following model (''the Program'') to the review of all New Molecular Entity New Drug Applications (NME NDAs) and original Biologics License Applications (BLAs), including applications that are resubmitted following a Refuse-to-File decision, received from October 1, 2017, through September 30, 2022. The goal of the Program is to promote the efficiency and effectiveness of the first cycle review process and minimize the number of review cycles necessary for approval, ensuring that patients have timely access to safe, effective, and high quality new drugs and biologics.

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

Expedited Reviews. In certain cases, an application reviewed in the Program will be for a product that the FDA review team identifies as meeting an important public health need. If the FDA review team determines that a first-cycle approval is likely for such an application, the 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. Expedited reviews are typically characterized by frequent contact between the applicant and the FDA review team throughout the review process. Any parameters of the Program that are intended to facilitate expedited reviews are noted throughout Section I.B.

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

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

1. 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.

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

e. Since applications are expected to be complete at the time of submission, unsolicited amendments are expected to be rare and not to contain major new information or analyses. Review of unsolicited amendments, including those submitted in response to an FDA communication of deficiencies, will be handled in accordance with the GRMP guidance. This guidance includes the underlying principle that FDA will consider the most efficient path toward completion of a comprehensive review that addresses application deficiencies and leads toward a first cycle approval when possible.

3. Day 74 Letter: FDA will follow existing procedures regarding identification and communication of filing review issues in the ''Day 74 letter.'' For applications subject to the Program, the timeline for this communication will be within 74 calendar days from the date of FDA receipt of the original submission. The planned review timeline included in the Day 74 letter for applications in the Program will include the planned date for the internal mid-cycle review meeting. The letter will also include preliminary plans on whether to hold an Advisory Committee (AC) meeting to discuss the application. If applicable, the Day 74 letter will serve as notification to the applicant that the review division intends to conduct an expedited review.

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

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

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

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

a. The update should include any significant issues identified by the review team to date, any information requests, information regarding major safety concerns and preliminary review team thinking regarding risk management, proposed date(s) for the late-cycle meeting, updates regarding plans for the AC meeting (if an AC meeting is anticipated), an update regarding FDA's review activities associated with a scheduling recommendation under the Controlled Substances Act (if applicable), and other projected milestone dates for the remainder of the review cycle.

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

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

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

b. For applications that will be discussed at an AC meeting, the following parameters apply:

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

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

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

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

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

e. Late-Cycle Meeting Discussion Topics: Potential topics for discussion at the late-cycle meeting include major deficiencies identified to date; issues to be discussed at the AC meeting (if planned); current assessment of the need for REMS or other risk management actions; status update of FDA's review activities associated with a scheduling recommendation under the Controlled Substances Act, if applicable; information requests from the review team to the applicant; and additional data or analyses the applicant may wish to submit.

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

7. 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. First Cycle Review Management

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

D. Review of Proprietary Names to Reduce Medication Errors

To enhance patient safety, FDA is committed to various measures to reduce medication errors related to look-alike and sound-alike proprietary names and such factors as unclear label abbreviations, acronyms, dose designations, and error prone label and packaging design. The following performance goals apply to FDA's review of drug and biological product proprietary names during development (as early as end-of-phase 2) and during FDA's review of a marketing application:

1. Proprietary Name Review Performance Goals During Drug Development

a. Review 90% of proprietary name submissions filed within 180 days of receipt. Notify sponsor of tentative acceptance or non-acceptance.

b. If the proprietary name is found to be unacceptable, the sponsor can request reconsideration by submitting a written rebuttal with supporting data or request a meeting within 60 days to discuss the initial decision (meeting package required).

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

d. A complete submission is required to begin the review clock.

2. Proprietary Name Review Performance Goals During Application Review

a. Review 90% of NDA/BLA proprietary name submissions filed within 90 days of receipt. Notify sponsor of tentative acceptance/non-acceptance.

b. A supplemental review will be done meeting the above review performance goals if the proprietary name has been submitted previously (IND phase after end-of-phase 2) and has received tentative acceptance.

c. If the proprietary name is found to be unacceptable, the sponsor can request reconsideration by submitting a written rebuttal with supporting data or request a meeting within 60 days to discuss the initial decision (meeting package required).

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

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

E. Major Dispute Resolution

1. Procedure:

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

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

3. Conditions:

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

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

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

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

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

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

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

F. Clinical Holds

1. Procedure:

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

2. Performance goal:

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

G. Special Protocol Question Assessment and Agreement

1. Procedure:

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

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

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

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

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

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

2. Performance goal:

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

3. Reporting:

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

H. Meeting Management Goals

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

Type A meetings are those meetings that are necessary for an otherwise stalled drug development program to proceed (i.e., a ''critical path'' meeting) or to address an important safety issue. Post-action meetings requested within three months after an FDA regulatory action other than approval (i.e., issuance of a complete response letter) will also generally be considered Type A meetings.

Type B meetings include pre-IND meetings and pre-NDA/BLA meetings, while Type B (EOP) meetings are reserved for certain End-of-Phase 1 meetings (i.e. for 21 CFR Part 312 Subpart E or 21 CFR Part 314 Subpart H or similar products) and End-of-Phase 2/pre-Phase 3 meetings. Meetings regarding REMS or postmarketing requirements that occur outside the context of the review of a marketing application will also generally be considered Type B meetings.

A Type C meeting is any other type of meeting.

1. Responses to Meeting Requests

a. Procedure: FDA will notify the requester in writing of the date, time, and place for the meeting, as well as expected Center participants following receipt of a formal meeting request. Table 3 below indicates the timeframes for FDA's response to a meeting request.

TABLE 3

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

i. For any type of meeting, the sponsor may request a written response to its questions rather than a face-to-face meeting, videoconference or teleconference. FDA will review the request and make a determination on whether a written response is appropriate or whether a face-to-face meeting, videoconference, or teleconference is necessary. If a written response is deemed appropriate, FDA will notify the requester of the date it intends to send the written response in the

Agency's response to the meeting request. This date will be consistent with the timeframes specified in Table 4 below for the specific meeting type.

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

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

2. Scheduling Meetings

a. Procedure: FDA will schedule the meeting on the next available date at which all applicable Center personnel are available to attend, consistent with the component's other business; however, the meeting should be scheduled consistent with the type of meeting requested. Table 4 below indicates the timeframes for the scheduled meeting date following receipt of a formal meeting request, or in the case of a written response, the timeframes for the Agency to send the written response. If the requested date for any meeting type is greater than the specified timeframe, the meeting date should be within 14 calendar days of the requested date.

TABLE 4

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

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

3. Meeting Background Packages

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

TABLE 5

Meeting Type	Receipt of Background Package
A	At the time of the meeting request
B	30 calendar days before the date of the meeting or expected written response
B(EOP)	50 calendar days before the date of the meeting or expected written response*
C6	47 calendar days before the date of the meeting or expected written response*

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

4. Preliminary Responses to Sponsor Questions

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

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

5. Sponsor Notification to FDA

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

6. Meeting Minutes

a. Procedure: The Agency will prepare minutes that will be available to the sponsor 30 calendar days after the meeting. The minutes will clearly outline the important agreements, disagreements, issues for further discussion, and action items from the meeting in bulleted form and need not be in great detail. Meeting minutes are not required if the Agency transmits a written response for any meeting type.

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

7. Conditions

For a meeting to qualify for these performance goals:

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

b. The written request must provide:

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

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

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

iv. A listing of planned external attendees;

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

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

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

8. Guidance

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

I. Enhancing Regulatory Science and Expediting Drug Development

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

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

FDA's philosophy is that timely interactive communication with sponsors during drug development is a core Agency activity to help achieve the Agency's mission to facilitate the conduct of efficient and effective drug development programs, which can enhance public health by making new safe and effective drugs available to the American public in a timely manner. Accordingly, FDA will maintain dedicated drug development communication and training staffs in CDER and CBER, focused on enhancing communication between FDA and sponsors during drug development.

One function of the staff is to serve as a liaison that will facilitate general and, in some cases, specific interactions between sponsors and each Center. The liaison will serve as a point of contact for sponsors who have general questions about drug development or who need clarification on which review division to contact with their questions. The liaison will also serve as a secondary point of contact in each Center for sponsors who are encountering challenges in communication with the review team for their IND (e.g., in instances when they have not received a response from the review team to a simple or clarifying question or referral to the formal meeting process within 30 days of the sponsor's initial request). In such cases, the liaison will work with the review team and the sponsor to facilitate resolution of the issue.

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

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

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

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

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

2. Ensuring Sustained Success of Breakthrough Therapy Program

Breakthrough therapy designation is intended to expedite the development and review of drug and biological products, alone or in combination, for serious or life-threatening diseases or conditions when preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies. 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. Additional resources will enable the Agency to continue to work closely with sponsors throughout the breakthrough therapy designation, development, and review processes. Both FDA and the regulated industry are committed to ensuring the expedited development and review of innovative therapies for serious or life-threatening diseases or conditions by investing additional resources into the breakthrough therapy program.

3. Early Consultation on the Use of New Surrogate Endpoints

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

4. Advancing Development of Drugs for Rare Diseases

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

The RDP staff will also continue to provide training to all CDER and CBER review staff related to development, review, and approval of drugs for rare diseases as part of the reviewer training core curriculum.μ The objective of the training will be to familiarize review staff with the challenges associated with rare disease applications and strategies to address these challenges; to promote best practices for review and regulation of rare disease applications; and to encourage flexibility and scientific judgment among reviewers in the review and regulation of rare disease drug development and application review. The training will also emphasize the important role of the RDP staff as members of the core review team to help ensure consistency of scientific and regulatory approaches across applications and review teams.

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

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

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

a. FDA will develop staff capacity and capability across the medical product centers and the Office of Combination Products (OCP) to more efficiently, effectively, and consistently review and respond to submissions that include combination products. These staff will advance the development of combination products by providing combination product expertise as part of the core review team as applicable, and through promoting best practices for review of combination products. The additional capacity will include staff who will focus on review of cGMP, engineering aspects, human factors and bridging study protocols and study reports, and labeling, to include instructions-for-use materials.

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

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

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

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

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

i. Human Factors Assessments (March 31, 2019)

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

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

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

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

i. Procedure for review of human factors protocols for combination products: Upon specific request by a sponsor (including specific questions that the sponsor desires to be answered) consistent with the steps below, the Agency will evaluate human factors protocols and issues to assess whether the design is adequate to meet scientific and regulatory requirements identified by the sponsor.

(1) The sponsor should submit a limited number of specific questions about the human factors protocol design and scientific and regulatory requirements for which the sponsor seeks agreement (e.g., are the study participant groups appropriate to represent intended users, is the study endpoint adequate, are the critical tasks that should be evaluated appropriately identified).

(2) Within 60 days of Agency receipt of the protocol and specific questions, the Agency will provide a written response to the sponsor that includes a succinct assessment of

the protocol and answers to the questions posed by the sponsor. If the Agency does not agree that the protocol design, execution plans, and data analyses are adequate to achieve the goals of the sponsor, the reasons for the disagreement will be explained in the response.

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

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

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

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

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

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

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

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

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

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

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

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

Benefits to patients, regulators, and biopharmaceutical companies of RWE in regulatory decision making;

RWE availability, quality, and access challenges, and approaches to mitigate these;

Methodological approaches for the collection, analysis, and communication of RWE; and

Appropriate contexts of use of RWE in regulatory decision-making regarding effectiveness.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

b. By the end of FY 2019, FDA will convene and/or participate in, at least one meeting, conducted through a qualified third party, to gather industry, patient, researcher, and other stakeholder input on key topics. This would include applying the benefit-risk framework throughout the human drug lifecycle, including best approaches to communicating FDA's benefit-risk assessment.

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

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

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

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

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

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

3. Advancing Model-Informed Drug Development

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

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

b. FDA will convene a series of workshops to identify best practices for MIDD. Topics will include: (1) physiologically-based pharmacokinetic modeling; (2) design analysis and inferences from dose-exposure-response studies; (3) disease progression model development, including natural history and trial simulation; and (4) immunogenicity and correlates of protection for evaluating biological products, including vaccines and blood products. Each workshop will focus on current and emerging scientific approaches, including methodological limitations. FDA will produce a written summary of the topics discussed in each workshop.

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

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

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

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

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

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

4. Enhancing Capacity to Review Complex Innovative Designs

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

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

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

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

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

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

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

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

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

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

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

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

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

a. FDA will develop the staff capacity to efficiently review and provide feedback to sponsors on the readiness of submitted analysis data sets and programs for statistical review. This staff will support pre- and post-submission discussion of standardized datasets and programs, and maintain the knowledge of and engage in collaborations about standards models used in the design, analysis and review of clinical and non-clinical studies. Examples of these standards

models could include the Standard for Exchange of Nonclinical Data (SEND), Clinical Data Acquisition Standards Harmonization (CDASH), Study Data Tabulation Model (SDTM), and Analysis Data Model (ADaM).

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

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

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

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

6. Enhancing Drug Development Tools Qualification Pathway for Biomarkers

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

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

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

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

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

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

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

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

K. Enhancement and Modernization of the FDA Drug Safety System

FDA will continue to use user fees to enhance and modernize the current U.S. drug safety system, including adoption of new scientific approaches, improving the utility of existing tools for the detection, evaluation, prevention, and mitigation of adverse events, standardization and integration of REMS into the healthcare system, enhancing communication and coordination between postmarketing and pre-market review staff, and improving tracking, communication and oversight of postmarketing safety issues. Enhancements to the drug safety system will improve public health by increasing patient protection while continuing to enable access to needed medical products.

User fees will provide support for A) advancing postmarketing drug safety evaluation through expansion of the Sentinel System and integration into FDA pharmacovigilance activities, and B) timely and effective evaluation and communication of postmarketing safety findings related to human drugs.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

II. ENHANCING MANAGEMENT OF USER FEE RESOURCES

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

A. Resource Capacity Planning and Modernized Time Reporting

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

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

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

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

4. FDA recognizes that revenue generated by the workload adjuster and the resource

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

B. Financial Transparency and Efficiency

FDA is committed to ensuring PDUFA user fee resources are administered, allocated, and reported in an efficient and transparent manner. FDA will conduct activities to evaluate the financial administration of the PDUFA program to help identify areas to enhance efficiency. FDA will also conduct activities to enhance transparency of PDUFA program resources.

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

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

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

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

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

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

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

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

III. IMPROVING FDA HIRING AND RETENTION OF REVIEW STAFF

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

A. Completion of Modernization of the Hiring System Infrastructure and Augmentation of System Capacity:

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

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

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

2. Complete implementation of an online position classification system.

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

3. Complete implementation of corporate recruiting.

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

B. Augmentation of Hiring Staff Capacity and Capability

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

C. Complete Establishment of a Dedicated Function to Ensure Needed Scientific Staffing for Human Drug Review Program

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

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

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

D. Set Clear Goals for Human Drug Review Program Hiring

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

TABLE 6

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

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

E. Comprehensive and Continuous Assessment of Hiring and Retention

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

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

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

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

IV. INFORMATION TECHNOLOGY GOALS

A. Objective

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

B. Improve the Predictability and Consistency of PDUFA Electronic Submission Processes

1. Electronic Submission Documentation:

By December 31, 2017, FDA will publish and maintain up-to-date documentation for the following:

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

b. The rejection process for electronic submissions.

c. The electronic submission validation criteria.

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

2. Electronic Submission and System Status:

By September 30, 2018, FDA will:

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

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

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

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

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

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

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

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

C. Enhance Transparency and Accountability of FDA Electronic Submission and Data Standards Activities

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

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

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

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

5. FDA will:

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

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

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

V. IMPROVING FDA PERFORMANCE MANAGEMENT

A. The Studies Conducted Under This Initiative are Intended to Foster

1. Development of programs to improve access to internal and external expertise

2. Reviewer development programs, particularly as they relate to the human drug review program

3. Advancing science and use of information management tools

4. Improving both inter- and intra-Center consistency, efficiency, and effectiveness

5. Improved reporting of management objectives

6. Increased accountability for use of user fee revenues

7. Focused investments on improvements in the process for the review of human drug applications

8. Improved communication between the FDA and industry

B. Studies Will Include

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

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

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

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

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

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

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

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

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

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

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

VII. DEFINITIONS AND EXPLANATION OF TERMS

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

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.

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

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).

Mr. ALEXANDER. Mr. President, I ask unanimous consent to have printed in the RECORD a copy of the commitment letter for the Biosimilar User Fee Act, BsUFA, reauthorization for fiscal years 2018 to 2022, known as BsUFA II.

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

BIOSIMILAR BIOLOGICAL PRODUCT REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2018 THROUGH 2022

I. Ensuring the Effectiveness of the Biosimilar Biological Product Review Program

A. Review Performance Goals

B. Program for Enhanced Review Transparency and Communication for Original 351(k) BLAs

C. First Cycle Review Management for Supplements with Clinical Data

D. Guidance

E. Review of Proprietary Names to Reduce Medication Errors

F. Major Dispute Resolution

G. Clinical Holds

H. Special Protocol Question Assessment and Agreement

I. Meeting Management Goals

II. Advancing Development of Biosimilar Biological Products Through Further Clarification of the 351(k) Regulatory Pathway

III. Enhancing Capacity for Biosimilar Regulations and Guidance Development, Reviewer Training, and Timely Communication

IV. Enhancing Management of User Fee Resources

A. Resource Capacity Planning and Modernized Time Reporting

B. Financial Transparency and Efficiency

C. Management of Carryover Balance

V. Improving FDA Hiring and Retention of Review Staff

A. Completion of Modernization of the Hiring System Infrastructure and Augmentation of System Capacity

B. Augmentation of Hiring Staff Capacity and Capability

C. Complete Establishment of a Dedicated Function to Ensure Needed Scientific Staffing for Human Drug Review Including for Review of Biosimilar Biological Products

D. Set Clear Goals for Biosimilar Biological Product Review Program Hiring

E. Comprehensive and Continuous Assessment of Hiring and Retention

VI. Definitions and Explanation of Terms

BIOSIMILAR BIOLOGICAL PRODUCT AUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FOR FISCAL YEARS 2018 THROUGH 2022

This document contains the performance goals and procedures for the Biosimilar User Fee Act (BsUFA) reauthorization for fiscal years (FYs) 2018–2022, known as BsUFA II. 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 biosimilar biological product review program that are important for facilitating timely access to safe and effective biosimilar medicines for patients. FDA is committed to meeting the performance goals specified in this letter, enhancing management of BsUFA resources, and ensuring BsUFA user fee resources are administered, allocated, and reported in an efficient and transparent manner.

Under BsUFA II, FDA is committed to ensuring effective scientific coordination and review consistency, as well as efficient governance and operations across the biosimilar biological product review program. In addition, FDA is committed to the principles articulated in the Good Review Management Principles and Practices (GRMP) guidance,[1] which FDA intends to update and apply to the review of biosimilar and interchangeable products.

FDA and the regulated industry will periodically and regularly assess the progress of the biosimilar biological product review program throughout BsUFA II. 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 biosimilar biological product review program.

I. ENSURING THE EFFECTIVENESS OF THE BIOSIMILAR BIOLOGICAL PRODUCT REVIEW PROGRAM

A. Review Performance Goals

1. Biosimilar Biological Product Application Submissions and Resubmissions

a. Review and act on 90 percent of original biosimilar biological product application submissions within 10 months of the 60 day filing date.

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

2. Supplements with Clinical Data

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

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

3. Original Manufacturing Supplements

a. In FY 2018, review and act on 70 percent of manufacturing supplements requiring prior approval within 4 months of receipt.

b. In FY 2019, review and act on 75 percent of manufacturing supplements requiring prior approval within 4 months of receipt.

c. In FY 2020, review and act on 80 percent of manufacturing supplements requiring prior approval within 4 months of receipt.

d. In FY 2021, review and act on 85 percent of manufacturing supplements requiring prior approval within 4 months of receipt.

e. In FY 2022, review and act on 90 percent of manufacturing supplements requiring prior approval within 4 months of receipt.

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

4. Goals Summary Tables

TABLE 1.—ORIGINAL AND RESUBMITTED APPLICATIONS AND SUPPLEMENTS

Original Biosimilar Biological Product Application Submissions.	90% in 10 months of the 60 day filing date.
Resubmitted Original Biosimilar Biological Product Applications.	90% in 6 months of the receipt date.
Original Supplements with Clinical Data.	90% in 10 months of the receipt date.
Resubmitted Supplements with Clinical Data.	90% in 6 months of the receipt date.

TABLE 2.—MANUFACTURING SUPPLEMENTS

	Prior approval	All other
Manufacturing Supplements	• FY 2018: 70% in 4 months of the receipt date • FY 2019: 75% in 4 months of the receipt date • FY 2020: 80% in 4 months of the receipt date • FY 2021: 85% in 4 months of the receipt date • FY 2022: 90% in 4 months of the receipt date	90% in 6 months of the receipt date.

5. Review Performance Goal Extensions

a. Major Amendments

i. A major amendment to an original application, supplement with clinical data, or resubmission of any of these applications, submitted at any time during the review cycle, may extend the goal date by three months.

ii. A major amendment may include, for example, a major new clinical study report; major re-analysis of previously submitted study(ies); submission of a risk evaluation and mitigation strategy (REMS) with elements to assure safe use (ETASU) not included in the original application; or significant amendment to a previously submitted REMS with ETASU. Generally, changes to REMS that do not include ETASU and minor changes to REMS with ETASU will not be considered major amendments.

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 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 supplement with clinical data, 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.

B. Program for Enhanced Review Transparency and Communication for Original 351(k) 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 original Biologics License Applications (BLAs) submitted under section 351(k) of the Public Health Service Act (''351(k) BLAs''), including applications that are resubmitted following a Refuse-to-File decision, received from October 1, 2017, through September 30, 2022. 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 biosimilar and interchangeable biological products.

The standard approach for the review of original 351(k) 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 original 351(k) BLA. The Formal Communication Plan may include elements of the standard approach (e.g., a mid-cycle communication or a late-cycle meeting) as well as other interactions that sometimes occur during the review process (e.g., a meeting during the filing period to discuss the application, i.e., an ''application orientation meeting''). If appropriate, the Formal Communication Plan should specify those elements of the Program that FDA and the sponsor agree are unnecessary for the application under review. If the review team and the applicant anticipate developing a Formal Communication Plan, the elements of the plan should be discussed and agreed to at the pre-submission meeting (see Section I.B.1) and reflected in the meeting minutes. The Formal Communication Plan may be reviewed and amended at any time based on the progress of the review and the mutual agreement of the review team and the applicant. For example, the review team and the applicant may mutually agree at any time to cancel future specified interactions in the Program (e.g., the late-cycle meeting) that become unnecessary (e.g. because previous communications between the review team and the applicant are sufficient). Any amendments made to the Formal Communication Plan should be consistent with the goal of an efficient and timely first cycle review process and not impede the review team's ability to conduct its review.

The remainder of this 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 BPD Type 4 (pre–351(k) BLA) meeting. This meeting will be attended by the FDA review team, including appropriate senior FDA staff.

a. The BPD Type 4 (pre–351(k) 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 regarding the approach to developing the content for REMS, where applicable, patient labeling (e.g., Medication Guide and Instructions For Use) and, where applicable, the development of a Formal Communication Plan. These discussions will be summarized at the conclusion of the meeting and reflected in the FDA meeting minutes.

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; stability updates, the final audited report of a preclinical study (e.g., toxicology) where the final draft report is submitted with the original application, or a limited amount of the data from an assessment of a single transition from the reference product to the proposed biosimilar biological product, where applicable.

ii. Major components of the application (e.g., the complete analytical similarity assessment, the complete study report of a comparative clinical study or the full study report of necessary immunogenicity 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 BPD Type 4 (pre–351(k) BLA) meeting, at the time of original submission of the application. If the applicant does not have a BPD Type 4 (pre–351(k) 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.A.1.a.

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 goal described in Section I.A.1.b 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 substantive review issues identified during the initial filing review to the applicant in the ''Day 74 letter.'' If no substantive review issues were identified during the filing review, FDA will so notify the applicant. FDA's filing review represents a preliminary review of the application and is not indicative of deficiencies that may be identified later in the review cycle.

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 timeline for review of the application included in the Day 74 letter for applications in the Program will include:

a. the planned date for the internal mid-cycle review meeting,

b. preliminary plans on whether to hold an Advisory Committee (AC) meeting to discuss the application,

c. a target date for communication of feedback from the review division to the applicant regarding proposed labeling and any postmarket requirements or postmarket commitments the Agency will be requesting.

4. Review performance goals: For original 351(k) BLA submissions that are filed by FDA under the Program, the BsUFA review clock will begin at the conclusion of the 60 calendar day filing review period that begins on the date of FDA receipt of the original submission. The review performance goals for these applications are as follows:

a. Review and act on 90 percent of original 351(k) BLA submissions within 10 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.

The update should include any significant issues identified by the review team to date, any information requests, and information regarding major concerns with the following:

a. The analytical similarity data, including the potential relevance of any issues (e.g. data analysis issues or potential clinical impact of observed analytical differences), intended to support a demonstration that the proposed biosimilar biological product is highly similar to the reference product.

b. The data intended to support a demonstration of no clinically meaningful differences, including discussion of any immunogenicity issues.

c. The data intended to support a demonstration of interchangeability.

d. CMC issues.

In addition, the update should include preliminary review team thinking regarding the content of the proposed REMS, where applicable, proposed date(s) for the late-cycle meeting, updates regarding plans for the AC meeting (if an AC meeting is anticipated), and other projected milestone dates for the remainder of the review cycle.

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 Advisory Committee (AC) meeting, the following parameters apply:

i. FDA intends to convene AC meetings no later than 2 months prior to the BsUFA goal date. The late-cycle meeting will occur not less than 12 calendar days before the date of the AC meeting.

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

iii. Following an AC meeting, FDA and the applicant may agree on the need to discuss feedback from the committee 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 prior to the BsUFA 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 before the late-cycle meeting. The package will consist of any discipline review (DR) letters issues to date, 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 content of proposed REMS or other risk management actions, where applicable.

e. Late-Cycle Meeting Discussion Topics: Potential topics for discussion at the late-cycle meeting include:

i. major deficiencies identified to date;

ii. analytical similarity data, including the potential relevance of any issues (e.g. data analysis issues or potential clinical impact of observed analytical differences), intended to support a demonstration that the proposed biosimilar biological product is highly similar to the reference product;

iii. data intended to support a demonstration of no clinically meaningful differences, including discussion of any immunogenicity issues;

iv. data intended to support a demonstration of interchangeability;

v. CMC issues;

vi. inspectional findings identified to date;

vii. issues to be discussed at the AC meeting (if planned);

viii. current assessment of the content of proposed REMS or other risk management actions, where applicable;

ix. information requests from the review team to the applicant; and additional data or analyses the applicant may wish to submit.

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 BsUFA goal date.

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

8. Assessment of the Program: The Program described in this Section I.B shall be evaluated to determine its impact on the efficiency and effectiveness of the first review cycle for biosimilar biological products. The assessment shall be conducted by an independent contractor with expertise in assessing the quality and efficiency of biopharmaceutical development and regulatory review programs. The statement of work for this effort will be published for public comment prior to beginning the assessment. The assessments will occur continuously throughout the course of the Program.

Aspects and other measures of the Program that will be assessed by the independent contractor include, but are not limited to the following:

adherence by the applicant and FDA to the current GRMP guidance or the GRMP guidance as updated in accordance with Section I.D, as applicable

completeness and quality of the submitted application

number of unsolicited amendments submitted by the applicant

timing and adequacy of Day 74 letters

conduct of the mid-cycle communication

any DR letters issued

late-cycle meeting background package

conduct of the late-cycle meeting

time to approval

percentage of applications that are approved during the first review cycle

percentage of application reviews that are extended due to a major amendment

number of review cycles for applications that are ultimately approved

time to resubmission for applications that receive a complete response in the first review cycle

This assessment will also include a de-identified analysis of the issues typically discussed during the mid-cycle communication and the late-cycle meeting and the ability of the additional FDA-applicant communications to (a) achieve resolution of these issues during the remainder of the review clock, or (b) allow the applicant to better prepare for a resubmission of the application. Following an FDA regulatory action, the independent contractor will conduct separate interviews of the applicant and the FDA review team to understand each party's perspectives on the review of the application, including whether issues were or should have been identified at the BPD meetings to facilitate application review.

An interim and final assessment of the Program will be published for public comment, with each report followed by a public meeting during which public stakeholders may present their views on the success of the Program to date, including the ability of the Program to help ensure that patients have timely access to safe, effective, and high quality biosimilar biological products. During each public meeting, FDA and the independent contractor will discuss the findings of the interim assessment, including anonymized aggregated feedback from sponsors and FDA review teams resulting from independent contractor interviews. FDA will discuss any issues identified to date including any proposed plans to improve the likelihood of the Program's success.

a. Interim Assessment: An interim assessment of the Program will be published by December 31, 2020, and FDA will hold a public meeting by March 31, 2021.

b. Final Assessment: A final assessment of the Program will be published by June 30, 2022, and FDA will hold a public meeting by September 30, 2022.

C. First Cycle Review Management for Supplements with Clinical Data

1. Notification of Issues Identified during the Filing Review

a. Performance Goal: For supplements with clinical data, FDA will report substantive review issues identified during the initial filing review to the applicant by letter.

b. The timeline for such communication will be within 74 calendar days from the date of FDA receipt of the supplement.

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

d. FDA's filing review represents a preliminary review of the application and is not indicative of deficiencies that may be identified later in the review cycle.

e. FDA will notify the applicant of substantive review issues prior to or on the goal date for 90% of applications.

2. Notification of Planned Review Timelines

a. Performance Goal: For supplements with clinical data, FDA will inform the applicant of the planned timeline for review of the application. The information conveyed will include a target date for communication of feedback from the review division to the applicant regarding proposed labeling, post-marketing requirements, and postmarketing commitments the Agency will be requesting.

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

c. The planned review timelines will be consistent with the GRMP guidance.

d. The planned review timeline will be based on the supplement as submitted.

e. FDA will inform the applicant of the planned review timeline for 90% of all supplements with clinical data.

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

g. To help expedite the development of biosimilar biological products, communication of the deficiencies identified in the supplement may occur through issuance of a DR letter(s) in advance of the planned target date for initiation of discussions regarding labeling, postmarketing requirements, and postmarketing commitments the Agency may request.

f. If the applicant submits a major amendment(s) (refer to Section I.A.5.a for additional information on major amendments) and the review division chooses to review such amendment(s) during that review cycle, the planned review timeline initially communicated (under Section I.C.2.a and b) will generally no longer be applicable. 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 supplement deficiencies and leads toward a first cycle approval when possible.

D. Guidance

FDA and industry share a commitment to ensuring an efficient and effective first cycle review process for all applications subject to the BsUFA program. This commitment is consistent with the principles articulated in the GRMP guidance, which FDA applies to the review of biosimilar and interchangeable products. FDA will update the GRMP guidance during BsUFA II to ensure that it encompasses all review activities for biosimilar and interchangeable products, including principles regarding notification to applicants regarding issues identified during FDA's initial review of the application, principles regarding FDA's notification to applicants regarding planned review timelines, and the importance of internal review timelines that govern aspects of biosimilar and interchangeable product review that are not part of BsUFA performance goals. FDA will publish a revised draft guidance for public comment no later than the end of FY 2018. FDA will work toward the goal of publishing a revised draft or final guidance within 18 months after the close of the public comment period.

E. 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 biosimilar biological product proprietary names during the biosimilar biological product development (BPD) phase and during FDA's review of a marketing application:

1. Proprietary Name Review Performance Goals During The BPD Phase

a. Review 90% of proprietary name submissions filed within 180 days of receipt. Notify sponsor of tentative acceptance or non-acceptance.

b. If the proprietary name is found to be unacceptable, the sponsor can request reconsideration by submitting a written rebuttal with supporting data or request a meeting within 60 days to discuss the initial decision (meeting package required).

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

d. A complete submission is required to begin the review clock.

2. Proprietary Name Review Performance Goals During Application Review

a. Review 90% of biosimilar biological product proprietary name submissions filed within 90 days of receipt. Notify sponsor of tentative acceptance/non-acceptance.

b. A supplemental review will be done meeting the above review performance goals if the proprietary name has been submitted previously (during the BPD phase) and has received tentative acceptance.

c. If the proprietary name is found to be unacceptable, the sponsor can request reconsideration by submitting a written rebuttal with supporting data or request a meeting within 60 days to discuss the initial decision (meeting package required).

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

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

F. Major Dispute Resolution

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

2. Performance goal: 90% of such responses 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).

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

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

G. 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.

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

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 any necessary clinical study or studies to prove biosimilarity and/or interchangeability (e.g., protocols for pharmacokinetics and pharmacodynamics studies, protocols for comparative clinical studies that will form the primary basis for demonstrating that there are no clinically meaningful differences between the proposed biosimilar biological product and the reference product, and protocols for clinical studies intended to support a demonstration of interchangeability). For such protocols to qualify for this comprehensive protocol assessment, the sponsor must have had a BPD Type 2 or 3 Meeting, as defined in section I.I, below, with the review division so that the division is aware of the developmental context in which the protocol is being reviewed and the questions being answered.

d. 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 protocols assessments and agreement requests completed and returned to sponsor within 45 days.

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

I. Meeting Management Goals

Formal BsUFA meetings between sponsors and FDA consist of Biosimilar Initial Advisory and BPD Type 1–4 meetings. These meetings are further described below.

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

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

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

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

A BPD Type 4 Meeting is a pre-submission meeting to discuss the format and content of a complete application for an original biosimilar biological product application under the Program or supplement submitted under 351(k) of the PHS Act. The purpose of this meeting is to discuss the format and content of the planned submission and other items, including identification of those studies that the sponsor is relying on to support a demonstration of biosimilarity or interchangeability, discussion of any potential review issues identified based on the information provided, identification of the status of ongoing or needed studies to adequately to address the Pediatric Research Equity Act (PREA), acquainting FDA reviewers with the general information to be submitted in the marketing application (including technical information), and discussion of the best approach to the presentation and formatting of data in the marketing application.

1. Response 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 and background package. Table 1 below indicates the timeframes for FDA's response to a meeting request.

TABLE 1

Meeting type	Response time (calendar days)
Biosimilar Initial Advisory	21
BPD Type 1	14
BPD Type 2–4	21

For Biosimilar Initial Advisory and BPD Type 2 meetings, the sponsor may request a written response to its questions, rather than a face-to-face meeting, videoconference or teleconference. If a written response is deemed appropriate, FDA will notify the requester of the date it intends to send the written response. This date will be consistent with the timeframes specified in Table 2 below for the specific meeting type.

b. Performance Goal: FDA will respond to meeting requests and provide notification within the response times noted in Table 1 for 90 percent of each meeting type.

2. Scheduling Meetings

a. Procedure: FDA will schedule the meeting on the next available date at which all applicable Center personnel are available to attend, consistent with the component's other business; however, the meeting should be scheduled consistent with the type of meeting requested. Table 2 below indicates the timeframes for FDA to schedule the meeting following receipt of a formal meeting request and background package, or in the case of a written response for Biosimilar Initial Advisory and BPD Type 2 meetings, the timeframes for the Agency to send the written response. If the requested date for any meeting type is greater than the specified timeframe, the meeting date should be within 14 calendar days of the requested date.

TABLE 2

Meeting type	Meeting scheduling or written response time
Biosimilar Initial Advisory.	75 calendar days from receipt of meeting request and background package.
BPD 2	90 calendar days from receipt of meeting request and background package.
Meeting Scheduling Time	
BPD 1	30 calendar days from receipt of meeting request and background package.
BPD 3	120 calendar days from receipt of meeting request and background package.
BPD 4	60 calendar days from receipt of meeting request and background package.

b. Performance goal:

TABLE 3

Meeting type	Goal
BPD Type 2	FY 2018–2019: 80% of meetings are held or written responses are sent within the timeframe. FY 2020–2022: 90% of meetings are held or written responses are sent within the timeframe.
Biosimilar Initial Advisory.	90% of meetings are held or written responses are sent within the timeframe.
BPD Type 1, 3, and 4.	90% of meetings are held within the timeframe for each meeting type.

3. Preliminary Responses

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 face-to-face, videoconference or teleconference meeting date for BPD Type 2 and Type 3 meetings.

b. Performance goal:

TABLE 4

Meeting type	
BPD Type 2	• FY 2018: 70% of preliminary responses to questions are issued by FDA no later than five calendar days before the meeting date. • FY 2019, 75% of preliminary responses to questions are issued by FDA no later than five calendar days before the meeting date. • FY 2020, 80% of preliminary responses to questions are issued by FDA no later than five calendar days before the meeting date. • FY 2021, 85% of preliminary responses to questions are issued by FDA no later than five calendar days before the meeting date. • FY 2022, 90% of preliminary responses to questions are issued by FDA no later than five calendar days before the meeting date.
BPD Type 3	90% of preliminary responses to questions are issued by FDA no later than five calendar days before the meeting date.

4. Meeting Minutes

a. Procedure: The Agency will prepare minutes which will be available to the sponsor 30 calendar days after the meeting. The minutes will clearly outline the important agreements, disagreements, issues for further discussion, and action items from the meeting in bulleted form and need not be in great detail. Meeting minutes are not necessary if the Agency transmits a written response for Biosimilar Initial Advisory and BPD Type 2 meetings.

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

5. Conditions: For a meeting to qualify for these performance goals:

a. A written request and supporting documentation (i.e., the background package) must be submitted to the appropriate review division or office.

b. The request must provide:

i. A brief statement of the purpose of the meeting, the sponsor's proposal for the type of meeting, and the sponsor's proposal for a face-to-face meeting, teleconference, or for a written response (Biosimilar Initial Advisory and BPD Type 2 meetings only);

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

v. A listing of planned external attendees; and

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

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

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

The Center may determine that a different type of meeting (i.e., Biosimilar Initial Advisory, or BPD Type 1–4) is more appropriate and it may grant a meeting of a different type than requested, which may require the payment of a biosimilar biological product development fee as described in section 744H of the Federal Food, Drug, and Cosmetic Act before the meeting will be provided. If a biosimilar biological product development fee is required under section 744H, and the sponsor does not pay the fee within the time frame required under section 744H, the meeting will be cancelled. If the sponsor pays the biosimilar biological product development fee after the meeting has been cancelled due to non-payment, the time frame described in

section I.I.1.a will be calculated from the date on which FDA received the payment, not the date on which the sponsor originally submitted the meeting request.

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

6. Guidance

a. FDA will publish revised draft guidance on Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants no later than September 30, 2018.

b. FDA will update the current draft or final guidance on Best Practices for Communication Between IND Sponsors and FDA During Drug Development, as appropriate, to apply to communications between IND sponsors and FDA during biosimilar biological product development. FDA will publish a revised draft or final guidance by December 31, 2018.

II. ADVANCING DEVELOPMENT OF BIOSIMILAR BIOLOGICAL PRODUCTS THROUGH FURTHER CLARIFICATION OF THE 351(K) REGULATORY PATHWAY

A. On or before December 31, 2017, FDA will publish draft guidance describing considerations in demonstrating interchangeability with a reference product. FDA will work toward the goal of publishing a revised draft or final guidance within 24 months after the close of the public comment period.

B. On or before December 31, 2017, FDA will publish draft guidance describing statistical considerations for the analysis of analytic similarity data intended to support a demonstration of ''highly similar'' for biosimilar biological products. FDA will work toward the goal of publishing a revised draft or final guidance within 18 months after the close of the public comment period.

C. On or before March 31, 2019, FDA will publish draft guidance describing processes and further considerations related to postapproval manufacturing changes for biosimilar biological products. FDA will work toward the goal of publishing a revised draft or final guidance within 18 months after the close of the public comment period.

D. FDA will work towards the goal of publishing revised draft guidance or final guidance documents on or before May 31, 2019 for draft guidances published between January 1, 2014 and September 30, 2017, other than those described in (II.A–C). These draft guidances will include:

1. Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (draft guidance published in May 2014)

2. Nonproprietary Naming of Biological Products (draft guidance published in August 2015)

3. Labeling for Biosimilar Biological Products (draft guidance published in March 2016)

III. ENHANCING CAPACITY FOR BIOSIMILAR REGULATIONS AND GUIDANCE DEVELOPMENT, REVIEWER TRAINING, AND TIMELY COMMUNICATION

A. FDA will strengthen the staff capacity to develop new regulations and guidance to clarify scientific criteria for biosimilar development and approval to provide certainty to industry and other stakeholders related to key regulatory issues including the scope of eligible biosimilar biological products.

B. FDA will strengthen staff capacity to develop or revise MaPPs, SOPPs, and review templates to facilitate rapid update and application of new policies and guidance by review staff, and to develop and deliver timely comprehensive training to all CDER and CBER review staff and special government employees involved in the review of 351(k) BLAs.

C. FDA will strengthen staff capacity to deliver timely information to the public to improve public understanding of biosimilarity and interchangeability.

D. FDA will strengthen staff capacity to deliver information concerning the date of first licensure and the reference product exclusivity expiry date, to be included in the Purple Book.

FDA will update the Purple Book to include the following information: the BLA number, product name, proprietary name, date of licensure, interchangeable or biosimilar determination, and whether the BLA has been withdrawn. FDA will update this information in the Purple Book within 30 days after approval or withdrawal. In addition, within 30 days after FDA determines the date of first licensure, the date of first licensure and the reference product exclusivity expiry date will be included in the Purple Book.

IV. ENHANCING MANAGEMENT OF USER FEE RESOURCES

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

A. Resource Capacity Planning and Modernized Time Reporting

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

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

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

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

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

B. Financial Transparency and Efficiency

FDA is committed to ensuring BsUFA user fee resources are administered, allocated, and reported in an efficient and transparent manner. FDA will conduct activities to evaluate the financial administration of the BsUFA program to help identify areas to enhance efficiency. FDA will also conduct activities to enhance transparency of BsUFA program resources.

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

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

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

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

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

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

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

C. Management of Carryover Balance

FDA is committed to reducing the carryover balance to no greater than 21 weeks of the FY 2022 target revenue by the end of FY 2022. However, if FDA is unable to reduce the carryover balance to no greater than 21 weeks during the final year (e.g., over collections in FY 2022 that increase the carryover balance beyond 21 weeks), FDA will (1) outline its plan to reduce the carryover balance to no greater than 21 weeks in the FY 2022 BsUFA financial report and (2) update the BsUFA five-year financial plan.

V. IMPROVING FDA HIRING AND RETENTION OF REVIEW STAFF

To speed and improve development of safe and effective biosimilar biological products

for patients, enhancements to the biosimilar biological review program require that FDA hire and retain sufficient numbers and types of technical and scientific experts to efficiently conduct reviews of 351(k) applications. In order to strengthen this core function and increase public access to biosimilar biological products, the FDA will commit to do the following:

A. Completion of Modernization of the Hiring System Infrastructure and Augmentation of System Capacity

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

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

b. FDA will complete implementation of the new position-based management system.

2. Complete implementation of an online position classification system

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

3. Complete implementation of corporate recruiting

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

B. Augmentation of Hiring Staff Capacity and Capability

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

C. Complete Establishment of a Dedicated Function to Ensure Needed Scientific Staffing for Human Drug Review Including for Review of Biosimilar Biological Products

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

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

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

D. Set Clear Goals for Biosimilar Biological Product Review Program Hiring

1. FDA will establish priorities for management of the metric goals for targeted hires within the biosimilar biological product review program staff for BsUFA II. In particular, FDA will target hiring 15 FTE in FY 2018, to enhance capacity for biosimilar guidance development, reviewer training, and timely communication.

2. FDA will confirm progress in the hiring of BsUFA I FTEs. FDA will report on progress against the hiring goal for BsUFA II on a quarterly basis posting updates to the FDA website BsUFA Performance webpage.

E. Comprehensive and Continuous Assessment of Hiring and Retention

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

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

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

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

V. DEFINITIONS AND EXPLANATION OF TERMS

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

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

ARMS SALES NOTIFICATION

Mr. CORKER. Mr. President, section 36(b) of the Arms Export Control Act requires that Congress receive prior notification of certain proposed arms sales as defined by that statute. Upon such notification, the Congress has 30 calendar days during which the sale may be reviewed. The provision stipulates that, in the Senate, the notification of proposed sales shall be sent to the chairman of the Senate Foreign Relations Committee.

In keeping with the committee's intention to see that relevant information is available to the full Senate, I ask unanimous consent to have in the RECORD the notifications which have been received. If the cover letter references a classified annex, then such annex is available to all Senators in the office of the Foreign Relations Committee, room SD–423.

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

DEFENSE SECURITY COOPERATION AGENCY,
Arlington, VA.

Hon. BOB CORKER,
Chairman, Committee on Foreign Relations, U.S. Senate, Washington, DC.

DEAR MR. CHAIRMAN: Pursuant to the reporting requirements of Section 36(b)(1) of the Arms Export Control Act, as amended, we are forwarding herewith Transmittal No. 17–38, concerning the Navy's proposed Letter(s) of Offer and Acceptance to the Government of Australia for defense articles and