Assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs in PDUFA V

Final Report: ***10/1/2012 – 6/30/2016***

PREPARED BY:

Eastern Research Group, Inc.
110 Hartwell Avenue
Lexington, MA 02420

November 18, 2016

Table of Contents

Tables

Figures

Executive Summary

Timely review of the safety and effectiveness of new drugs and biologics is central to the Food and Drug Administration's (FDA's) mission to protect and promote public health. Since passage of the Prescription Drug User Fee Act (PDUFA) in 1992, FDA has reviewed and taken regulatory action on New Drug Applications (NDAs) and Biologics License Applications (BLAs) in shorter and more predictable timeframes. With the fifth authorization of PDUFA, FDA endeavored to make further progress by instituting a new review model for New Molecular Entity (NME) NDAs and original BLAs that promoted enhanced communication and predictability between FDA and applicants – with the aim of improving the effectiveness and efficiency of the review. This review model is known as the "Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs" or "the Program".[1]

FDA enlisted a contractor, Eastern Research Group, Inc. (ERG), to conduct an independent assessment of the Program. In March 2015, ERG prepared an Interim Report to provide initial data about Program implementation and outcomes during the first two Fiscal Years (FYs) of PDUFA V: October 1, 2012 to September 30, 2014. This Final Report provides results of the Program after nearly four years: October 1, 2012 to June 30, 2016. The data encompass NME NDAs and original BLAs[2] that were submitted and received a first-cycle action (Approval [AP], Complete Response [CR], or Withdrawal after Filing [WD]) during this time. Baseline data encompasses NME NDAs and original BLAs that were submitted during PDUFA IV (FYs 2008-2012) and received a first-cycle action by June 30, 2016. ERG collected data for this study from FDA databases, direct observations, primary documentation, and post-action interviews with Program applicants and FDA review teams.

Table ES-1 provides an overview of applications included in this final assessment of the Program.

[1] FDA's decision about whether an application is included in the Program is separate from its determination of whether the drug product contains a "new chemical entity," as defined under 21 Code of Federal Regulations (CFR) 314.108(a). Determinations about new chemical entity exclusivity are made at the time of application approval.

[2] FDA decides at filing whether an application represents an NME NDA or original BLA and whether it will be reviewed in the Program. Sometimes an application loses its NME status during the review (e.g., if a drug containing the same active moiety is approved first), but the application remains in the Program. This evaluation includes all applications reviewed in the Program, including those that lost their NME status. For consistency, the baseline cohort also includes all applications considered NME NDAs or original BLAs at filing, including those that later lost their NME status.

Table ES-1. Applications in the baseline and Program cohorts for this study*

Applications		Baseline	Program
Filed and acted upon	NME NDA	147	109
	Original BLA	72	62
	Total	219	171
First-cycle actions	Approval (AP)	120	136
	Complete Response (CR)	92	29
	Withdrawal after Filing (WD)	7	6
	Total	219	171
Second-cycle actions	Approval (AP)	48	8
	Complete Response (CR)	15	1
	Withdrawal after Filing (WD)	1	0
	Total	64	9
First-cycle approval rate		54.8%	79.5%
Second-cycle approval rate**		75.0%**	88.9%**
Overall approval rate**		82.6%**	84.2%**
Average number of review cycles to approval**		1.42**	1.10**

** NME NDAs and original BLAs received during FYs 2008-2012 and acted on by June 30, 2016 (baseline) or received and acted on from October 1, 2012 to June 30, 2016 (Program).*

*** Baseline applications (from PDUFA IV) have had at least 4 years to be resubmitted and acted on, while Program applications are still being submitted and reviewed. Therefore, second-cycle approval rates, overall approval rates, and number of review cycles to approval cannot reasonably be compared. Over the next few years, additional Program applications with a first-cycle CR will be resubmitted and acted upon, changing approval rate and number of review cycles to approval; only then will it be reasonable to compare values for these measures.*

Changes Since the Interim Report

This Final Report contains a larger set of Program data (applications received and acted on from October 1, 2012 to June 30, 2016) compared to the interim report (applications received and acted in in FYs 2013-2014). The baseline cohort (applications received during PDUFA IV and acted on by June 30, 2016) remains the same. With the larger set of Program data, ERG developed updated results as well as some statistical analyses that were not possible with the smaller set of data available for the Interim Report. Our conclusions remain largely consistent with those described in the Interim Report, reinforcing the results and findings previously reported. The main differences in this Final Report are:

- The first-cycle approval rate in the Program is even higher than previously reported. With the greater number of applications available for analysis and the higher first-cycle approval rate, the difference compared to the baseline is now statistically significant for Standard applications as well as for Priority applications and applications overall. In the Interim Report, the higher first-

cycle approval rate in the Program compared to the baseline was statistically significant for applications overall and Priority applications but not for Standard applications.

- Data are included for resubmitted applications, second-cycle approval rates, overall approval rates, and time to approval. The number of resubmitted applications in the Program is small because (1) the high first-cycle approval rate means that relatively few applications received a CR and are eligible for resubmission, and (2) not enough time has elapsed for many of the applications that received a CR in the first review cycle to be resubmitted. Because the number of resubmitted applications is small (11 resubmissions, 9 with second-cycle actions as of June 30, 2016), ERG presents data on resubmissions but draws no conclusions from the data.
- Three findings and recommendations were removed (see Findings and Recommendations section below). After the interim assessment, FDA took action to address the findings, so they no longer reach a threshold for inclusion in the final assessment.

Answers to Evaluation Questions

Using the data collected on NME NDAs and original BLAs received and acted on from October 1, 2012 to June 30, 2016, ERG answered a set of evaluation questions for this final report. These questions and answers appear below. These results are largely consistent with those presented in the Interim Report for this evaluation.

1a. What is the relationship between Program attributes and NME NDA/original BLA first-cycle regulatory outcomes?

A central goal of the Program is to improve the effectiveness and efficiency of the first cycle of review for NME NDAs and original BLAs, thereby increasing the likelihood of first-cycle approval for applications of sufficient quality to warrant approval. For applications with substantive but resolvable issues, for example, effective and efficient reviews enable FDA and applicants to resolve the issues in time for approval within the first review cycle. Thus, first-cycle approval rate is one measure of review effectiveness and efficiency.[3]

The first-cycle approval rate was higher in the Program than in the baseline, an effect that was statistically significant. These findings suggest that the Program has created conditions that enhance the ability of applicants and FDA reviewers to work toward application approval in the first review cycle. This appeared to be especially true for applications with substantive but resolvable issues. Overall, applicants viewed the Program as having value (enhanced review transparency, communication, predictability, efficiency) regardless of whether their applications were approved.

Another measure of review effectiveness and efficiency is the number of review cycles to reach approval. As of June 30, 2016, 11 applications receiving a first-cycle CR were resubmitted to FDA and 9

[3] First-cycle approval rate alone cannot be used to judge review effectiveness and efficiency because FDA has no control over the quality of applications received. First-cycle approval rate can only be as high as the percent of applications received that are of sufficient quality to be approved in the first review cycle.

received a second-cycle action. As explained in the footnote to Table ES-1, this number is insufficient to detect a statistically significant difference in the number of review cycles required to achieve approval in the Program compared to the baseline.

1b. What is the relationship between Program attributes and time to NME NDA/original BLA first-cycle regulatory outcomes?

As expected given the 2-month difference in review clocks, first-cycle reviews for Program applications were statistically significantly longer than those for baseline applications. Nevertheless, as noted above, quantitative and qualitative findings suggest that the Program has created conditions that enhance the ability of applicants and FDA reviewers to work toward application approval in the first review cycle. Overall, applicants viewed the Program as having value (enhanced review transparency, communication, predictability, efficiency) regardless of the time to first-cycle approval for their applications.

2a. What is the relationship between review process attributes and NME NDA/original BLA first-cycle regulatory outcomes?

Most review process attributes showed no statistically significant relationship with first-cycle approval rate. The main exception was time from application submission to primary review completion; longer-than-average primary review completion time was associated with a lower first-cycle approval rate, possibly due to a disproportionate number of challenging applications and/or less time remaining in the review clock to address any identified deficiencies. Conversely, with Program applications that address a compelling public health need—and lack major clinical/efficacy deficiencies—FDA review teams often aimed for early action (and thus early resolution of issues and early completion of primary reviews). Program applications with a major amendment were also correlated with a higher first-cycle approval rate than those without a major amendment. This finding aligns with the expectation that extending the goal date to review a major amendment should lead to approval in the first cycle rather than requiring resubmission and a second cycle of review.

2b. What is the relationship between review process attributes and time to NME NDA/original BLA first-cycle regulatory outcomes?

Two review process attributes were associated with a longer mean time from application submission to first-cycle approval:

- *A longer-than-average time from application submission to primary review completion.* Later primary review completion times, sometimes due to the desire to incorporate Advisory Committee (AC) feedback into the review, might lead to later identification of issues, with late attempts at resolving those issues potentially requiring use of the entire review clock.
- *Major amendment that triggered a goal extension.* A 3-month goal extension will clearly result in a longer mean time from application submission to first-cycle approval.

3a. What is the relationship between application attributes and NME NDA/original BLA first-cycle regulatory outcomes?

In general, Program applications for drugs/biologics indicated for areas of unmet medical need were associated with a higher first-cycle approval rate than other Program applications. For example, Priority applications correlated with a statistically significantly higher first-cycle approval rate than Standard applications. In addition, applications with Rolling Review, Breakthrough Therapy designation, Orphan Drug designation, Fast Track designation, and certain therapeutic categories were associated with higher first-cycle approval rates than those without these attributes, but the differences were not statistically significant or could not be assessed statistically due to small numbers.

3b. What is the relationship between application attributes and time to NME NDA/original BLA first-cycle regulatory outcomes?

As expected, given the 4-month difference in review clocks, Priority applications in the Program were correlated with a statistically significantly shorter mean time to first-cycle approval than Standard applications in the Program. The overall review clock is 2 months longer in the Program than it was in the baseline, so it is also unsurprising that mean time to first-cycle approval was significantly longer for Priority applications in the Program than in the baseline—but the difference was less than the 2-month difference in review clocks. ERG found no other statistically significant relationships between application attributes and time to first-cycle regulatory outcome.

4a. How do applicants and FDA review staff characterize enhanced communication under the Program?

Program applicant feedback was overwhelmingly positive. A large majority of interviewees (including those receiving a CR as well as those receiving an Approval) characterized communication under the Program as follows:

- Communication was excellent, very constructive, with a spirit of cooperation.
- New Program milestone communications were valuable, facilitating a more holistic discussion of the application, broader FDA input (both horizontally and vertically), greater understanding of each party's perspectives, and more efficient resolution of questions and issues.
- Regulatory Project Managers (RPMs) and other FDA review team members were responsive, constructive, and flexible—even better than before the Program.
- 21st Century Review Process Desk Reference Guide was an invaluable resource for understanding the review process, expectations, and timelines in the Program.
- Communication was less clear/frequent regarding the status and results of inspections.

FDA review staff feedback on enhanced communication under the Program varied, with a few at either extreme and many in a middle range. Many but not all review staff:

- Affirmed that Program elements contributed to enhanced communication. (Some believed that the Program offered no additional value to already excellent communication practices within their review division.)
- Believed that the new Program communications added value by ensuring that FDA staff bring together all of their inputs to consider the application as a whole, prioritize issues, plan for review milestones, involve leadership, and review the status of the overall application with the applicant.

Most FDA reviewers believed that the new Program communications imposed an additional workload on staff but that this additional burden was manageable. Some reviewers expressed concern that any additional new burdens might introduce a risk of missed deadlines or affect the thoroughness of reviews.

4b. How do applicants and FDA review staff characterize application reviews under the Program?

Again, Program applicant feedback was overwhelmingly positive. Most characterized reviews in the Program as very transparent, predictable, and efficient.

Like applicants, most FDA review staff characterized application reviews in the Program as transparent and predictable. Many reviewers suggested that the Program might be most beneficial for applications that require substantive discussion and issue resolution throughout the review.

Nearly all FDA review staff agreed that the new Program communications imposed an additional workload/burden/pressure on staff, including additional time required for scheduling, preparing for, conducting, and documenting meetings and preparing the LCM background package. Reviewers frequently commented that to date Program implementation has not been resource-neutral. Most reviewers believed that the additional burden was manageable.

Findings and Recommendations

Based on data collected for Program applications received and acted on between October 1, 2012 and June 30, 2016, ERG developed a set of findings and recommendations (Table ES-2) organized in two categories: overarching (related to the Program overall) and specific (related to particular aspects of the Program or review process).

In the Interim Report, the interim findings and recommendations were based on data from the first two years of the Program. In 2014, FDA implemented refined guidelines to address some of the issues raised. Assessment data collected since then suggest that these aspects of the Program are running smoothly and no longer belong in the findings and recommendations for this Final Report:

- ***Mid-Cycle Communication (MCC) procedures.*** In the Interim Report, ERG observed that MCCs were most efficient and productive when FDA (1) selected FDA attendees based on anticipated need rather than including the entire review team, (2) provided applicants with an informal (telephone, email) “heads-up” about meeting topics, and (3) permitted two-way communication

to clarify questions. These practices have become nearly universal in the Program, and feedback has been positive.

- ***Early involvement of signatory authority.*** Early involvement of the signatory authority can help ensure that all parties at FDA are knowledgeable about the application and can foster early agreement, thereby facilitating timely labeling decisions and avoiding late surprises if the review Office identifies concerns that the review Division did not. FDA has reminded review Offices and Divisions that early involvement of the signatory authority is a Program expectation, and this practice has become more consistent.

- ***Flexibility for expedited reviews.*** Early in the Program, a few reviewers expressed concern that implementation of Program milestone communications might hamper FDA's ability to approve certain Priority applications as early as desired—particularly when the reviewers are working toward early action to help address unmet medical needs for serious diseases and already have well-established practices for open, "real-time" communication with applicants. In September 2014, FDA responded with refined guidelines[4] providing greater flexibility for applications receiving expedited review (defined as a review where FDA anticipates acting at least one month before the PDUFA goal date and communicates this anticipation in the filing letter).

[4] CDER 21st Century Review Process Desk Reference Guide: http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM218757.pdf

Table ES-2. Findings and recommendations based on Program data from October 1, 2012 to June 30, 2016

Type	No.	Finding	Recommendation(s)
Overarching	O1	Overall, the Program has been successful in enhancing review transparency and communication.	No action needed.
	O2	Overall, new Program milestone communications (mid-cycle communications [MCCs] and late-cycle meetings [LCMs]) have enhanced the predictability of reviews by: • Serving as "anchor" points for applicant and FDA planning and work. • Providing a forum for holistic, multi-disciplinary discussion of application status and paths forward to resolve approvability issues promptly, if possible.	No action needed.
	O3	By providing more opportunity to identify, discuss, and resolve substantive issues during the review, the Program has created conditions that enhance the ability of applicants and FDA reviewers to work toward application approval in the first review cycle where possible. This is especially true for applications with substantive but resolvable issues where the full review clock is needed.	No action needed.
	O4	Program implementation has not been resource-neutral as assumed during PDUFA V negotiations. Implementation of new Program milestone communications has increased the burden on FDA's primary reviewers and RPMs, diverting effort from review work to meeting preparation and sometimes resulting in a need for additional primary review addenda (to document additional work after primary review completion). FDA review teams have been able to manage this burden, but have noted that any additional new burdens might in some cases introduce a risk of missed deadlines or compromise the thoroughness of reviews.	If/when new review process requirements are added as part of a new authorization of the PDUFA Program, analyze the associated burden to determine whether additional staff or other resources will be needed to maintain the timeliness and thoroughness of reviews.
Specific	S1	Regardless of sponsor size and experience, many sponsors need more information on the format and structure of an application to meet FDA expectations by review division/team and indication/therapeutic area. To meet this need, sponsors sometimes request an additional Type C meeting many months prior to a data-oriented pre-submission meeting (PSM). Some FDA review teams believe that existing guidelines should be sufficient and that holding an earlier meeting without data is premature.	Evaluate efficient options for when and how to communicate information about the format and structure of applications by therapeutic area or division. Options could include but are not limited to internal reviewer aids and increased use of Type C Written Responses Only (WRO).

Type	No.	Finding	Recommendation(s)
	S2	For some Priority applications where early action is expected / desired, holding an Application Orientation Meeting within a month or so after submission has helped (1) acquaint FDA disciplines with application datasets and (2) establish early communication between applicants and FDA about review expectations and perspectives.	Consider the value of providing information about Application Orientation Meetings to FDA review teams, along with the option to conduct such meetings at the review team's discretion (e.g., for certain Priority / Breakthrough Therapy / expedited review applications).* **FDA is proposing this option for PDUFA VI.*
	S3	Given the high volume of information requests, providing target dates for responses is a good practice. Applicants would also benefit from receiving confirmation that their responses are complete.	First, adopt inclusion of target dates for information request responses as a good practice. Second, develop a simple optional approach for tracking information requests and amendments that can be shared between review teams and applicants.
	S4	Providing explanations/rationales for proposed label changes is a good practice for applicants and FDA review teams. This practice has helped both parties understand the others' reasoning, enabling them to respond effectively – which then reduces the amount of back-and-forth required and the time required to complete negotiations.	Include explanations/rationales for proposed label changes (either in written form or by telephone) as a good practice.
	S5	Inconsistent availability/communication of information about the status and results of inspections has hindered review transparency and predictability, both internally at FDA and between FDA and applicants.* **In January 2015, FDA launched the CDER Office of Pharmaceutical Quality (OPQ) to consolidate product quality activities into a unified office. Comments about inspection transparency have not changed since that time.*	Examine inspection information flows and communication channels, with the aim of identifying improvements. **FDA is undertaking such an examination.*

1. Introduction

1.1 The Program

Timely review of the safety and effectiveness of new drugs and biologics is central to the Food and Drug Administration's (FDA's) mission to protect and promote public health. Prior to enactment of the Prescription Drug User Fee Act (PDUFA) in 1992, FDA's drug review process was relatively slow and not very predictable. As a result of concerns expressed by both industry and patients at the time, Congress enacted PDUFA, which provided the added funds through user fees that enabled FDA to hire additional reviewers and support staff and upgrade its information technology systems. In return for additional resources, FDA agreed to certain review performance goals, such as completing reviews of New Drug Applications (NDAs) and Biologics License Applications (BLAs) and taking regulatory actions on them in predictable timeframes. These changes revolutionized the drug review process in the United States and enabled FDA to speed the review of new drug and biologics applications without compromising the Agency's high standards for demonstration of safety, efficacy, and quality prior to approval.

The original authorization of PDUFA in 1992 was for a five-year term. Since then, it has been reauthorized every five years. PDUFA was authorized for the fifth time, for Fiscal Years (FYs) 2013-2017, with the passage of the FDA Safety and Innovation Act (FDASIA) in July 2012. With PDUFA V came a new review model (known as the "Program") for New Molecular Entity (NME) NDAs and original BLAs[5] to promote greater review transparency and improve communication between FDA and applicants. To that end, FDA built in a variety of review practices and milestone communications with applicants; keystone additions include a Mid-Cycle Communication (MCC) and Late-Cycle Meeting (LCM) between FDA and applicants. To accommodate this increased interaction during regulatory review and to address the need for additional time to review these complex applications, FDA's review clock begins after the 60-day administrative filing review period. The Program applies to all NME NDAs and original BLAs[6] received from October 1, 2012, through September 30, 2017,[7] including applications resubmitted after Refuse to File (RTF) actions. Applications filed over protest are not reviewed in the Program.

The goals of the Program are to increase the efficiency and effectiveness of the first review cycle and decrease the number of review cycles necessary for approval of NME NDAs and original BLAs where warranted so that patients have timely access to safe, effective, and high quality new drugs and biologics. For additional information about the Program, please see FDA's "Commitment Letter."[8] Appendix A provides a list of acronyms and glossary of terms.

---

[5] FDA's decision about whether an application is included in the Program is separate from its determination of whether the drug product contains a "new chemical entity," as defined under 21 Code of Federal Regulations (CFR) 314.108(a). Determinations about new chemical entity exclusivity are made at the time of application approval.

[6] Including those submitted to FDA's Center for Biologics Evaluation and Research (CBER) and those submitted to FDA's Center for Drug Evaluation and Research (CDER).

[7] FDA decides at filing whether an application represents an NME NDA or original BLA and whether it will be reviewed in the Program. Sometimes an application loses its NME status during the review (e.g., if a drug containing the same active moiety is approved first), but the application remains in the Program. This evaluation includes all applications reviewed in the Program, including those that later lost their NME status. For consistency, the baseline cohort also includes all applications considered an NME NDA or original BLA at filing, including those that later lost their NME status.

[8] *http://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm270412.pdf*

1.2 Program Assessment

FDA enlisted Eastern Research Group, Inc. (ERG) to conduct an independent assessment of the Program to determine its impact on the efficiency and effectiveness of NME NDA and original BLA reviews. Specifically, FDA asked ERG to:

- Using information from FDA's corporate databases, construct and analyze a baseline data set of NME NDAs and original BLAs received and acted on prior to implementation of the Program (i.e., during PDUFA IV, FYs 2008-2012) to assess the impact on the key evaluation measures for applications reviewed under the Program.
- Using information from FDA's databases as well as other databases (e.g., database or other tracking mechanism developed by contractor), collect and analyze data on all NME NDA and original BLAs reviewed under the Program.
- Determine the nature of relationships between attributes of the Program and the regulatory outcome and its timing in the first review cycle.
- Determine the nature of relationships between other attributes of the review process and applications that are reviewed under the Program and the timing of the regulatory outcome in the first review cycle.
- Collect and analyze applicant and FDA review staff feedback on applications reviewed under the Program, including any best practices, key concerns, or challenges with regard to the enhanced communication and review of these applications.

ERG translated these tasks into a set of specific questions to be answered by the independent assessment (see text box).

Program Assessment Questions

1a. What is the relationship between reviews with Program attributes and NME NDA/original BLA first-cycle regulatory outcome?

1b. What is the relationship between reviews with Program attributes and time to NME NDA/original BLA first-cycle regulatory outcome?

2a. What is the relationship between review process attributes and NME NDA/original BLA first-cycle regulatory outcome?

2b. What is the relationship between review process attributes and time to NME NDA/original BLA first-cycle regulatory outcome?

3a. What is the relationship between application attributes and NME NDA/original BLA first-cycle regulatory outcome?

3b. What is the relationship between application attributes and time to NME NDA/original BLA first-cycle regulatory outcome?

4a. How do applicants and FDA review staff characterize enhanced communication under the Program?

4b. How do applicants and FDA review staff characterize application reviews under the Program?

For the assessment of the Program, ERG analyzed and reported on results as follows:

- **Baseline analysis report** to FDA
  Counts of baseline (PDUFA IV, FYs 2008-2012) activities and results from applications with at least a first-cycle action by September 30, 2014.
- **Quarterly reports** to FDA
  Counts of Program activities and results from Program applications with at least a first-cycle action by the end of each quarter during PDUFA V.
- **Interim report** published in *Federal Register*[9]
  Initial results from Program applications with at least a first-cycle action by September 30, 2014, with comparisons to the baseline cohort.
- **Final report** (this document) for publication in *Federal Register* and public comment
  Results from Program applications with at least a first-cycle action by June 30, 2016, with comparisons to the baseline cohort.

1.3 This Report

This Final Report includes findings based on an analysis of Program applications that received a first-cycle action from October 1, 2012 to June 30, 2016, as well as a comparison of Program data with data from a baseline cohort, defined as NME NDAs and original BLAs submitted during PDUFA IV (October 1, 2007 to September 30, 2012) that received at least a first-cycle action by June 30, 2016.

[9] Assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs in PDUFA V. Eastern Research Group, Inc. March 27, 2015.
http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM436448.pdf

2. Methods

ERG used a systematic process to identify, collect, and analyze comprehensive data for the Program assessment. This process involved five key steps:

1. Develop evaluation metrics
2. Develop evaluation protocols and instruments
3. Collect data
4. Analyze data
5. Develop findings and recommendations

ERG collected two datasets: one for the baseline cohort (PDUFA IV) and one for the Program (PDUFA V). For the baseline cohort, ERG did not collect data for Program-specific attributes (such as MCCs and LCMs) that did not exist in PDUFA IV.

2.1 Evaluation Metrics

ERG began by establishing a set of objective, measurable evaluation metrics that are directly related to the elements of the Commitment Letter underpinning FDA's Program for review of NME NDAs and original BLAs in PDUFA V. The evaluation metrics address Program, review process, and application attributes, categorized as follows:

- Regulatory outcomes
- Pre-submission meetings (PSMs)
- Original application information
- Filing letters
- Mid-cycle communications (MCCs)
- Discipline Review (DR) letters
- Late-cycle meetings (LCMs) / Advisory Committee (AC) meetings

Please see Appendix B for a complete list of evaluation metrics.

2.2 Evaluation Protocols and Instruments

The evaluation metrics establish a structure for data that need to be collected to generate results. Accordingly, ERG prepared evaluation protocols and instruments for collecting needed data (see Table 2-1). Appendix C provides a copy of these protocols and instruments.

Table 2-1. Evaluation protocols and instruments

Protocol	Associated Instruments
Evaluation of FDA-applicant interactions	Pre-Submission Meeting Evaluation Instrument Mid-Cycle Communication Evaluation Instrument Late-Cycle Meeting Evaluation Instrument
Evaluation of FDA-applicant communications	Filing Letter Evaluation Instrument Discipline Review Letter Evaluation Instrument
Evaluation of applications	Original Application Evaluation Instrument
Post-action interviews	Post-Action Interview Script: FDA Post-Action Interview Script: Applicant

In general, these evaluation protocols and instruments required ERG to collect information via direct observations, extraction of data from FDA databases, and examination of documentation. The post-action interviews entailed collection of information from non-federal employees (applicants), necessitating clearance from the Office of Management and Budget under the Paperwork Reduction Act. The OMB control number for the information collection is 0910-0746 and the approved interview protocol and instrument are available in Appendix C.

2.3 Data Collection

ERG collected all data, both qualitative and quantitative, in accordance with the procedures specified in our evaluation protocols and instruments. ERG entered data into a Program Evaluation Tracking Tool (PETT) that we developed to store raw data and compute metrics values based on the raw data. We developed a data collection Standard Operating Procedure (SOP) to specify the data fields and formulae used to calculate metrics values.[10]

2.4 Data Analysis

The data collected served as a foundation for analysis in order to generate meaningful information with which to answer the assessment questions. ERG performed three types of data analysis:

- **Descriptive analysis—**to describe the information collected about the Program and outcomes.

  ERG collected large volumes of data with details about the Program and baseline cohorts. To summarize and interpret these data sets, ERG developed descriptive data that highlight main features and themes.

- **Statistical analysis—**to identify statistical correlations between Program attributes and outcomes where possible.

[10] Assessment of the Program for Enhanced Communication and Review Transparency for NME NDAs and Original BLAs in PDUFA V—Standard Operating Procedure: Data Collection. Eastern Research Group, Inc. Last updated October 31, 2016.

ERG built statistical models to analyze the quantitative data we collected in order to identify any statistically significant correlations between Program attributes and outcomes, and between the Program and the baseline cohort. Appendix D provides a copy of the statistical framework that served as a guide for the statistical analysis.

- **Qualitative analysis—**to gain insights into Program implementation and applicant and FDA review team opinions, in order to help explain and supplement quantitative results.

  ERG collected and organized unstructured and semi-structured data from observations of Program milestone communications and post-action interviews with Program applicants and FDA review teams. We explored these data to identify common themes and topics, imported the data into NVivo (a qualitative analysis software tool), coded the data, and queried the data to generate a set of qualitative analysis results.

2.5 Findings and Recommendations

Based on the analyses described above, ERG developed cohesive, integrated answers to the assessment questions. ERG then distilled all results into a set of findings and recommendations.

3. Results

This introduction to Section 3 provides:

- An overview of the Program and baseline applications included in this assessment.
- Definitions for key terms that will appear throughout Section 3.
- A list of categories of results discussed in the remainder of Section 3.

Overview of Program and Baseline Applications

This Final Report provides data on the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs in PDUFA V—specifically, Program implementation and outcomes from October 1, 2012 to June 30, 2016. The data encompass NME NDAs and original BLAs that FDA received and acted on during this time.[11] Baseline data encompass NME NDAs and original BLAs received during PDUFA IV (FYs 2008-2012) and acted on by June 30, 2016. Table 3-1 presents a summary of these applications, and Table 3-2 shows their distribution by fiscal year of receipt.

Table 3-1. Applications in the baseline and Program cohorts for this study*

Applications		Baseline	Program
Filed and acted upon	NME NDA	147	109
	Original BLA	72	62
	Total	219	171
First-cycle actions	Approval (AP)	120	136
	Complete Response (CR)	92	29
	Withdrawal after Filing (WD)	7	6
	Total	219	171
Percent of filed applications approved in first cycle		54.8%	79.5%

** NME NDAs and original BLAs received during FYs 2008-2012 and acted on by June 30, 2016 (baseline) or received and acted on from October 1, 2012 to June 30, 2016 (Program).*

Table 3-2. Counts of baseline and Program applications by fiscal year*

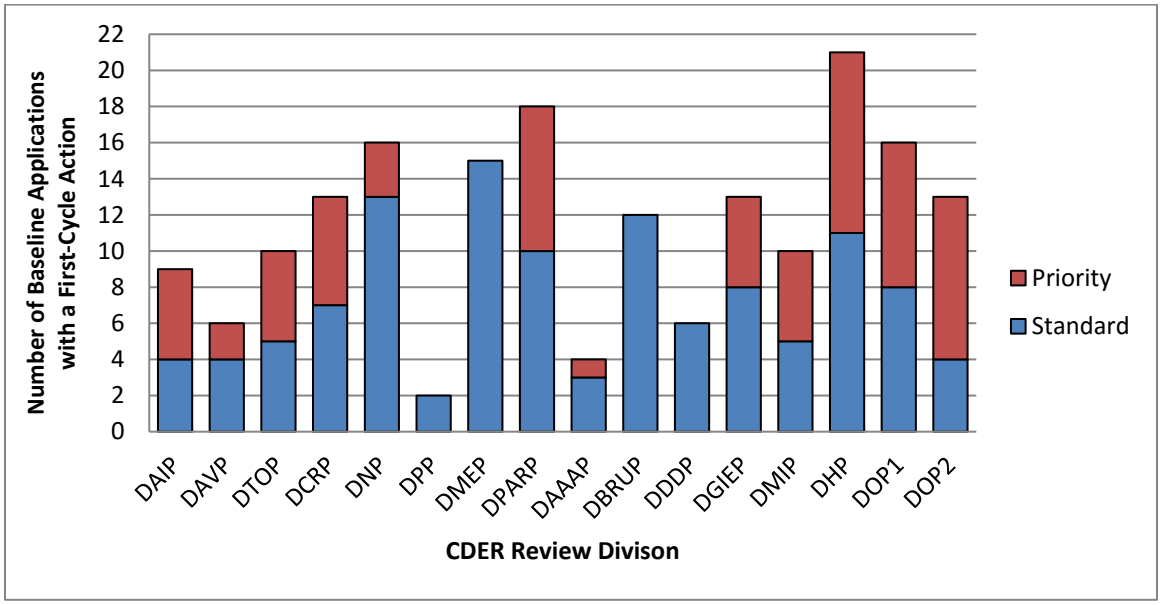
Applications		FY 08	FY 09	FY 10	FY 11	FY 12	Baseline Total	FY 13	FY 14	FY 15	FY 16	Program Total
Filed and acted upon	NME NDA	33	30	22	29	33	**147**	36	38	33	2	**109**
	Original BLA	17	23	7	10	15	**72**	20	19	21	2	**62**
	Total	50	53	29	39	48	**219**	56	57	54	4	**171**

**NME NDAs and original BLAs received during FYs 2008-2012 and acted on by June 30, 2016 (baseline) or received and acted on from October 1, 2012 to June 30, 2016 (Program). Application counts for FY 2016 are small because many applications received that year had not received first-cycle actions by the end of that fiscal year.*

[11] FDA decides at filing whether an application represents an NME NDA or original BLA and whether it will be reviewed in the Program. Sometimes an application loses its NME status during the review (e.g., if another application for the same drug is approved first), but the application remains in the Program. This evaluation includes all applications reviewed in the Program, including those that later lost their NME status. For consistency, the baseline cohort also includes all applications considered an NME NDA or original BLA at filing, including those that later lost their NME status.

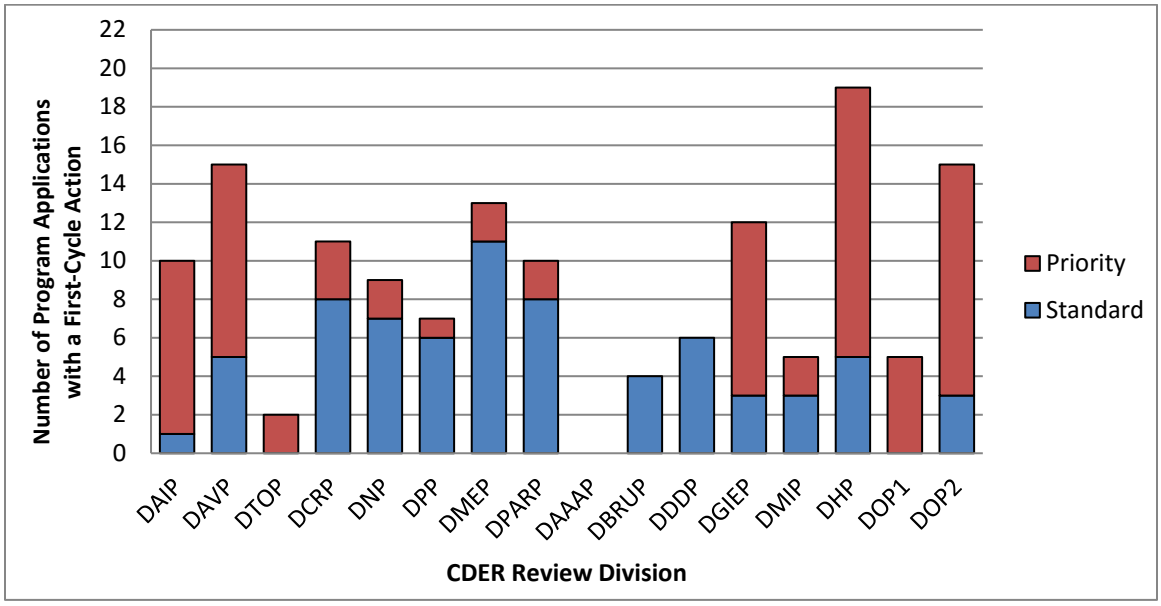
Figure 3-1 and Figure 3-2 show the distribution of baseline and Program applications in CDER, and Figure 3-3 and Figure 3-4 show the distribution of applications in CBER. CDER reviewed 84% of Program applications and CBER reviewed 16%, the same proportion seen in PDUFA IV (84% CDER and 16% CBER).

Figure 3-1. Distribution of baseline applications,* by CDER review division



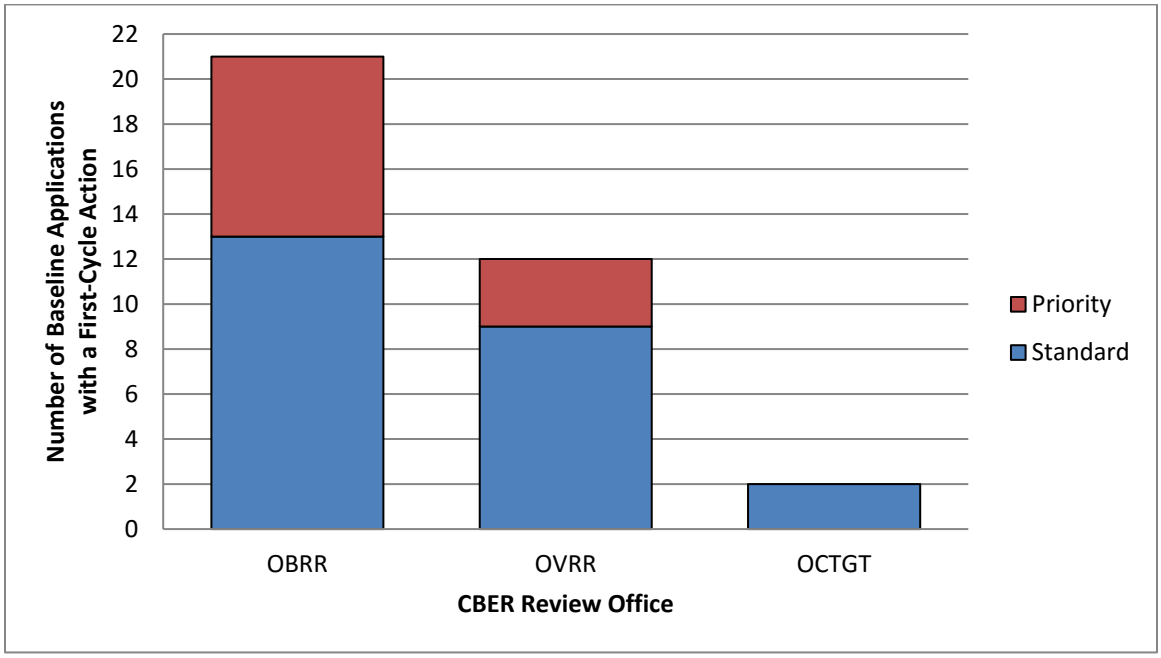
**CDER NME NDAs and original BLAs received during FYs 2008-2012 and acted on by June 30, 2016.*

Figure 3-2. Distribution of Program applications,* by CDER review division



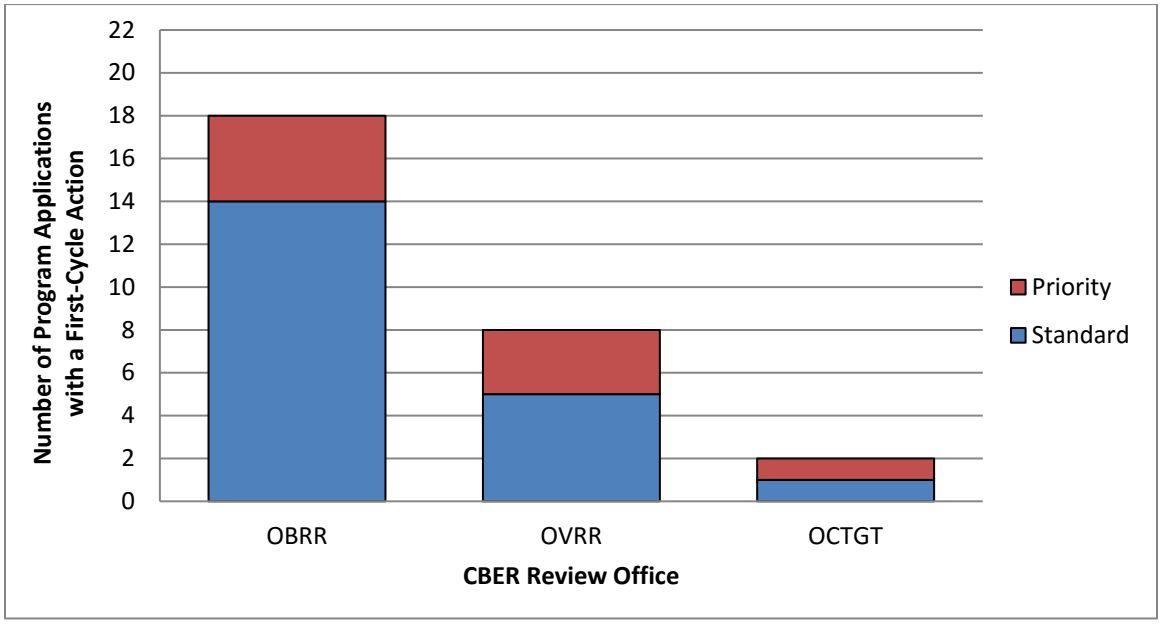
**CDER NME NDAs and original BLAs received and acted on from October 1, 2012 to June 30, 2016.*
Acronyms in order of appearance – Division of Anti-Infective Products (DAIP), Division of Antiviral Products (DAVP), Division of Transplant & Ophthalmology Products (DTOP), Division of Cardiovascular & Renal Products (DCRP), Division of Neurology Products (DNP), Division of Psychiatry Products (DPP), Division of Metabolism & Endocrinology Products (DMEP), Division of Pulmonary, Allergy & Rheumatology Products (DPARP), Division of Anesthesia, Analgesia & Addiction Products (DAAAP), Division of Bone, Reproductive & Urology Products (DBRUP), Division of Dermatology & Dental Products (DDDP), Division of Gastroenterology & Inborn Errors Products (DGIEP), Division of Medical Imaging Products (DMIP), Division of Hematology Products (DHP), Division of Oncology Products I (DOP1), Division of Oncology Products II (DOP2).

Figure 3-3. Distribution of baseline applications,* by CBER review office



**CBER original BLAs received during FYs 2008-2012 and acted on by June 30, 2016.*

Figure 3-4. Distribution of Program applications,* by CBER review office



**CBER original BLAs received and acted on from October 1, 2012 to June 30, 2016.*
Acronyms in order of appearance – Office of Blood Research and Review (OBRR), Office of Vaccine Research and Review (OVRR), Office of Cellular, Tissue and Gene Therapies (OCTGT).

Regulatory Outcome Definitions

The goals of the Program are to increase the efficiency and effectiveness of the first review cycle and decrease the number of review cycles necessary for approval of NME NDAs and original BLAs where warranted so that patients have timely access to safe, effective, and high quality new drugs and biologics. Thus, ERG analyzed data on the regulatory outcomes of Program and baseline applications:

Regulatory outcome or action: Decision on an NDA or BLA. Decisions that close the PDUFA goal (end the review) include:

Approval (AP)—FDA decision that permits the applicant to market the drug or biologic.

Complete Response (CR)—FDA decision that the application will not be approved in its present form. After resolving any deficiencies, the applicant may resubmit the application for another cycle of review.

Withdrawal after Filing (WD)—Applicant decision to withdraw the application from FDA review after the Agency has filed it (accepted it for review). As above, the applicant may resubmit the application for another cycle of review.

Decisions made before filing are not part of this Program assessment because FDA did not review the application. Such decisions include:

Refuse to File (RTF)—FDA decision not to accept the application for review due to incompleteness or other inadequacies.

Withdrawal before Filing (WF)—Applicant decision to withdraw the application from FDA consideration before the Agency has filed it (accepted it for review).

Decisions made after one or more review cycles are called:

First-cycle action—Decision on an NDA or BLA made after a first review (not after a resubmission and an additional review cycle).

Second-cycle action[12]—Decision on an NDA or BLA made after a second review (after a first-cycle CR followed by resubmission).

PDUFA review clock or PDUFA goal date: The review clock is the target time for application review (for the Program, 6 months after filing date for Priority review or 10 months after filing date for Standard reviews). The goal date is the date by which FDA expects to issue a first-cycle action on the application.

[12] As of June 30, 2016, no application in the Program underwent more than two review cycles. In the baseline, enough time has elapsed for some applications to have up to four review cycles.

Approval rate: The percent of applications that received approval in the first review cycle (first-cycle approval rate), second review cycle (second-cycle approval rate), or after any/all review cycles (overall approval rate).

Time to first-cycle action: Time from FDA receipt of an original application to first-cycle action.

Time to approval: Time from FDA receipt of an original application to its approval in the first review cycle (time to first-cycle approval) or in any subsequent review cycle regardless of the number of review cycles (overall time to approval).

Categories of Results in Remainder of Section 3

In the remainder of Section 3, we present categories of Program assessment results as follows:

- Section 3.1, Program Overall
- Section 3.2, Pre-Submission Meetings
- Section 3.3, Filing Letters
- Section 3.4, Mid-Cycle Communications
- Section 3.5, Discipline Review Letters
- Section 3.6, Late-Cycle Meetings / Advisory Committee Meetings
- Section 3.7, Inspections
- Section 3.8, Review Process and Application Attributes

For these topics, we focus on relevant results from our qualitative, descriptive, and statistical analyses. We provide additional information in appendices:

- Appendix B, Evaluation Metrics
- Appendix D, Statistical Framework
- Appendix E, Statistical Results / Data Tables

Note: In Section 3 we present statistically significant results from our statistical analysis; Appendix E includes complete results of statistical analyses (including those that did not achieve statistical significance or could not be run due to insufficient numbers or variability in the data).

3.1 Program Overall

Key Findings

- ***New to this Final Report:*** First-cycle approval rates for Standard applications in the Program (as well as Priority applications and applications overall) was statistically significantly higher than in the baseline.
- Overall Program results reported here are consistent with the interim results presented in the Interim Report for this evaluation.
- In the Program, FDA-applicant communications have been excellent and constructive, with a spirit of cooperation, for both Program milestone meetings (MCCs and LCMs) and regular contact outside these meetings.
- Review transparency has been excellent, with some applicants citing their experience in the Program as "the best ever."
- Some FDA reviewers believe that the Program has not increased communication and review transparency beyond existing practices in their review divisions.
- The Program has added burden to review teams, which was especially challenging to manage when an Advisory Committee (AC) meeting or an early approval was expected.
- Time to first-cycle approval was statistically significantly higher than in the baseline, but by less than the 2-month difference in review clocks (especially for Priority applications).

Communication in the Program

In post-action interviews, Program applicants characterized communication with FDA as excellent and very constructive, with a spirit of cooperation—both within and outside of the new milestone communications (MCCs and LCMs). Most FDA review staff affirmed with varying degrees of enthusiasm that the Program contributed to enhanced communication, though some believed that the Program offered no additional value to (or duplicated) already excellent communication practices in their divisions. Table 3-3 summarizes applicant and FDA review team feedback on Program communications.

Table 3-3. Post-action interview feedback on Program communications

Applicant Feedback	FDA Review Team Feedback
Program communications were very useful to: • Resolve issues quickly and efficiently as they arise. • Identify mutually agreeable solutions to issues. • Understand FDA information needs (including timing). • Generate productive working relationships and good will. • Avoid surprises during review. • Help applicants plan effectively (for responses to IRs, labeling negotiations, manufacturing scale-up and launch, etc.). • Know when and how to plan and allocate resources based on meeting timing and issues. *Note: Many applicants praised FDA RPMs as constructive, helpful, accessible, communicative, and responsive.*	Program communications were very useful to: • Resolve issues quickly and efficiently as they arise. • Identify mutually agreeable solutions to issues. • Obtain information from applicants when needed to proceed with review. • Generate productive working relationships and good will.

Review Transparency

As with Program communications, applicants characterized Program application reviews as very transparent—due to the big-picture multidisciplinary status updates provided during the new Program milestone communications as well as the more narrowly focused discussions involved in informal email and telephone interactions. Many applicants identified inspections as an exception to the rule due to a lack of availability of information about status and issues. They described inspections as a "black box" because they could not discern who was in charge, who to communicate with, what progress was being made, etc. A small minority of applicants also commented that identification of significant issues late in the review (e.g., at the LCM) might reflect a lack of transparency; they sometimes wondered whether FDA had been aware of the issues earlier but waited until later to tell the applicant.

Applicants also characterized Program application reviews as very predictable due to the new Program communications that "anchor" the review with predictable milestones, communicate anticipated future review process dates, and facilitate planning and work to advance the review. In addition, they described reviews as very efficient due to the FDA review team's commitment to ongoing review progress and the Program's new milestone communications that helped propel the review forward efficiently.

Like applicants, most FDA review staff characterized Program application reviews as transparent and predictable to the applicant. Many stated that MCCs and LCMs added value by ensuring that FDA staff bring together all their inputs to consider the application as a whole, prioritize issues, plan for review milestones, involve leadership, and review the status of the overall application with applicant. Many reviewers attributed these achievements at least in part to the Program, while some felt that the Program's impact was minimal. Some reviewers suggested that the Program might be most beneficial for applications that require substantive discussion and issue resolution throughout the review.

Review Process

The Program instituted two key changes to the review process for NME NDAs and original BLAs:

- Begin the PDUFA review clock on the day of filing (instead of the day of application receipt), giving FDA two additional months for review.
- Hold two milestone meetings (MCCs and LCMs) during the review to update the applicant on the status of their application.

Use of Two Additional Months

Beginning the PDUFA review clock at filing in effect adds two months to the overall review period from application submission to FDA regulatory action. In interviews, both FDA review teams and applicants commented on the value of the additional two months. For some applications, the additional two months enabled applicants and FDA reviewers to resolve application or inspection issues in time for first-cycle approval—instead of requiring a CR and a second review cycle. For other applications with few deficiencies or deficiencies that were resolved early in the review process, FDA was able to issue an early action, at least a month before the PDUFA goal date.

According to senior managers at FDA, the two months added to the overall review process in the Program are intended to provide sufficient time toward the end of the review for senior managers and the signatory authority to examine the application and for the parties to resolve any remaining issues where possible. In practice, this was often the case, though FDA review teams sometimes used the two months somewhat differently based on their assessment of the application, procedures within their division, and their work priorities relative to other timelines and deadlines. For example:

- **Filing review—**Complete administrative filing review (before application review begins) to ensure that FDA reviewers can adequately assess the completeness and fileability of the application.
- **End-of-review activities—**Address outstanding issues or inspectional deficiencies.
- **Tertiary review—**Give the signatory authorities and "tertiary" reviewers more time to complete a thorough review, since they typically review the application after primary reviews are completed.

Burden Associated with New Program Milestone Communications

Though Program implementation was originally expected to be resource-neutral, most FDA reviewers interviewed for this assessment believed that the new Program communications imposed additional burdens and time pressures on staff, including additional time required for preparing for meetings (which include internal meetings to prepare for the MCC and LCM), completing primary reviews while addressing these competing priorities, and preparing the LCM background package (and AC meeting package, if applicable). Nevertheless, most reviewers believed that the additional burden was manageable.

Early in the Program, a few reviewers expressed concern that the additional work associated with the Program might compromise the thoroughness of their reviews if a review team or division must juggle multiple complex Program applications at once. However, no reviewer interviewed has stated that this was the case in their review. A few reviewers commented on the possibility that *additional* new burdens might introduce a risk of missed deadlines, less thorough scientific reviews, or slower approvals. In the past year, fewer reviewers have commented on the burden associated with new Program milestone communications, as they had already provided this feedback previously.

Other Good Practices in Review Process

During post-action interviews, FDA reviewers identified some good practices that they employed during the review that applicants (separately and unprompted) also stated were helpful:

- **Offer an Application Orientation Meeting—**Held soon (roughly 30 days) after submission, an Application Orientation Meeting is an opportunity for the applicant to present their application to FDA, explaining the organization of the submission and format of data sets. FDA staff can then provide early thoughts on the application, describe their data needs, and provide timeline information for planning purposes. Representatives of specific disciplines (e.g., Statistical or Clinical) from both parties can also meet to navigate scientific aspects of the application. The Application Orientation Meeting appeared to add value to some Priority reviews where early action (one more or more before the PDUFA goal date) was anticipated.

- **Involve senior management early on—**Having signatory authorities gain a general familiarity with an application helped both applicants and FDA review teams during the review. Early involvement can prevent late surprises by identifying issues earlier in the review when there is still time remaining to resolve the issues.
- **Maintain regular review team communication and collaboration—**Though the frequency varied (weekly, bi-weekly, monthly), some review teams appreciated regular internal meetings to check in with all reviewers, including Office of Compliance (OC) or Office of Pharmaceutical Quality (OPQ) staff,[13] to ensure that the entire team was informed and on the same page with the direction of the review. Some applicants found it difficult when the RPM and the Chemistry, Manufacturing, and Controls (CMC) lead or other disciplines did not coordinate, resulting in overlapping information requests (IRs) that forced the applicant to provide the same information multiple times.
- **Provide rationale for labeling changes—**During labeling negotiations, having FDA staff and applicants provide rationales for proposed label changes facilitated understanding of the other party's perspectives; in turn, this understanding facilitated well-focused responses, leading to efficient agreements.

Regulatory Outcomes

This report focuses on first-cycle actions in the Program because sufficient data exist for those regulatory outcomes. Many Program applications that received a CR in the first review cycle (20 of 29) have not yet been resubmitted or undergone a second review; therefore, we present limited data on second-cycle and overall regulatory outcomes.

First-Cycle Approval Rates

From October 1, 2012 to June 30, 2016, the first-cycle approval rate for all applications was statistically significantly higher in the Program than in the baseline (79.5% [n=171] vs. 54.8% [n=219], $p < 0.001$). The first-cycle approval rate for Priority applications was also statistically significantly higher in the Program than in the baseline (90.1% [n=81] vs. 71.8% [n=78], $p = 0.003$). This was also true when ERG used a more complex logistic regression model that controlled for explanatory factors. The first-cycle approval rate for Standard applications was also higher in the Program than in the baseline, and the increase was statistically significant (70.0% [n=90] vs. 45.4% [n=141], $p < 0.001$). The significance of this result previously could not be determined in the Interim Report, owing to the smaller number of applications in the Program, but the additional data gained since then has shown statistical significance.

The increase in first-cycle approval rate for Program applications is consistent with a general upward trend in first-cycle approval rates over the past eight years, reaching a peak in FY 2014 (see Table 3-4). In both the Program and the baseline, first-cycle approval rates were higher for Priority applications than for Standard applications. Among the Program applications, the difference in first-cycle approval rate

[13] During the first half of the Program (October 2012 to January 2015, FDA CDER's OC was responsible for preapproval and surveillance inspection activities. After being launched in January 2015, FDA CDER's new OPQ assumed these responsibilities.

Table 3-4. First-cycle approval rates in the baseline and Program, by fiscal year of application receipt and review priority*

Review Priority	First-Cycle Approval Rate										
	FY 08	FY 09	FY 10	FY 11	FY 12	Baseline Total	FY 13	FY 14	FY 15	FY 16	Program Total
Standard	28.1%	38.9%	50.0%	50.0%	64.5%	**45.4%**	61.1%	76.9%	75.0%	0.0%**	**70.0%**
Priority	61.1%	52.9%	72.7%	86.7%	88.2%	**71.8%**	90.0%	93.5%	84.6%	100%	**90.1%**
Total	40.0%	43.4%	58.6%	64.1%	72.9%	**54.8%**	71.4%	86.0%	79.6%	100%	**79.5%**

**Data encompass NME NDAs and original BLAs received during FYs 2008-2012 and acted on by June 30, 2016 (baseline) or received and acted on from October 1, 2012 to June 30, 2016 (Program).*

***No Standard applications received in FY 2016 reached a first-cycle action by June 30, 2016.*

between Priority and Standard applications was statistically significant (90.1% [n=81], 70.0% [n=90], $p < 0.001$). FDA grants Priority reviews to applications for drugs and biologics that have the potential to treat a serious condition and provide a significant improvement in safety or efficacy; thus, FDA reviewers might be motivated by public health interests to work toward prompt approval of these applications when warranted.

Given that the first-cycle approval rate was higher in the Program than in the baseline, it follows that first-cycle CR rate was lower: 17.0% in the Program compared to 42.0% in the baseline. Table 3-5 presents a summary of issues cited in the CR letters for these applications. For both Standard and Priority applications, CR letters in the Program cited safety issues slightly less often and efficacy issues slightly more often than CR letters in the baseline.

Overall, the added communications and review time with the Program were particularly beneficial for applications with substantive review issues that had the potential to be resolved in the first review cycle, and where FDA needed the full review clock. In contrast, no review program is likely to benefit applications with serious deficiencies or applicants who do not respond promptly to IRs.

Table 3-5. Issues cited in baseline and Program CR letters, by review priority*

Issue Cited in CR Letter**	Standard Applications Given a CR		Priority Applications Given a CR	
	Baseline (n=71)	Program (n=22)	Baseline (n=21)	Program (n=7)
Efficacy	40.8%	50.0%	81.0%	85.7%
Product quality	50.7%	45.5%	76.2%	71.4%
Safety	71.8%	45.5%	57.1%	42.9%

** Data encompass NME NDAs and original BLAs received during FYs 2008-2012 and acted on by June 30, 2016 (baseline) or received and acted on from October 1, 2012 to June 30, 2016 (Program).*

***Note that CR letters can cite more than one issue with the application. This is why these percentages do not sum to 100%.*

Time to First-Cycle Approval

In the Program, FDA aims to review 90% of Standard applications within 10 months of the 60-day filing date and 90% of Priority applications within 6 months of the 60-day filing date—unless a goal extension is taken, in which case the PDUFA goal date is 3 months later. In the baseline, FDA aimed to review applications within 10 months and 6 months of the original receipt date for Standard applications and Priority applications, respectively—unless subject to a 3-month goal extension.

Based on PDUFA goal dates, we would expect that the median time to first-cycle action would be 60 days (2 months) longer in the Program than in the baseline. As expected, the median time to first-cycle approval was longer in the Program than in the baseline (see Table 3-6).

When examining mean (rather than median) time to first-cycle approval, ERG found that time to first-cycle approval was statistically significantly longer in the Program than in the baseline, but by less than the 2-month difference in review clocks, especially among Priority applications. (For more details, see Appendix E: Statistical Results, Data tables, page E11.)

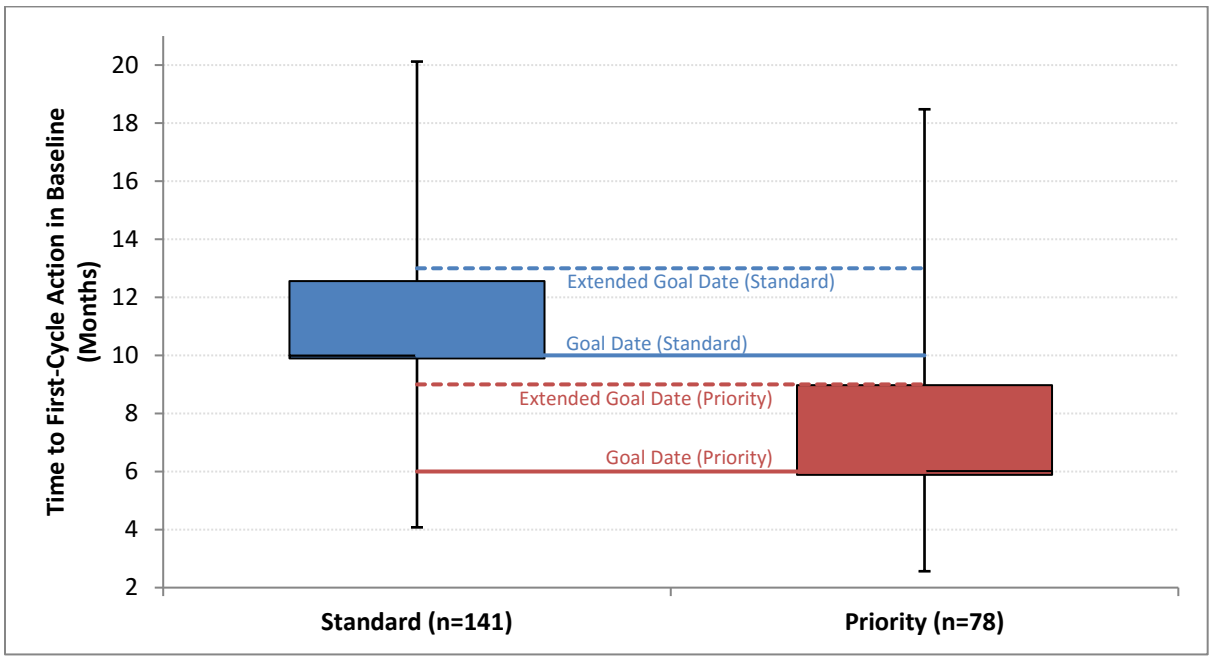
FDA missed only 5 of 171 PDUFA goal dates in the Program between October 1, 2012 and June 30, 2016. Thus, median first-cycle review times (from receipt to action) for Standard and Priority applications were close to 12 and 8 months, respectively, although goal extensions for some Program applications and early action on others led to a range of first-cycle review times. The range was larger in the baseline, with some review times being much longer than any in the Program (see Figure 3-5 and Figure 3-6).

Table 3-6. Median time to first-cycle action in the baseline and Program,* by type of action and review priority

Cohort	Median Time from Application Receipt to First-Cycle Action (Months)					
	Approval		Complete Response		Withdrawal	
	Standard	Priority	Standard	Priority	Standard	Priority
Baseline	10.0	6.0	10.0	6.0	6.4	3.9
Program	12.0	7.9	12.0	7.9	8.7	6.2

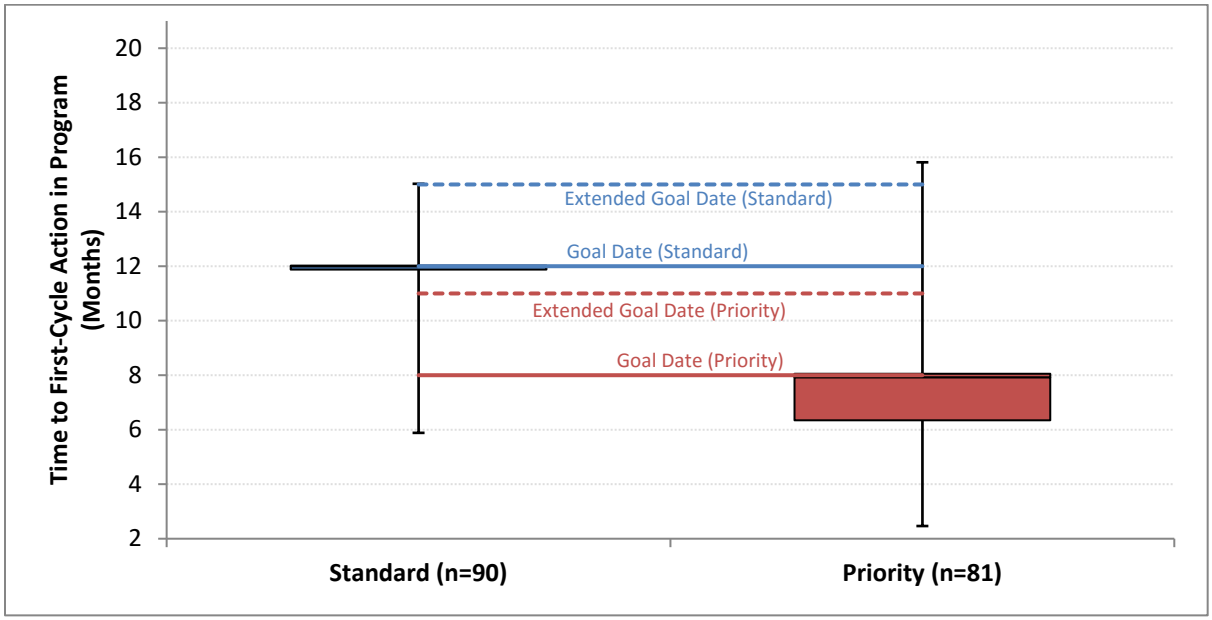
**Data encompass NME NDAs and original BLAs received during FYs 2008-2012 and acted on by June 30, 2016 (baseline) or received and acted on from October 1, 2012 to June 30, 2016 (Program).*

Figure 3-5. First-cycle review times for baseline applications,* by review priority



**NME NDAs and original BLAs received in FYs 2008-2012 and acted on by June 30, 2016.*

Figure 3-6. First-cycle review times for Program applications,* by review priority



**NME NDAs and original BLAs received and acted on from October 1, 2012 to June 30, 2016 (Program).*

Note: Solid horizontal lines show the PDUFA goal date, while dotted lines show the extended goal date if FDA receives a major amendment. The boxes show the times from original application submission to first-cycle action for the middle two quartiles in the range; the vertical lines show the overall range.

These figures also demonstrate that review times for Program applications were closer to the original PDUFA goals than those for baseline applications, with the middle 50% of Program applications showing much less variation in review times compared to the baseline. The size of this range is attributable in part by a low rate of meeting PDUFA goal dates in the early years of PDUFA IV—especially in the first year, when PDUFA goal dates were met for only 68.0% of applications and 30% of applications received goal extensions.[14] Some applications did receive early actions, however, especially in the Program (see Table 3-7). In fact, several Priority applications in the Program received early approvals—a month or more before the goal date. When Standard applications received an early action, they were more likely to receive an early CR or WD.

Table 3-7. Early actions among baseline and Program applications*

Cohort	Percent of Applications that Received an Early Action (at least 1 month before goal date)	
	Standard	Priority
Baseline	7.8% *(11/141)* *3 AP,3 CR, 5 WD*	15.4% *(12/78)* *10 AP,1 CR, 1 WD*
Program	11.1% *(10/90)* *3 AP, 3 CR, 4 WD*	30.9% *(25/81)* *24 AP, 1 WD*

** NME NDAs and original BLAs received during FYs 2008-2012 and acted on by June 30, 2016 (baseline) or received and acted on from October 1, 2012 to June 30, 2016 (Program).*

Resubmissions

The Program has generated fewer CRs and thus fewer resubmissions than the baseline because (1) data exist for fewer than 4 years of the Program compared to a full 5 years for the baseline, and (2) the CR rate is lower in the Program than the baseline. In the Program, 37.9% of CR applications were resubmitted by June 30, 2016, while 70.7% of baseline CR applications were resubmitted by this date. This difference is likely due to the greater amount of time (4 years) that has elapsed since PDUFA IV, providing more time for sponsors of baseline applications to address CR issues and prepare a resubmission.

Table 3-8 presents data on time from first-cycle CR to resubmission in the Program and baseline. The range is smaller in the Program because less time has elapsed for sponsors to resubmit applications. We present median values for time to resubmission because the median is less influenced than the mean by the large range of values that exists for baseline resubmissions. Table 3-8 also presents second-cycle and overall approval rates. Program rates might change after more CR applications are resubmitted, so it is difficult to determine whether a comparison of Program and baseline rates is meaningful at this time.

[14] During the first year of PDUFA IV, FDA needed to focus resources on implementing new statutory requirements—an effort that most observers cite as a reason for the relatively low rate of meeting PDUFA goal dates that year.

Table 3-8. Timing and outcomes of resubmissions in baseline and Program, by review priority*

Measure	Baseline		Program	
	Standard (n=51)	Priority (n=14)	Standard (n=7)	Priority (n=4)
Time from first-cycle CR to resubmission: median (months)	10.4	7.7	11.6	4.8
Time from first-cycle CR to resubmission: range (months)	36.6 [0.2, 36.8]	51.1 [1.6, 52.7]	23.8 [2.0, 25.8]	11.0 [2.6, 13.6]
Second-cycle approval rate	76.0%**	71.4%	100%**	66.7%**

** NME NDAs and original BLAs received during FYs 2008-2012 and acted on by June 30, 2016 (baseline) or received and acted on from October 1, 2012 to June 30, 2016 (Program).*

***Second-cycle approval rate encompasses 50 Standard applications in the baseline, and 6 Standard and 3 Priority applications in the Program because three resubmitted applications did not receive a second-cycle action by June 30, 2016.*

In the Program, there is no discernable association between CR issue and second-cycle approval. The number of CRs and resubmissions is small, however, so it is unclear whether there will be a consistent pattern over time. Similarly, in the baseline, there is no discernable association between CR issue and second-cycle approval.

Overall Time to Approval and Overall Approval Rate

Table 3-9 provides overall time to approval in the baseline and in the Program. The approval rates in the baseline and Program are:

- First-cycle approval rate: Baseline 54.8% (120/219), Program 79.5% (136/171)
- Second-cycle approval rate: Baseline 75.0% (48/64), Program 88.9% (8/9)
- Overall approval rate: Baseline 82.6% (181/219), Program 84.2% (144/171)

As discussed above, these values are not comparable due to the large difference in time available for baseline versus Program applications to receive multiple cycles of review. Thus, we present these data for completeness but draw no conclusions from them.

Table 3-9. Overall time to approval in baseline and Program*

Measure	Baseline		Program	
	Standard (n=111)	Priority (n=70)	Standard (n=69)	Priority (n=75)
Overall time to approval: median (months)	13.0	6.0	12.0	7.9
Overall time to approval: range (months)	62.8 [6.9, 69.7]	95.0 [2.6, 97.6]	24.8 [9.1, 33.9]	24.8 [2.5, 27.3]

** NME NDAs and original BLAs received during FYs 2008-2012 and acted on by June 30, 2016 (baseline) or received and acted on from October 1, 2012 to June 30, 2016 (Program).*

Refuse to File and Withdrawal before Filing Actions

In the Program, six applications received an RTF; most of these were due to problems with application organization and documentation or inadequate efficacy data. One RTF was resubmitted, and it received a CR. No applications were withdrawn by the applicant before FDA filing. These numbers are too small for further analysis.

3.2 Pre-Submission Meetings (PSMs)

Key Findings

- PSM results reported here are consistent with those presented in the Interim Report for this evaluation.
- Most Program applicants requested a PSM from FDA.
- A majority of Program PSMs were held no less than two months prior to the planned submission date, and most involved discussion of meeting topics laid out in the Commitment Letter, either explicitly or implicitly.
- Both Program applicants and FDA review teams consider the PSM to be a valuable practice.
- Open communication between sponsors and FDA in the IND stage (NDA/BLA submission) can help mitigate significant issues during the review.

Format and Conduct

Also called a pre-NDA or pre-BLA meeting, a PSM is a meeting between FDA staff and a sponsor to discuss the content and format of an anticipated NDA or BLA submission. The PSM represents a shared responsibility between the sponsor and FDA staff, with the sponsor requesting the meeting and both parties contributing to running the meeting. Holding a PSM before NDA/BLA submission has been a common and long-established practice at FDA and continues to be strongly recommended (but not required) in PDUFA V.

Commitment Letter Expectations

- Hold no less than 2 months prior to planned submission
- Reach agreement on the content of a complete application
- Reach agreement on delayed submission of minor components
- Include preliminary discussion on REMS or other risk management strategies
- Summarize agreements and discussions

Commitment Letter Recommendation

- Hold a PSM prior to application submission

From October 1, 2012 to June 30, 2016, 142 of 171 Program applications were preceded by a PSM, with 118 conducted after October 1, 2012 (during PDUFA V) and 24 conducted before October 1, 2012 (during PDUFA IV). ERG did not include the 24 PSMs in our assessment because they occurred before the Program; nevertheless, we note that some FDA review teams held brief follow-up meetings to ensure that Commitment Letter expectations for PSMs were satisfied. For the remaining 29 Program applications, in 19 cases FDA granted requests for PSMs that were subsequently canceled (often due to sponsor satisfaction with FDA's preliminary meeting comments), in 8 cases a PSM was not requested, and in 2 cases a PSM was not granted due to timing.

This section focuses on the 118 applications with a Program PSM. For 80% of Program applications with a Program PSM, the meeting was held at least 2 months before application submission, as outlined in the PDUFA Commitment Letter. In the meetings, both Program applicants and FDA raised discussion topics cited in the Commitment Letter, though FDA staff were often the ones to ensure the topics had been addressed. In some cases, the parties did not address certain topics because:

- They addressed the topics implicitly and did not feel the need to address them explicitly.
- They addressed some topics in communications outside of PSMs (e.g. teleconferences, preliminary comments or written responses) and did not need to address them again.

Regardless, both Program applicants and FDA staff considered the PSM to be a valuable practice, providing an opportunity to share and discuss top-line results and assess readiness for application submission. In post-action interviews, both parties noted that open communication about an application prior to submission (outside of the PSM as well) facilitated conversations about potential paths forward for the application, including how to resolve issues; in turn, this facilitated thorough preparation for application submission and review.

Because PSMs were so common in the Program, there was not enough variability in the data to determine whether there is a statistically significant correlation between holding a Program PSM and having a positive regulatory outcome. Interestingly, ERG found that Program applications with PSMs in which agreements and discussions were summarized had a significantly higher first-cycle approval rate (87.7% [n=65], 71.9% [n=32], p = 0.05). Summarizing meeting agreements and discussions is a good practice, but this by itself was unlikely to be a causal factor in the statistical relationships found. Instead, ERG speculates that summarization reflected a broader pattern of clear and good communication practices. It is also possible the statistical relationship might simply be coincidental.

Other Communications before Application Submission

In the Program, a Type B multidisciplinary Pre-NDA/Pre-BLA meeting[15] is considered the formal PSM. Sponsors may request other Type B or Type C meetings as well. If granted by FDA, these can be held individually or in combination, or all together in the formal PSM:

- **Chemistry, Manufacturing, and Controls (CMC) meeting—**To provide an opportunity for FDA and sponsor CMC staff to discuss technical product quality topics.
- **Top-line results/data meeting—**To enable the sponsor to share top-line results of clinical trials or other study data to obtain feedback and guidance in preparation for application submission.
- **Format/content meeting—**To receive guidance from FDA review divisions on the structure, format, and content of an anticipated application.

In post-action interviews, some Program applicants stated that it would be helpful to hold a content/format meeting several months before a data-oriented PSM. Although FDA has some guidance on this topic, some applicants stated that FDA review offices, divisions, and teams have different standards and expectations for applications (e.g., format and presentation of the datasets). Some applicants found FDA written responses to be helpful, obviating the need for an additional meeting. This experience suggests that using Type C Written Response Only (WRO) feedback might be an efficient method of conveying answers to questions about application format and content. To that end, reviewers might benefit from internal reviewer aids so they have pre-written documents explaining their current expectations for applications.

From PSM to Submission—Application Completeness

[15] A Type B meeting is a meeting between FDA staff and a sponsor before submission of an IND or NDA/BLA or certain preclinical or clinical milestones. Multidisciplinary refers to the presence of more than one scientific discipline (rather than being focused on one discipline).

The Program PSM is an opportunity for the sponsor and FDA review team to reach a shared understanding of the content of a complete application. To facilitate a timely review, FDA then expects the sponsor to submit an application that is complete at the time of original submission. ERG determined whether Program applications were complete on submission as follows:

- CDER: Examine filing review to ascertain whether the review team considered the application to be complete; ask review teams in post-action interviews.
- CBER: Ask review teams in post-action interviews.[16]

Using this method, ERG estimated that 86% of Program applications were complete on original submission. FDA reviewers explained that sometimes applications appeared to be complete based on an initial review of submission files (because documents were uploaded/present for all necessary modules and components), but on closer examination after filing they found that some of the data/files were inadequate. Some reviewers also noted that FDA occasionally decided to file an incomplete application because the drug/biologic had the potential to address an unmet medical need; the applicant submitted the missing information during the filing and review periods so FDA's review could be complete.[17] The high rate of application completeness plus these two reasons for filing incomplete applications likely account for the very low rate of RTFs in the Program: only six applications received RTF decisions, two of which were actually a single submission with two indications that FDA had split into two applications for administrative purposes.

In post-action interviews, both FDA reviewers and Program applicants commented that communication before application submission (during the IND stage) had been critical. This communication had allowed Program applicants to inform the Agency of their plans for submission and application content—and receiving clear feedback from FDA staff helped ensure the completeness of the application upon submission.

From PSM to Submission—Delayed Application Components

During Program PSMs, sponsors and FDA review teams may agree that certain minor application components will be submitted late, within 30 days of original application submission. In accordance with the expectation that applications be complete on original submission, formal use of this option has been modest: Program applicants and FDA review teams made agreements on delayed application components for 18.1% (31/171) of Program applications received and acted on from October 1, 2012 to June 30, 2016.

Examples of delayed application components include:

- Exposure- or dose-response analyses
- PK/PD trial datasets
- Stability data/updates

[16] ERG had limited access to CBER filing review data but determined that asking reviewers during interviews provided the most consistent and meaningful information about application completeness available.

[17] The data were insufficient to (1) analyze the prevalence of this situation in the Program, and (2) compare the quality and completeness of original submissions in the Program and baseline.

- In vivo study data
- SPL format labeling
- Summary of statistics and plots for PK samples
- Clinical site information

In most cases, Program applicants submitted the delayed components within the prescribed 30 days of original submission; some Program applicants submitted the "delayed" components with the original submission itself.

Other Feedback on PSMs

Table 3-10 provides additional feedback about Program PSMs gleaned from post-action interviews with Program applicants and FDA review teams.

Table 3-10. Post-action interview feedback on PSMs

Applicant Feedback on Program PSMs	FDA Review Team Feedback on Program PSMs
Most applicants valued the opportunity at PSMs to: • Obtain initial FDA feedback on their topline results and other information. • Address any initial questions and issues in advance of submission. • Understand FDA's needs for reviewing a complete application (types of data, format, etc.). Some applicants suggest holding two PSMs: • One several months before submission to discuss content and format. • Second closer to submission to discuss topline results and data. Some applicants find that meeting with FDA during the IND stage overall helps to: • Understand FDA's needs during development. • Gain familiarity with reviewers, knowing what they are looking for. • Establish a positive working relationship.	Most FDA review teams value the opportunity to: • Gain a preliminary understanding of data to be submitted. • Develop shared expectation for submission and review. Many FDA review teams agree that no less than 2 months prior to submission is an appropriate timeframe, though some note that it is challenging to conduct an effective PSM if the sponsor does not have / present sufficient data. Some reviewers have noted that communication during the IND stage overall is useful to: • Guide sponsors in development of study designs. • Establish active communication channels with sponsors before application submission. • Gain familiarity with data that will be included in future NDA/BLAs.

3.3 Filing Letters

Key Findings

- Filing letter results reported here are consistent with those presented in the Interim Report for this evaluation.
- FDA issued filing letters for all applications in the Program, largely conforming with Commitment Letter expectations.
- FDA use of filing letters in the Program was similar to that in the baseline.
- A greater volume of information exchange in the filing review period took place in the Program compared to the baseline:*
  - ✓ Some review teams requested information to ensure fileability of the application.
  - ✓ Some review teams had already initiated their reviews, so they began sending information requests early.

*Increasing the volume of information exchange is not discussed in the Commitment Letter or Program guidance.

Filing Letters

A filing letter is a formal correspondence that the FDA review team sends to an applicant within 74 calendar days of original application submission (the "Day 74 letter") to communicate FDA's filing decision, review priority of application, planned review timeline, filing issues, and preliminary plans on whether to hold an AC meeting. From October 1, 2012 to June 30, 2016, FDA issued filing letters for all Program applications following existing guidance. The letters included the topics expected in the Commitment Letter for PDUFA V.

Commitment Letter Expectations

- May use existing procedures on issuing filing (Day 74) letters
- Send within 74 calendar days of FDA receipt of original submission
- Include notification of potential review issues
- Include planned review timeline and planned date for internal mid-cycle review meeting
- Include preliminary plans on whether to hold an AC meeting

Filing letters represent an opportunity for the FDA review team to convey any potential review issues identified during the filing period. For Program applications received and acted on from October 1, 2012 to June 30, 2016, filing letters cited potential review issues as follows:

- None identified: 52.6%
- Potential review issues identified: 46.8%
  (1 to 76 potential review issues per letter, mostly in the areas of Product Quality and Clinical)

CDER also has a practice of issuing IRs in filing letters. CBER generally issues IRs outside of filing letters. Of the 561 items requested in 77 of 143 filing letters issued by CDER, most were related to one of two disciplines:

- Product Quality (316 of 561, 56.3%)
- Clinical (79 of 561, 14.1%)

Information Exchange in Filing Review Period

Many FDA review divisions communicate with applicants and engage in information exchange during the filing review period, before issuing the filing letter. Table 3-11 shows the mean number of IRs per application issued during the filing period, by review priority, other designations, and early action. On average, applications with Priority reviews, special designations, and early actions all received more IRs during the filing review period than Standard applications.

In post-action interviews, FDA reviewers stated that they issued IRs during the filing review period primarily for two reasons:

- FDA needed small bits of information to file the application. (Applications did not need large, substantive amendments in order to be filed.)
- FDA began its primary reviews early and thus began issuing IRs early. This was especially common with applications that received Priority reviews, special designations, and early actions.

Table 3-11. Mean number of IRs per application issued during filing review period, by review priority, other designations, and early action*

Subset of Applications	Mean Number of IRs Issued			
	First 30 Days of Filing Review		Full 60-Day Filing Review Period	
	Baseline	Program	Baseline	Program
All applications	1.1 (n=182**)	1.5 (n=171)	2.6 (n=182**)	4.0 (n=171)
Standard	0.5 (n=124**)	0.6 (n=90)	1.4 (n=124**)	1.9 (n=90)
Priority	2.4 (n=58**)	2.5 (n=81)	5.2 (n=58**)	6.4 (n=81)
Breakthrough Therapy designation	N/A***	3.6 (n=34)	N/A***	9.4 (n=34)
Fast Track designation	2.8 (n=50**)	1.7 (n=49)	5.6 (n=50**)	5.6 (n=49)
Early action (at least 1 month before goal date)	5.0 (n=20**)	3.1 (n=35)	9.0 (n=20**)	8.4 (n=35)

**Data encompass NME NDAs and original BLAs received during FYs 2008-2012 and acted on by June 30, 2016 (baseline) or received and acted on from October 1, 2012 to June 30, 2016 (Program).*

***IRs for BLAs in CDER are excluded due to limitations in data availability. For example, communications issued prior to BLA migration to DARRTS (in the later years of PDUFA IV) were not consistently accessible for data collection.*

****Breakthrough Therapy designation was established on July 9, 2012, but no baseline applications received the designation in their first review cycle.*

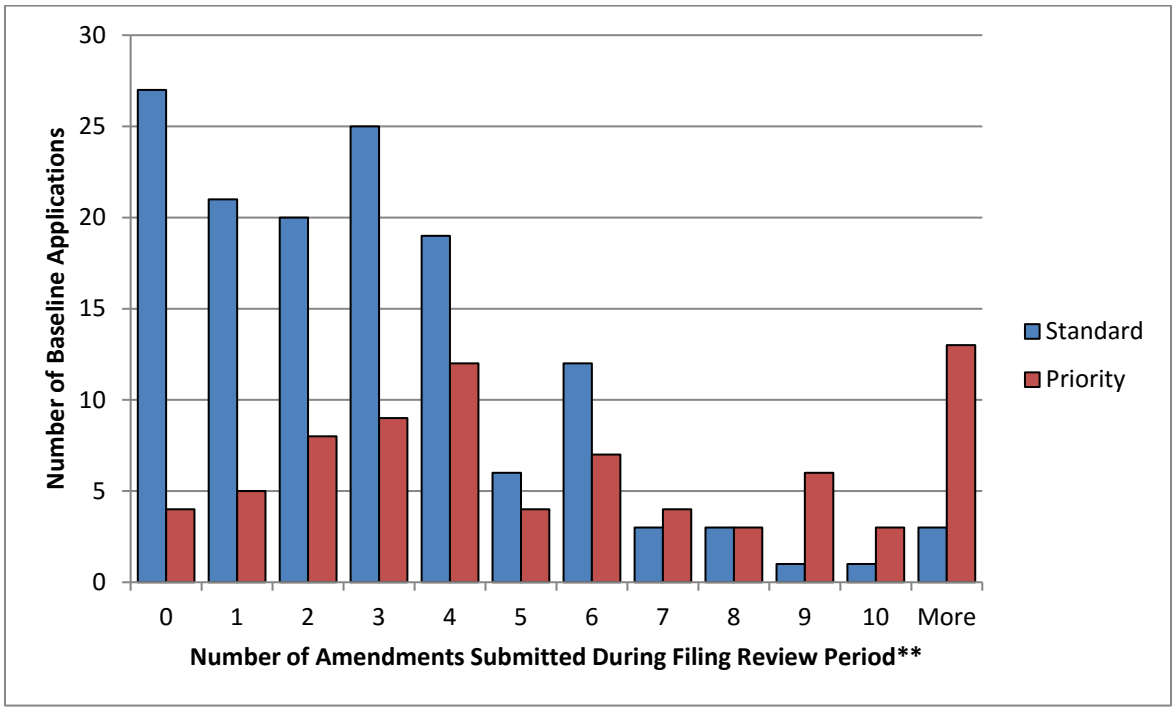
Just as FDA review teams issued IRs during the filing review period, applicants submitted amendments during this time as well. Both in the baseline and in the Program, applicants with Priority applications tended to submit more amendments than did applicants with Standard applications (see Table 3-12 and Figure 3-7 and Figure 3-8). Within the Program, applications with a Breakthrough Therapy or Fast Track designation or early action (at least one month before goal date) were also associated with more amendments during filing than applications without these traits.

Table 3-12. Mean number of amendments per application issued during filing review period, by review priority*

Subset of Applications	Mean Number of Amendments Issued	
	Baseline	Program
Standard	3.0 (n=141)	3.9 (n=90)
Priority	6.6 (n=78)	8.3 (n=81)
All applications	4.2 (n=219)	6.0 (n=171)

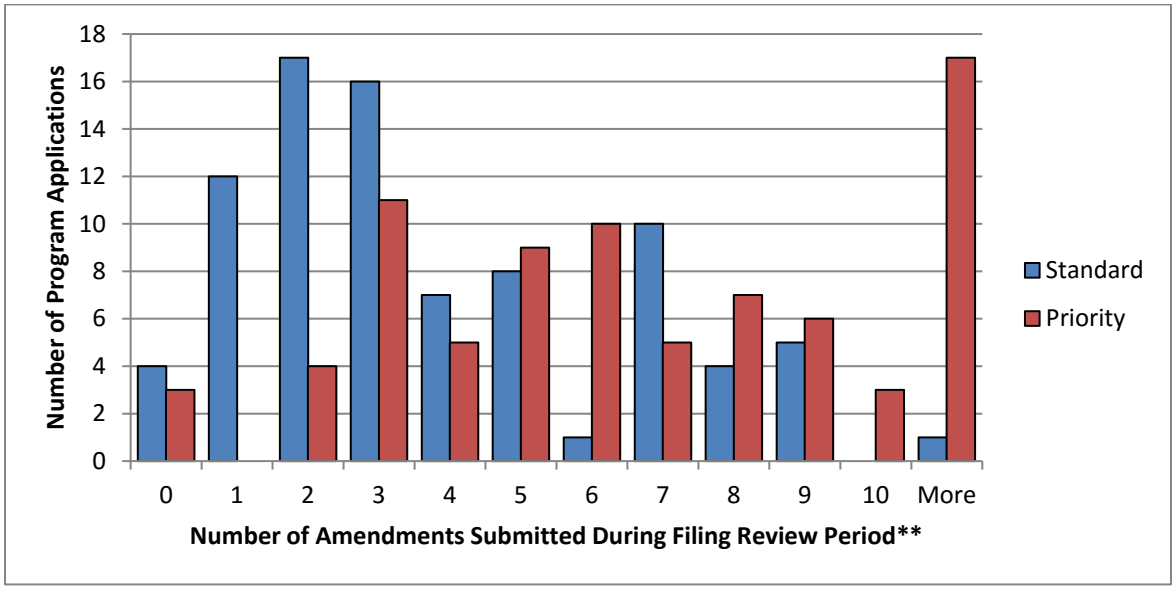
**Data encompass NME NDAs and original BLAs received during FYs 2008-2012 and acted on by June 30, 2016 (baseline) or received and acted on from October 1, 2012 to June 30, 2016 (Program).*

Figure 3-7. Distribution of amendments during the filing review period in the baseline*



** NME NDAs and original BLAs received during FYs 2008-2012 and acted on by June 30, 2016.*
***As cited in action letter (CDER) or RMS-BLA (CBER).*

Figure 3-8. Distribution of amendments during the filing review period in the Program*



** NME NDAs and original BLAs received and acted on from October 1, 2012 to June 30, 2016.*
***As cited in action letter or GSReview (CDER) or RMS-BLA (CBER).*

In both the baseline and the Program, applicants submitted a variety of types of amendments during the filing review period, such as:

- Requests for proprietary name reviews
- Notice of administrative changes
- Justification for applicability of foreign clinical studies
- Raw CMC data submissions that support the summaries provided in analysis
- Pharmacovigilance plans
- ClinPharm modeling data and study reports
- Labeling revisions/drafts

3.4 Mid-Cycle Communications (MCCs)

Key Findings

- MCC results reported here are consistent with those presented in the Interim Report for this evaluation.
- FDA conducted MCCs for all eligible applications, generally conforming with the spirit (but not always all the details) of Commitment Letter expectations.
- Applicants and FDA review teams appreciated that the MCC anchored the review schedule with a predictable milestone, and that the meeting helped propel the review forward.
- Almost all applicants also valued the opportunity for a holistic, broad-based discussion of the application, while some FDA review teams considered the MCC to be redundant to their already open, real-time communication practices.
- MCCs were most helpful when dialogue/questions were permitted, and when FDA provided an informal agenda or heads-up in advance so applicants knew how to prepare.
- A lack of significant issues identified at MCCs tended to be indicative of a strong application.

Format and Conduct

An MCC is a meeting held between FDA review staff and the applicant, typically within 2 weeks of FDA's internal mid-cycle meeting, to provide the applicant with an update on the status of their review. Normally held as a teleconference, applicants can expect to hear updates on various parts of the review, such as any identified review issues, safety concerns, and upcoming milestone dates in the review.

Commitment Letter Expectations

- Hold as a teleconference
- Conduct within 2 weeks of internal mid-cycle meeting
- Discuss major safety concerns
- Notify applicant about preliminary thinking on risk management
- Discuss significant issues identified to date
- Notify applicant of proposed date for LCM
- Provide update on plans for an AC
- Provide projected milestone dates for remainder of review cycle
- Ensure that RPM and appropriate review team members are present

From October 1, 2012 to June 30, 2016, FDA review teams held MCCs for all 170 eligible Program applications; FDA did not conduct an MCC for one application that received a CR before the scheduled date of the MCC. MCCs conducted generally conformed with the spirit of Commitment Letter expectations and recommendations.[18] That is, FDA review teams:

- Conducted 80.0% of MCCs within 2 weeks of the internal mid-cycle meeting.
- Held 98.8% of MCCs as teleconferences; two were held as face-to-face meetings at the applicants' request.

[18] As noted in the text, FDA reviewers sometimes addressed some topics listed in the Commitment Letter outside the MCC and did not repeat the topic in the MCC. In this way, FDA conduct of MCCs generally conformed with the spirit, but not always the details, of Commitment Letter expectations at the meeting itself.

- Provided updates on expected topics as relevant. They sometimes omitted topics that were addressed outside of the MCC.

MCCs were usually held as a two-way dialogue between FDA and applicant, with both FDA reviewers and applicants valuing the opportunity to gain a shared understanding of application and review issues. The size of MCCs varied, with some involving as few as two FDA staff and others including the entire review team. After the first two years of the Program, FDA clarified that review teams may select key review team members (along with the division/office director) to attend the MCC based on anticipated need rather than the entire review team. Post-action interview feedback suggests that this aspect of the Program has been running smoothly.

Both FDA reviewers and applicants viewed MCCs as a helpful "anchor" in the review process, facilitating early identification and clarification of issues, planning, and forward movement—which might set the stage for progress toward first-cycle approval. They cited the value of bringing together key review team members and senior management for a holistic, broad-based discussion of the application, noting that this cannot occur in routine day-to-day communications, no matter how committed FDA reviewers are to open, real-time communication. While nearly all applicants viewed MCCs favorably, some FDA reviewers felt that MCCs were unnecessary. This was mainly true in review divisions where open, real-time communications were already established practices. In those cases, some reviewers stated that the added burden of preparing for MCCs was not worthwhile because it diverted resources away from completing the primary reviews.

Discussion Topics

By the MCC, FDA's primary disciplines are in the process of reviewing the application and are expected to disclose any significant review issues they have identified to date. For most applications, representatives of review disciplines at the meeting spoke up only if they had issues to share with the applicant; those without issues usually did not comment unless asked by the applicant. Across 170 MCCs, 919 discussion items were identified. A majority of issues shared with applicants during MCCs pertained to Clinical (20.9%, 192/919) or Product Quality (17.7%, 163/919).

Applications that did not require discussion of certain disciplines (Clinical and Product Quality) at the MCC were associated with somewhat higher first-cycle approval rates than those where these issues were raised (see Table 3-13). This was true regardless of review priority. Similarly, applications with one or more issues identified as significant at the MCC had a statistically significantly lower first-cycle approval rate than those without significant issues (73.4% [n=124], 97.8% [n=46], $p < 0.001$). One potential explanation for this is that strong applications (well-organized, with robust evidence in support of the proposed indication) are less likely to encounter significant or approvability issues during the review. Alternatively, this could also indicate that earlier identification and resolution of issues, prior to the MCC, can lead to a greater likelihood of first-cycle approval.

Table 3-13. First-cycle approval rates for Program applications, by MCC discussion topic*

Discipline / MCC Topic	First-Cycle Approval Rate	
	Applications with Topic Discussed in MCC	Applications with Topic Not Discussed in MCC
Product Quality	76.2% (77/101)	85.5% (59/69)
Clinical	74.7% (71/95)	86.7% (65/75)
Nonclinical	75.8% (25/33)	81.0% (111/137)
Statistics	68.8% (22/32)	82.6% (114/138)
Labeling	94.4% (17/18)	78.3% (119/152)
PMRs/PMCs**	100% (14/14)	78.2% (122/156)

**Data encompass NME NDAs and original BLAs received and acted on from October 1, 2012 to June 30, 2016, excluding one application that did not have an MCC due to an early CR.*

***PMR = Post-Marketing Requirement. PMC = Post-Marketing Commitment. These topics are usually discussed in advanced stages of the review.*

There was also a higher first-cycle approval rate (81.2% [n=69], 64.3% [n=24], p = 0.077)[19] when an agenda was sent prior to the MCC, although an agenda in and of itself is unlikely to be a causal factor. Instead, it might reflect a broader pattern of good communication practices, which in turn might be correlated with higher first-cycle approval rates. Regardless, FDA has adopted transmittal of an agenda prior to the MCC as a good practice to give applicants a sense of what will be discussed.

[19] For some Program applications, ERG could not determine whether an agenda was sent. This statistical analysis includes only those applications where we could determine with certainty that an agenda was or was not sent.

3.5 Discipline Review Letters (DR Letters)

Key Finding

- DR letter results reported here are consistent with those presented in the Interim Report for this evaluation.
- FDA rarely sent DR letters to applicants in the Program and in the baseline.

FDA sends DR letters to convey thoughts about possible deficiencies identified by a discipline review team at the conclusion of that discipline's review. In the Program, FDA follows existing guidance on DR letters and strives to issue them in advance of the Program's LCM, or alternatively as part of the background package for the LCM.

Commitment Letter Expectations

- Follow existing guidance on issuing DR letters
- Send before planned LCM or include in LCM briefing package

In both the Program and the baseline, FDA rarely issued DR letters:

- Program: 11 DR letters for 7.6% of applications

  Most common disciplines: Clinical (7), Product Quality (5)
- Baseline: 49 DR letters for 13.2% of applications

  Most common disciplines: Product Quality (16), Unspecified (14), Clinical Pharmacology (6), Statistics (5)

Although the PDUFA V Commitment Letter encourages use of DR letters when appropriate, frequent communication with applicants during the review might actually decrease the need for these letters. In the Program, DR letters might be deemed redundant or unnecessary given previous communications with the applicant about review issues.

3.6 Late-Cycle Meetings (LCMs) / Advisory Committee Meetings (ACs)

Key Findings

- LCM and AC results reported here are consistent with those presented in the Interim Report for this evaluation.
- FDA conducted LCMs for most eligible Program applications, and the FDA's management of these meetings largely conformed with Commitment Letter expectations and recommendations.
- Applicants valued the opportunity to meet with the FDA review team, regardless of the approvability status of their applications. The LCM anchored the review schedule with a predictable milestone and provided a vehicle for holistic, multi-disciplinary discussion of application status, helping to focus the attention of key players on resolving the remaining issues.
- LCMs were most helpful when there were significant issues to discuss that could be resolved in the first-cycle. They also provided an opportunity to discuss labeling/PMR/PMC (if there were no significant issues).
- To help ease the added burden and time pressures associated with an AC (especially for Priority reviews), good practices included:
  - ✓ Early notification and confirmation of the AC (e.g., in filing letter and MCC as recommended in the Commitment Letter).
  - ✓ Providing ample time between the LCM and AC (when possible).

Late-Cycle Meetings

LCMs are meetings held late in the review cycle between members of the FDA review team and the applicant to discuss the status of the review, including topics like AC preparation, outstanding IRs, and any remaining deficiencies in the application.

Commitment Letter Expectations

- Send briefing package in advance
- Include signatory authority or assigned deputy, along with appropriate review team members
- Schedule according to prescribed timelines

Potential Topics for Discussion

- Major deficiencies identified to date
- AC issues/topics
- Assessment of need for REMS or other risk management actions
- Information requests or additional data applicant wishes to submit

FDA review teams held 155 LCMs for 167 eligible Program applications. Three LCMs were not conducted for applications that received a CR before the LCM was scheduled. Nine LCMs were not conducted for applications where the applicant declined to meet; all received a first-cycle approval. The LCMs conducted typically conformed with Commitment Letter expectations and recommendations.

By the LCM, most primary disciplines have completed their review of the application. As with MCCs, the discussion at LCMs largely focused on the disciplines that identified issues during the review. For applications with few or no approvability issues, FDA and applicants frequently used the LCM to discuss end-of-review topics, such as PMRs/PMCs and labeling. First-cycle approval rates were higher for such applications than for those that still required discussion of Clinical, Product Quality, or Statistics aspects of the application (see Table 3-14).

Table 3-14. First-cycle approval rates for Program applications, by LCM discussion topic*

Discipline / LCM Topic	First-Cycle Approval Rate	
	Applications with Topic Discussed at LCM	Applications with Topic Not Discussed at LCM
PMRs/PMCs	93.5% (86/92)	66.7% (42/63)
Labeling	90.7% (88/97)	69.0% (40/58)
Clinical	74.3% (55/74)	90.1% (73/81)
Product Quality	77.8% (56/72)	86.7% (72/83)
Statistics	63.2% (12/19)	85.3% (116/136)
Nonclinical	70.6% (12/17)	84.1% (116/138)

**Data encompass NME NDAs and original BLAs received and acted on from October 1, 2012 to June 30, 2016, excluding the 16 applications without LCMs.*

The data were sufficient to test for differences in time to approval for seven LCM attributes; for three of the seven attributes, we found a statistically significant difference between applications with these attributes and applications without:

- Applications with one or more major deficiencies identified at the LCM were correlated with a longer time (mean 1.31 months longer, $p = 0.001$)[20] to reach first-cycle approval than those where no major deficiencies were identified at the LCM.
- Applications where the applicant notified FDA of an intent to submit additional data were correlated with a longer time (mean 1.12 months longer, $p = 0.025$)[21] to reach first-cycle approval than those where the applicant did so notify FDA at the LCM.
- Applications with the LCM scheduled in accordance with Program timelines were correlated with a shorter time (mean 1.31 months shorter, $p = 0.001$)[22] to reach first-cycle approval than those where the LCM was not scheduled in accordance with Program timelines.

  Applications with LCMs that were not scheduled in accordance with Program timelines were more likely to have an AC, which could be the reason for the association with a longer mean time to approval.

About 50% of LCMs were conducted as face-to-face meetings. FDA and applicants especially preferred a face-to-face meeting over a teleconference when significant issues or major deficiencies needed to be discussed. In these cases, LCMs were considered a helpful forum for a holistic, multi-disciplinary

[20] In a simple linear regression controlling for review priority.
[21] In a simple linear regression controlling for review priority. Of the 12 applications where applicants notified FDA of the intent to submit additional data, 3 were associated with goal extensions issued after the LCM.
[22] In a simple linear regression controlling for review priority.

discussion of application status, helping to focus the attention of key players on resolving the remaining issues. LCMs were especially helpful when these issues / deficiencies could be resolved in the first review cycle. If they appeared not to be resolvable during the first review cycle, applicants still found the discussion helpful for future planning—though in seven cases FDA took an early CR action or the applicant withdrew the application before the LCM.

Applications with no significant issues or deficiencies to be discussed in the LCM tended to be on pace for a first-cycle approval, with some reaching approval before the PDUFA goal date. Some of these applicants requested a teleconference rather than a face-to-face meeting (see Table 3-15). In post-action interviews, some review teams suggested that FDA offer the ability to opt out of the LCM entirely (if applicants agree) when there are no significant issues to discuss; applicants generally valued the LCM, though, and did not suggest this option. Table 3-16 provides additional applicant and FDA review team feedback on LCMs.

Table 3-15. Characteristics of face-to-face and teleconference LCMs*

Characteristic	Face-to-Face LCM (n=78)	Teleconference LCM (n=77)
Mean meeting duration	60.2 minutes**	33.4 minutes**
Mean number of significant review issues discussed per LCM	3.1	1.3
Application presented to AC	34.6%	19.5%
First-cycle approval rate	83.3%	92.2%

**Data encompass NME NDAs and original BLAs received and acted on from October 1, 2012 to June 30, 2016, excluding the 16 applications without LCMs.*

***Mean excludes two LCMs for which ERG did not have meeting duration data.*

Table 3-16. Post-action interview feedback on LCMs

Applicant Feedback	FDA Review Team Feedback
Applicants generally found LCMs very useful to anchor review process with a reliable and predictable milestone. Applicants found the LCM background package to contain useful information, which helped them decide who to include and how to prepare for the meeting. Some applicants found it challenging to plan their work when the LCM and AC were scheduled close together. A few applicants found it challenging to know the status of their applications if communication decreased after the LCM.	FDA reviewers generally found LCMs to serve as a useful milestone for internal review planning. Many FDA reviewers commented that LCMs were at least somewhat helpful in: • Enhancing communication, transparency, and predictability. • Clearly delineating issues to ensure shared understanding and advance progress toward resolution where possible. • Formally identifying review issues as "significant" to underscore importance and encourage applicant to respond. Some review teams found it challenging to: • Accommodate the additional work associated with LCM. • Address significant issues (too late in process to resolve for some Priority applications). • Develop topics to discuss if no significant issues remained. • Include in short reviews and approve product as quickly as desired.

Advisory Committee Meetings

ACs provide independent, expert advice on NDAs and BLAs and incorporate public comment and discussion. Due to the complexity of NME NDAs and original BLAs, it is not uncommon to hold AC meetings to solicit feedback from experts and others outside the FDA review team. Nevertheless, ACs were somewhat less common in the Program than in the baseline, with about 25% of Program applications being presented to ACs compared to about 39% percent of baseline applications.

Commitment Letter Recommendations

- (Intent to) Convene AC meetings no later than 3 months prior to the PDUFA goal date for Standard reviews and no later than 2 months prior for Priority reviews.
- LCM will occur not less than 12 calendar days before the date of the AC.
- AC briefing package will accompany the LCM briefing document no less than 20 days prior to the AC
- (Intent to) Provide final questions for the AC to the applicant and the AC 2 calendar days in advance of the AC meeting.

Although they provide an opportunity for more feedback about applications, ACs also add significant burden and time pressures to both FDA review teams and applicants—especially for Priority reviews, where the review clock is shorter. From October 1, 2012 to June 30, 2016, Program applications under Priority review with ACs took more time to reach first-cycle approval than those without an AC; see Table 3-17 for more information. This difference is largely attributable to Priority applications without an AC that were approved on average one month earlier than the PDUFA goal date.

Applicants found early updates about the likelihood of an AC (in filing letter) and early confirmation to be very helpful, enabling them to plan and allocate resources accordingly. This practice helped ease the burden and time pressures associated with ACs, at least to some extent. In post-action interviews, some FDA review teams and applicants suggested easing LCM deadlines when an AC is expected. Scheduling LCMs around ACs is particularly challenging for FDA review teams, who have limited control over when ACs can take place. In some cases, they had to schedule LCMs very close to ACs (see Table 3-18), resulting in a great deal of work in a short period of time. Both FDA review teams and applicants suggested allowing ample time between LCMs and ACs when possible.

Table 3-17. Time to first-cycle approval for Program applications with and without an AC*

Review Priority	Time to First-Cycle Approval (mean)	
	With AC	Without AC
Standard	12.6 months (n=14)	12.7 months (n=49)
Priority	9.0 months (n=20)	7.4 months (n=53)

**Data encompass NME NDAs and original BLAs received and acted on from October 1, 2012 to June 30, 2016.*

Table 3-18. Scheduling of LCM/AC activities for Program applications with an AC*

Schedule Item	Program Applications with AC Meetings	
	Standard (n=17)	Priority (n=25)
Mean time from LCM briefing package to AC	30.3 days (Commitment Letter expectation: no less than 20 days)	26.6 days (Commitment Letter expectation: no less than 20 days)
Mean time from LCM to AC	21.6 days (Commitment Letter expectation: no less than 12 days)	17.6 days (Commitment Letter expectation: no less than 12 days)

**Data encompass NME NDAs and original BLAs received and acted on from October 1, 2012 to June 30, 2016 that had ACs.*

3.7 Inspections

Key Findings

- Inspection results reported here are consistent with those presented in the Interim Report for this evaluation.
- Inspections represented a "black box" to many FDA reviewers and applicants. This was in stark contrast to the high levels of transparency and open communication associated with other aspects of the review process.
- Both FDA reviewers and applicants noted that late inspections have the potential to affect the timeliness of first-cycle actions and are therefore of concern.
- An analysis of inspection practices at FDA could generate insights into how to improve transparency and communication (both internally and with applicants); FDA is conducting such an analysis.

In the Program, FDA strives to complete all inspections within 6 months of receipt of original application submission for Priority reviews and within 10 months of receipt of original application submission for Standard reviews to allow for resolution of any potential issues in the remaining months. For the purpose of this Program assessment, "all inspections" consists of Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) inspections.[23] We define inspection completion as follows:

- GMP inspections: Complete when the Office of Compliance (OC) or Office of Pharmaceutical Quality (OPQ)[24] makes an overall recommendation (CDER) or the investigator concludes the onsite inspection of the last site (CBER).
- GCP inspections: Complete on the published date of the Clinical Inspection Summary (CDER) or when the investigator concludes the onsite inspection of the last site (CBER).

Commitment Letter Expectations

- Complete all GCP/GLP/GMP inspections within 6 months of original receipt for Priority applications
- Complete all GCP/GLP/GMP inspections within 10 months of original receipt for Standard applications

Inspections were completed within Program timetables for 46.1% of the applications received and acted on from October 1, 2012 to June 30, 2016 (see Figure 3-9 and Figure 3-10). When inspections were not completed within Program timelines, in most (87.6%) cases the delays were attributable to late completion of GMP inspections. On-time inspection completion rates were somewhat higher among two groups of Program applications:

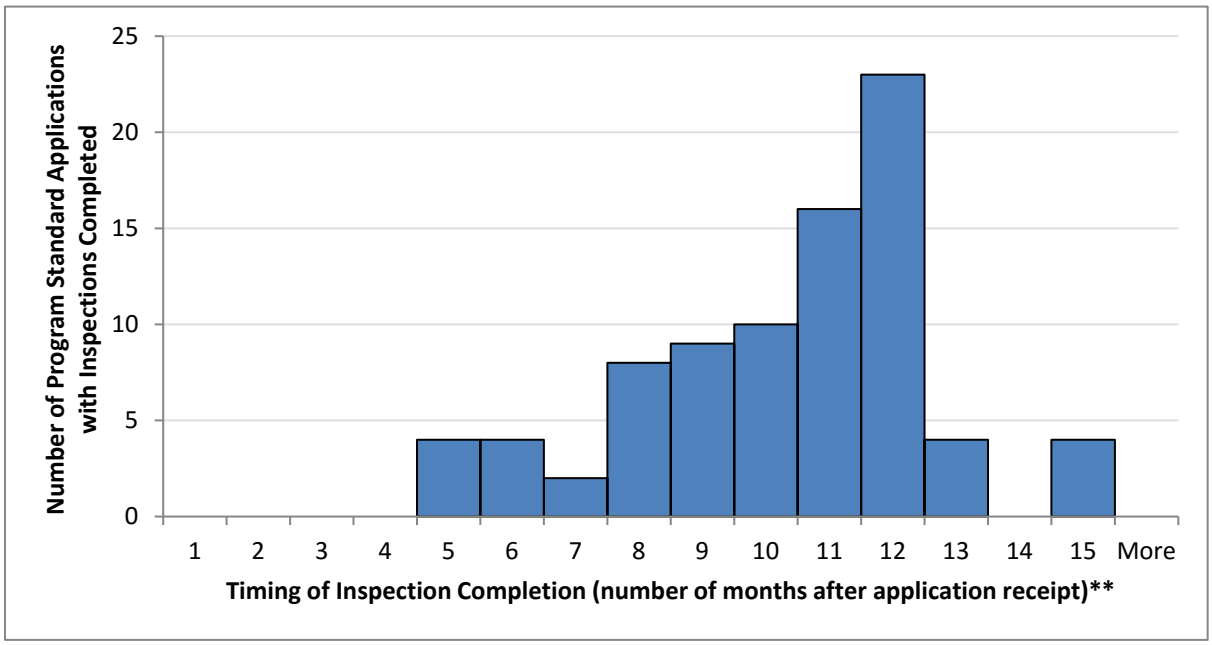
- Applications with Breakthrough Therapy designation: 58.8% (20 of 34)
- Applications receiving early actions (at least one month before goal date): 90.0% (27 of 30)

[23] GLP inspections are not included due to the very low number of GLP inspections being conducted during the review cycle; many occur during the IND stage.

[24] During the first half of the Program (October 2012 to January 2015, FDA CDER's OC was responsible for preapproval and surveillance inspection activities. After being launched in January 2015, FDA CDER's new OPQ assumed these responsibilities.

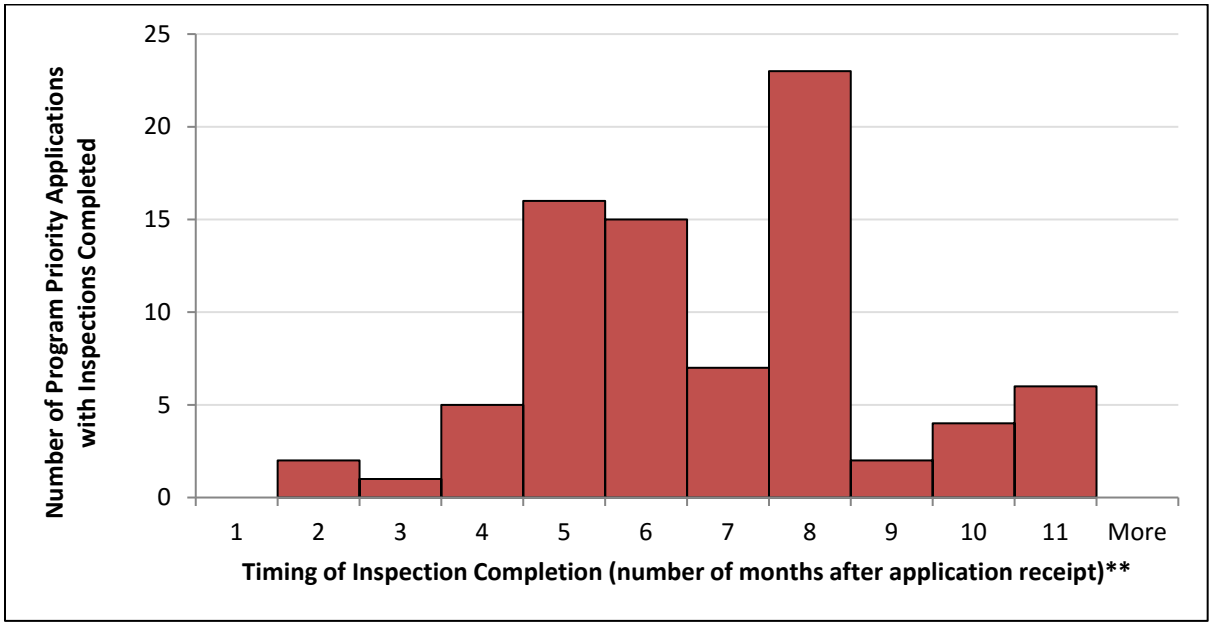
When inspections were completed within Program timelines, time to first-cycle approval was less (mean 1.66 months less, $p < 0.001$)[25] than that for applications with late inspections.

Figure 3-9. Timing of inspection completion for Program Standard applications*



**NME NDAs and original BLAs received and acted on from October 1, 2012 to June 30, 2016.*
***Inspections completed at 13 months or later were due to goal extensions.*

Figure 3-10. Timing of inspection completion for Program Priority applications*



**NME NDAs and original BLAs received and acted on from October 1, 2012 to June 30, 2016.*
***Inspections completed at 9 months or later were due to goal extensions.*

[25] In a simple linear regression controlling for review priority.

In some cases, especially when a product represents an advance in an area of medical need (as with Breakthrough Therapy products or applications receiving early actions), in the interest of public health, FDA review teams have taken steps to expedite the inspection process to ensure availability of the product upon approval. Some review teams have commented that they have established positive relationships with inspection staff and are able to communicate these needs early, in some cases before submission of the application.

Other FDA review teams have experienced frustration with the difficulties they face in attempting to obtain information about the status of inspections, which they needed both for their own planning and for updating the applicant. Similarly, some applicants expressed confusion about the inspection process, stating that they had difficulty (1) understanding who was in charge of inspections and (2) receiving regular status updates about those inspections.

Because inspections are largely a responsibility outside of the primary review team, a thorough analysis of inspection processes, information flows, and communication touch points was outside the scope of this Program assessment. Nevertheless, ERG has observed the following:

- In some cases, timely completion of inspections is hindered by logistical challenges in inspecting foreign facilities. Generally, inspection staff try to coordinate both surveillance and pre-approval or pre-license inspections to optimize efficiencies when scheduling trips to foreign facilities. This leads to some inspectors being scheduled for multiple sites for different products while abroad, but these plans might not align with Program timelines due to multiple competing priorities.
- Inspections often require staff with technical expertise and knowledge of specific manufacturing processes, depending on the product. This need adds to planning and staffing challenges.
- In some cases, technical constraints also pose challenges. For instance, a Contract Research Organization might manufacture a product at specific times of the year, which presents a challenge to inspectors for biologics who need to be present to witness the manufacture of the product.

3.8 Review Process and Application Attributes

Key Findings

- ***New to the Final Report:*** Updated FDA guidelines for expedited review provide flexibility to meet Program requirements while still achieving early action where warranted.
- Review and application attribute results reported here are consistent with those presented in the Interim Report for this evaluation.
- As measured by number of IRs, information exchange between applicants and FDA was greater in the Program than in the baseline—especially among Priority applications and those with special designations such as Breakthrough Therapy and Fast Track.
- FDA used goal extensions less frequently in the Program than in the baseline; in most cases, goal extensions in the Program made it possible to approve the applications in the first review cycle.
- Applications with shorter-than-average primary review times were associated with a higher first-cycle approval rate and shorter time to first-cycle approval compared to applications with longer primary review times.
- Applications with special designations had relatively high first-cycle approval rates and relatively short times to first-cycle approval.
- About half of all Program applications are concentrated in a few therapeutic areas (neoplasms, congenital/genetic disorders, and infections).

ERG analyzed data on numerous review process and application attributes that are independent of the Program. We found interesting results for five attributes: IRs, goal extensions, primary review completion times, special review designations, and expedited reviews.

Information Requests

Throughout the review process, FDA may request information from applicants to clarify aspects of the submission or provide additional data/analyses. Though IRs and responses are not the only form of communication between FDA and applicants, they are an indicator of the frequency of information exchange during review.[26] In interviews, both FDA and applicants stated that providing IRs in real time, as the need arises—rather than waiting for IRs from several disciplines in order to bundle and send them in larger batches less frequently—is critical to advancing reviews. In the Program, FDA reviewers issued IRs more frequently throughout the review than in the baseline. Some applicants found it challenging to manage the volume and timing of IRs, but they still preferred receiving IRs in real time to help advance the review efficiently.

[26] Frequency of information exchange is not representative of the total amount of data or information requested during review.

On average, FDA issued more IRs per CDER NME NDA[27] in the Program than in the baseline (see Table 3-19). This effect was primarily driven by Priority applications (Figure 3-11 and Figure 3-12). FDA patterns of issuing IRs also varied by regulatory outcome, with applications receiving an Approval in the first cycle generally having more IRs than those receiving a CR (Figure 3-13 and Figure 3-14). In the figures below, some IRs are shown as being issued before application receipt. This is because FDA issued IRs for applications granted "rolling reviews", in which applicants submit the application component by component, and the application is considered received when the applicant submits the final component.

Table 3-19. Number of IRs and requested items in baseline and Program NDAs*

	Baseline (n=147)	Program (n=109)
Mean number of IRs per application	14.3	21.4
Mean number of requested items per application**	38.6	48.2

**Data encompass CDER NME NDAs received in FYs 2008-2012 and acted on by June 30, 2016 (baseline) or received and acted on from October 1, 2012 to June 30, 2016 (Program). Due to data limitations, ERG did not include BLAs in this dataset.*

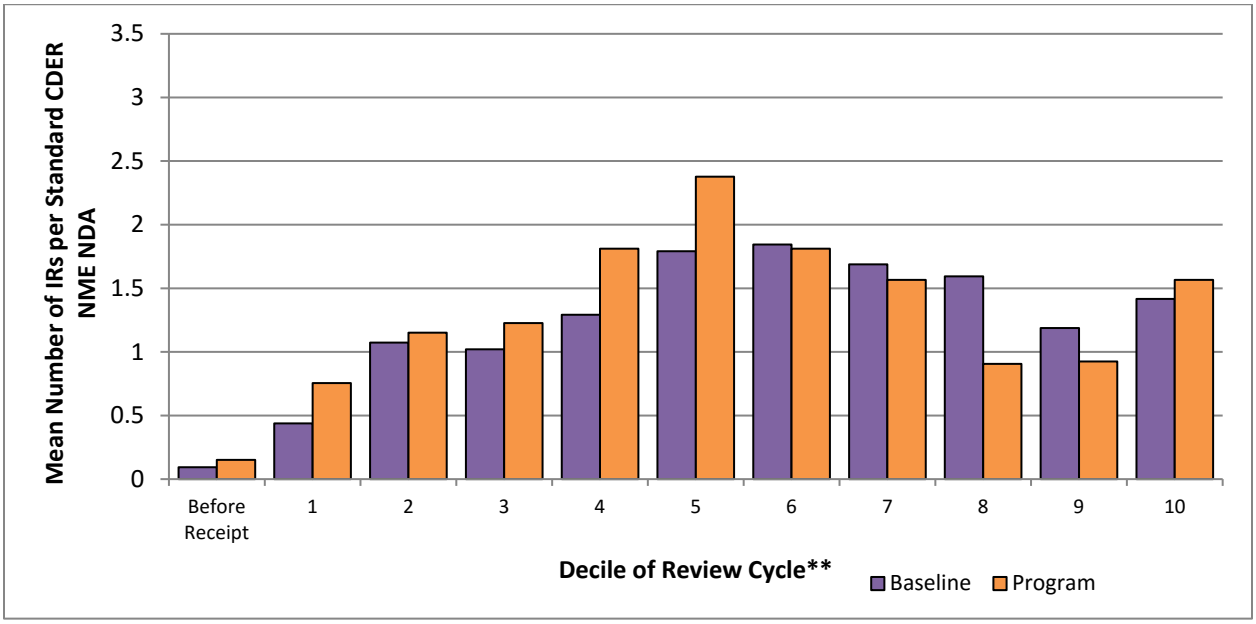
***An "item" is a single dataset/analysis/submission requested in an IR; an IR often includes multiple items. Mean number of items is the sum of all items requested in IRs during application reviews.*

In interviews, FDA review teams and applicants cited some good practices that facilitate efficient, on-target responses to IRs:

- Provide target dates for IR responses (and be willing to negotiate with the applicant as needed). This helped applicants organize and prioritize IRs.
- Write IRs clearly, with context/rationale. This helped applicants understand FDA needs the first time, reducing the need for back and forth communications to clarify the request or re-request the information.
- Accept IR responses via email prior to formal submission via the electronic submission gateway. This enabled FDA reviewers to view the responses as quickly as possible.

[27] ERG excluded BLAs from comparisons of IRs in the baseline and Program due to limitations in the data available from FDA databases.

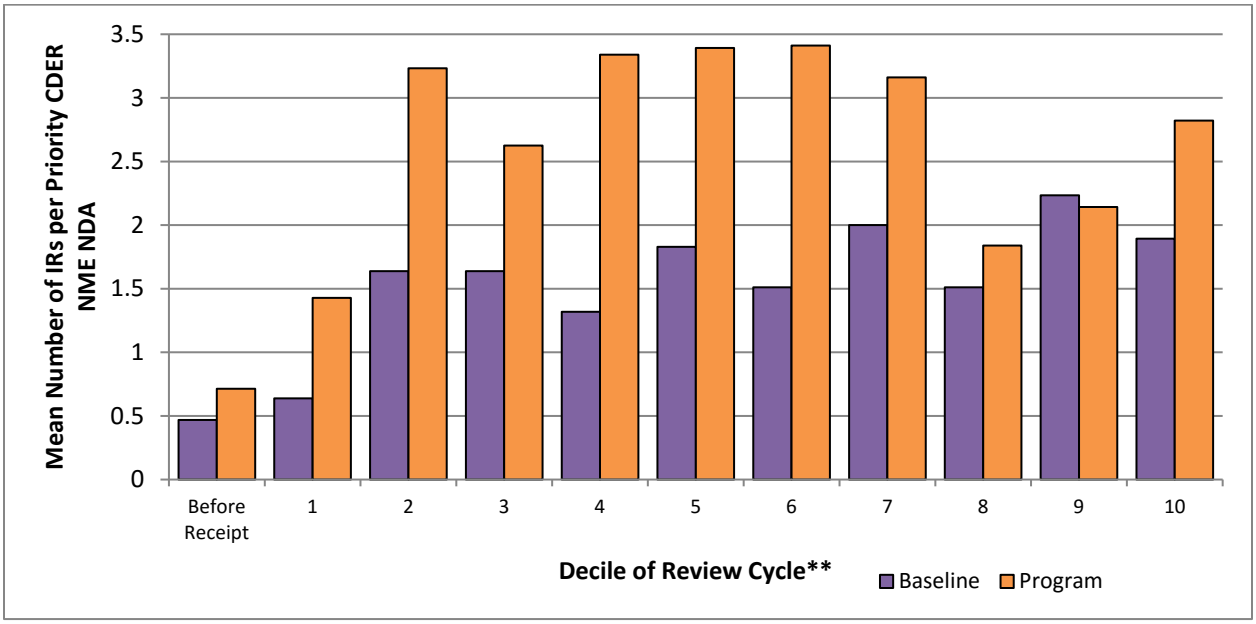
Figure 3-11. Mean number of IRs per Standard CDER NDA per decile of review cycle in the baseline and Program*



**Data encompass CDER NME NDAs received in FYs 2008-2012 and acted on by June 30, 2016 (baseline) or received and acted on from October 1, 2012 to June 30, 2016 (Program). Due to data limitations, ERG did not include BLAs in this dataset.*

***ERG calculated mean values by decile of review to account for differences in review times for PDUFA IV versus PDUFA V applications, Standard versus Priority applications, and applications with/without goal extensions.*

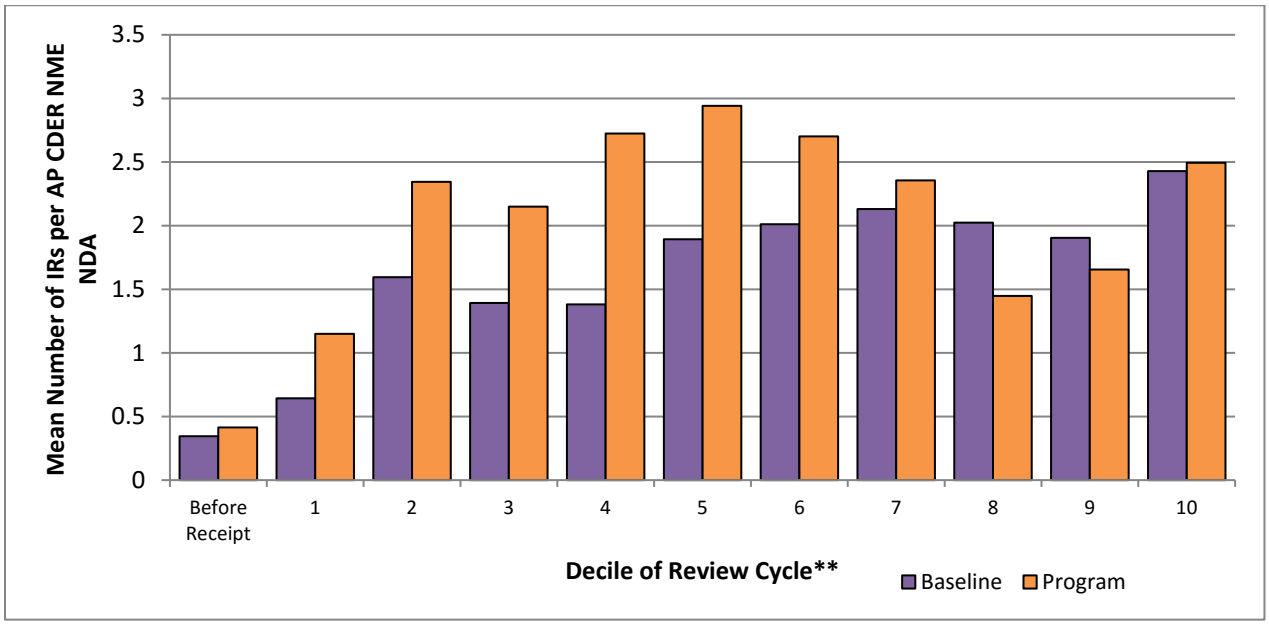
Figure 3-12. Mean number of IRs per Priority CDER NDA per decile of review cycle in the baseline and Program*



**Data encompass CDER NME NDAs received in FYs 2008-2012 and acted on by June 30, 2016 (baseline) or received and acted on from October 1, 2012 to June 30, 2016 (Program). Due to data limitations, ERG did not include BLAs in this dataset.*

***ERG calculated mean values by decile of review to account for differences in review times for PDUFA IV versus PDUFA V applications, Standard versus Priority applications, and applications with/without goal extensions.*

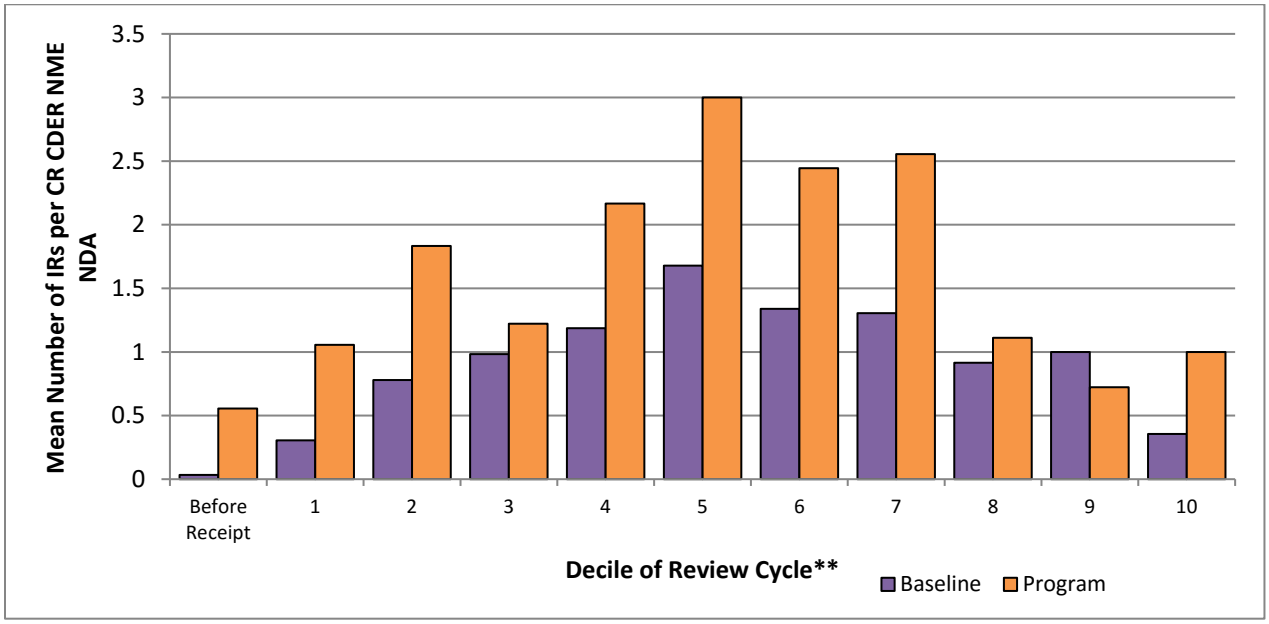
Figure 3-13. Mean number of IRs per approved CDER NDA per decile of review cycle in the baseline and Program*



*Data encompass CDER NME NDAs received in FYs 2008-2012 and acted on by June 30, 2016 (baseline) or received and acted on from October 1, 2012 to June 30, 2016 (Program). Due to data limitations, ERG did not include BLAs in this dataset.

**ERG calculated mean values by decile of review to account for differences in review times for PDUFA IV versus PDUFA V applications, Standard versus Priority applications, and applications with/without goal extensions.

Figure 3-14. Mean number of IRs per complete response CDER NDA per decile of review cycle in the baseline and Program*



*Data encompass CDER NME NDAs received in FYs 2008-2012 and acted on by June 30, 2016 (baseline) or received and acted on from October 1, 2012 to June 30, 2016 (Program). Due to data limitations, ERG did not include BLAs in this dataset.

**ERG calculated mean values by decile of review to account for differences in review times for PDUFA IV versus PDUFA V applications, Standard versus Priority applications, and applications with/without goal extensions.

Goal Extensions

When FDA is reviewing an NME NDA or original BLA, receipt of a major amendment can trigger a goal extension of 3 months. In PDUFA IV, FDA was permitted to issue a goal extension upon receipt of a major amendment only during the last 3 months of the review clock, whereas in PDUFA V FDA may issue an extension upon receipt of a major amendment any time during the review clock. In the Program, FDA exercised that flexibility, issuing goal extensions for 39 applications from 2.0 to 12.0 months after application submission (see Table 3-20).

Table 3-20. Goal extensions in the first cycle among baseline and Program applications*

Cohort	Percent of Applications that Received a Goal Extension	Percent of Applications With a Goal Extension that Received First-Cycle Approval	Time After Original Submission When Goal Extension Was Issued
Baseline	26.0% *(57/219)*	59.7% *(34/57)*	Standard: 6.2 to 9.9 months Priority: 3.2 to 5.9 months
Program	22.8% *(39/171)*	89.7% *(35/39)*	Standard: 3.4 to 12.0 months Priority: 2.0 to 8.0 months

** NME NDAs and original BLAs received during FYs 2008-2012 and acted on by June 30, 2016 (baseline) or received and acted on from October 1, 2012 to June 30, 2016 (Program).*

Nevertheless, the rate of goal extensions was slightly lower in the Program than in the baseline, and a higher proportion of Program applications with a goal extension received first-cycle approval. Within the Program, applications with a goal extension also exhibited a higher first-cycle approval rate than applications without a goal extension (89.7% [n=39], 76.5% [n=132], p = 0.072). [28] This is in accordance with the Commitment Letter expectation that, except for rare cases, goal extensions are to be used when the amendment can be expected to resolve the deficiencies in the current cycle. Applications with goal extensions, on average, took 3.74 months longer (p = <0.001)[29] to reach first-cycle approval than applications without goal extensions. This is generally less than would be experienced with a first-cycle CR followed by resubmission and a second review cycle.

Some FDA review teams and applicants suggested that FDA provide clarification about how the timing of milestone communications (MCCs and LCMs) shifts in the event of a goal extension. FDA's September 2014 update of the Desk Reference Guide provides some guidance on this topic.

[28] In this assessment, ERG generally defines statistical significance at p ≤ 0.05. With a p-value of 0.072, the higher first-cycle approval rate of applications with goal extensions warrants mention, even if ERG does not describe the difference as statistically significant.

[29] In a simple linear regression controlling for review priority; note also that this increase in time is greater than the 3-month extension, likely due to a number of priority applications receiving approval earlier than the goal date.

Primary Review Completion Times (in CDER)

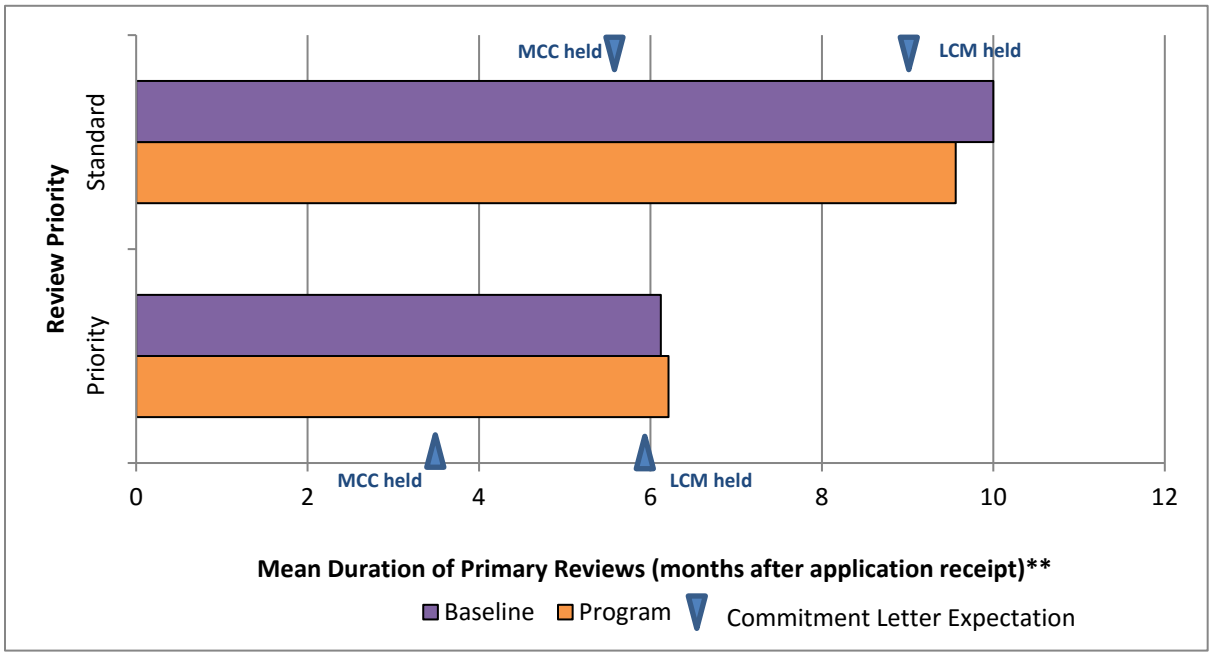
For CDER, the timeline for primary review completion is the same in the Program as it was in PDUFA IV.[30] In post-action interviews, a few FDA reviewers stated that the added burden associated with MCCs and LCMs diverted resources from primary reviews, giving the impression that there was less time to complete the primary reviews. This impression was especially prominent when the review team needed to prepare for an AC or was aiming for an early action. In fact, mean primary review times in the Program were similar to those in the baseline (see Figure 3-15).

Controlling for review priority, applications with primary reviews that were completed in a longer-than-average time were correlated with a statistically significantly lower first-cycle approval rate (73.9% [n=92], 86.1% [n=79], $p = 0.049$) and took, on average, 2.19 months longer ($p < 0.001$)[31] to reach first-cycle approval. Possible explanations include:

- Applications that are well-organized with compelling data and analyses to support the proposed indication might be less likely to have major issues or deficiencies (and be easier and quicker to review), increasing the likelihood of a first-cycle approval and a quicker time to action.
- FDA review teams might be motivated to review and approve promising new drugs and biologics that address unmet medical needs more quickly in the interest of public health, pushing the review along faster than required.
- When primary reviews are completed later and more issues are identified, less time remains to resolve the issues, potentially slowing first-cycle approval or leading to a first-cycle CR.

[30] http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM218757.htm
[31] In a simple linear regression controlling for review priority.

Figure 3-15. Mean duration of CDER primary reviews for baseline and Program applications,* by review priority



** CDER NME NDAs and original BLAs received during FYs 2008-2012 and acted on by June 30, 2016 (baseline) or received and acted on from October 1, 2012 to June 30, 2016 (Program). CDER and CBER have different definitions for primary review completion, so ERG included only CDER applications to ensure comparability of the data.*

***Based on date of last primary review completion for each application's review team. Completion dates vary by discipline (Clinical, Product Quality, Statistics, Microbiology, Clinical Microbiology, Pharmacology/Toxicology, Clinical Pharmacology). In the baseline, the mean duration of primary reviews was longer than 6 months due to goal extensions.*

Special Designations

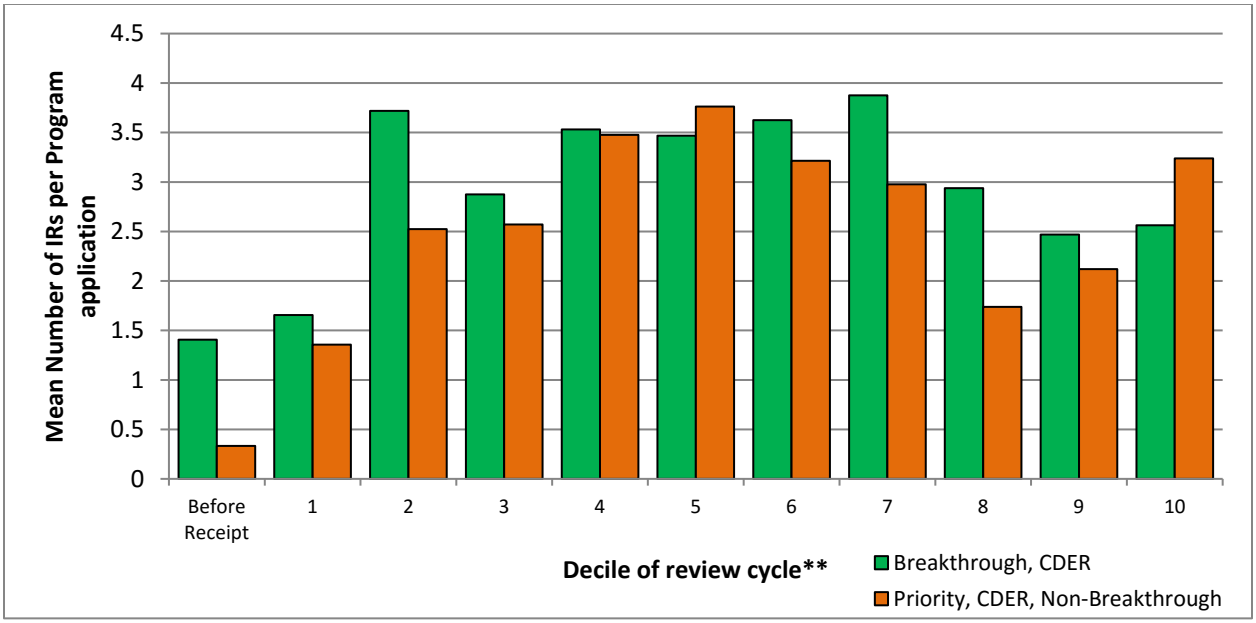
FDA has several programs to expedite the development of drugs and biologics that target therapeutic areas where there are urgent medical needs. Applications for products falling into these categories may receive special designations, such as Breakthrough Therapy and Fast Track. Some products may also be designated as orphan drugs if they meet certain criteria. Many orphan designated products also receive the Breakthrough and/or Fast Track designation to expedite their development. In the Program, these applications were marked by relatively high levels of information exchange (see Figure 3-16 and Figure 3-17) and relatively high first-cycle approval rates, and relatively short times to first-cycle approval (see Table 3-21). The applicants generally praised FDA review times as providing excellent communication and transparency, facilitating prompt first-cycle approval when possible.

A majority of applications with special designations fell within three therapeutic areas, which are characterized by relatively high first-cycle approval rates:

- Neoplasms benign, malignant, and unspecified (including cysts and polyps): 94.1% (n=34)
- Congenital, familial, and genetic disorders: 82.4% (n=17)
- Infections and infestations: 85.3% (n=34)

Nearly half (49.7%) of Program applications fell in these three categories, compared to 35% of baseline applications.

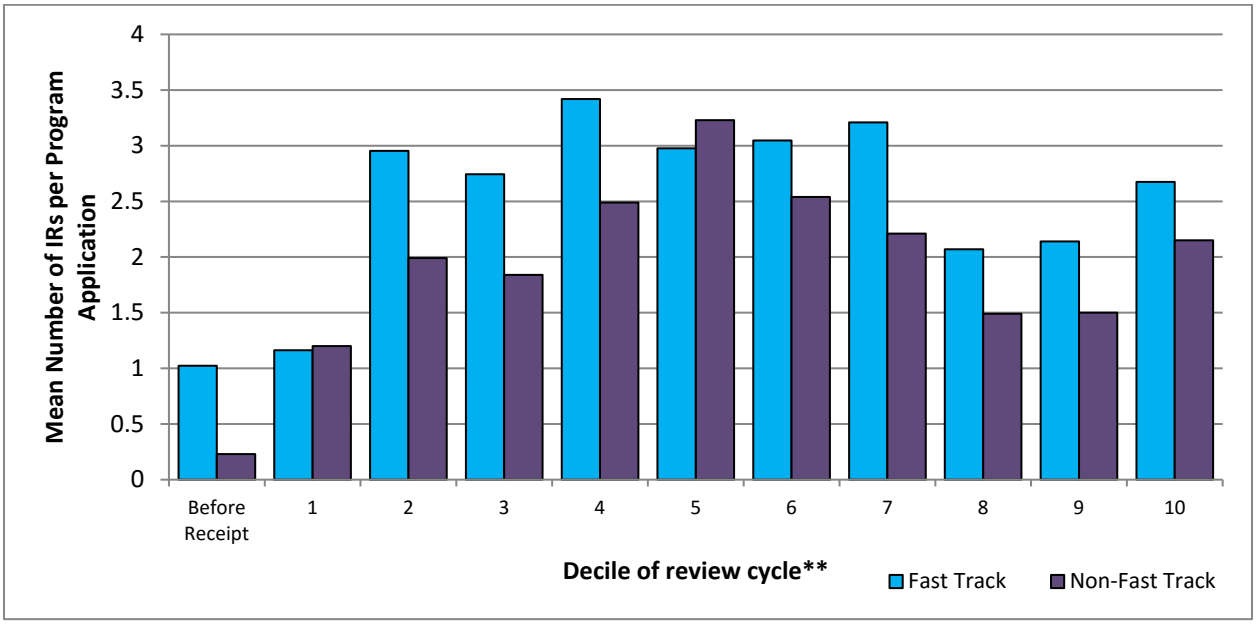
Figure 3-16. Mean number of IRs per CDER application with Breakthrough Therapy designation per decile of review cycle in the Program*



*Data encompass CDER Program applications received and acted on from October 1, 2012 to June 30, 2016, including NDAs and BLAs.

**ERG calculated mean values by decile of review to account for differences in review times for PDUFA IV versus PDUFA V applications, Standard versus Priority applications, and applications with/without goal extensions.

Figure 3-17. Mean number of IRs per CDER application with Fast Track designation per decile of review cycle in the Program*



*Data encompass CDER Program applications received and acted on from October 1, 2012 to June 30, 2016, including NDAs and BLAs.

**ERG calculated mean values by decile of review to account for differences in review times for PDUFA IV versus PDUFA V applications, Standard versus Priority applications, and applications with/without goal extensions.

Table 3-21. Outcomes of Program applications with special designations*

Category	Group of Program Applications			
	Breakthrough Therapy (n=34)	Fast Track (n=49)	Orphan Drug (n=64)	All Program (n=171)
First-cycle approval rate	85.3%	87.8%	85.9%	79.5%
Median time to first-cycle approval	6.3 months	8.0 months	8.0 months	11.0 months
Mean number of IRs per application	32.0	27.1	28.6	22.8
Mean number of IR items per application	94.6	92.1	93.3	75.4
Received Priority review	97.1%	83.7%	75.0%	47.4%

**Data encompass NME NDAs and original BLAs received and acted on from October 1, 2012 to June 30, 2016.*

Expedited Reviews

Early in the Program, a few reviewers expressed concern that implementation of Program milestone communications might hamper FDA's ability to approve certain Priority applications as early as desired—particularly when the reviewers are working toward early action to help address unmet medical needs for serious diseases and already have well-established practices for open, "real-time" communication with applicants. In September 2014, FDA responded with refined guidelines[32] providing greater flexibility for applications receiving "expedited review," which FDA defines as a review where the review team anticipates acting at least one month before the PDUFA goal date and states this anticipation in the filing letter. Both before and after FDA instituted the refined guidelines, FDA reviewers have acted on many applications well before the PDUFA goal date. For purpose of this assessment, ERG analyzed data for both "expedited reviews" (n=9) and "early actions" (n=27), which we define as an action issued at least one month before the PDUFA goal date, whether or not the review was designated as an expedited review in a filing letter.

By June 30, 2016, nine Program applications received FDA approval following an expedited review. All nine also had at least one special designation, with Orphan Drug (88.9%) and Breakthrough Therapy designations (77.8%) being the most common. A majority (77.8%) of the applications belonged to the "neoplasms benign, malignant, and unspecified (including cysts and polyps)" therapeutic area.

On average, the subset of Program applications with expedited review were approved more quickly than Priority applications as a whole and applications with early actions as a whole (Table 3-22). The number of Program applications with expedited review was too small for statistical analysis, however.

[32] CDER 21st Century Review Process Desk Reference Guide: http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM218757.pdf

Table 3-22. Time to first-cycle approval in the Program,* by subset of applications

Measure	Subset of Program Applications		
	All Priority Applications* (n=73)	All Applications with Early Action** (n=27)	Applications with Expedited Review (n=9)
Time from application receipt to AP: mean (months)	7.9	6.0	5.4
Time from application receipt to AP: median (months)	7.9	5.4	5.1
Time from application receipt to AP: range (months)	13.3 *(2.5, 15.8)*	7.9 *(2.5, 10.4)*	5.8 *(4.2, 10.0)*

** Includes applications with expedited review and early action.*
*** Includes applications with expedited review.*

In addition to the flexibility provided by the FDA guidelines for expedited review, FDA reviewers and applicants cited several factors that contribute to the ability to achieve early action where warranted:

- Selection of applications with few to no anticipated issues, resulting in "easy" MCCs and LCMs with relatively little burden to FDA reviewers.
- Frequent, real-time communication with applicant—including IND-stage communications, Application Orientation Meetings, frequent IRs, and ad hoc communications—in order to address quickly any issues that arise during filing and review.

4. Assessment Questions and Answers

1a. What is the relationship between Program attributes and NME NDA/original BLA first-cycle regulatory outcomes?

One of the goals of the Program is to improve the effectiveness and efficiency of the first cycle of review for NME NDAs and original BLAs. To that end, the Program creates new opportunities for FDA-applicant communications so review/approvability issues can be identified, discussed, and resolved earlier than in the past—potentially making it possible to reach approval in the first review cycle rather than a subsequent review cycle. (Of course, some applications do not meet FDA's standards for safety and effectiveness and will not be approved in any review cycle.) Thus, first-cycle approval rate is one potential measure of review effectiveness and efficiency.[33]

Based on data from the Program (October 1, 2012 to June 30, 2016) and the baseline (FYs 2008-2012), ERG found that first-cycle approval rates in the Program were statistically significantly higher than in the baseline when controlled for review priority. Even when explanatory variables were included,[34] the significance remained.

Another measure of review effectiveness and efficiency is the number of review cycles to reach approval. As of June 30, 2016, 11 applications receiving a first-cycle CR were resubmitted to FDA and 9 of these received a second-cycle action. These numbers are insufficient to detect a statistically significant difference in the number of review cycles required to achieve approval in the Program compared to the baseline.

Based on descriptive statistics, ERG's observations, and feedback from post-action interviews, we conclude that the Program has created conditions that enhance the ability of applicants and FDA reviewers to work toward application approval in the first review cycle. This was especially true for applications that met one or both of two conditions:

- Application was complex or otherwise had substantive issues that were resolvable during the review cycle—rather than having no major issues to resolve (in which case the Program's new milestone communications were more beneficial for review transparency than for issue resolution) or issues too substantive to be resolvable during a review cycle (in which case no review program would yield a first-cycle approval).
- Review needed the full review clock—rather than being slated for early action, in which case the FDA review team typically maintained frequent communications outside of the new Program milestones in order to speed the review process.

[33] First-cycle approval rate alone cannot be used to judge review effectiveness and efficiency because FDA has no control over the quality of applications received. First-cycle approval rate can only be as high as the percent of applications received that are of sufficient quality to be approved in the first review cycle.

[34] These explanatory factors include whether a goal extension was issued, whether an AC meeting was held, and whether the application received an Orphan Drug or Fast Track designation. Further explanations of the explanatory variables appear in Section 3.8—Review Process and Application Attributes and in Appendix E—Statistical Results.

It is important to note that applicants viewed the Program as having value in terms of enhanced review transparency, communication, predictability, and efficiency regardless of the first-cycle regulatory outcome.

1b. What is the relationship between Program attributes and time to NME NDA/original BLA first-cycle regulatory outcomes?

Another measure for improved effectiveness and efficiency of NME NDA and original BLA reviews might be a reduction in overall time to approval (across all review cycles). This can be accomplished by increasing the first-cycle approval rate, thereby avoiding the additional time involved in preparing for and resubmitting an application and undergoing one or more additional review cycles. This can also be accomplished by reducing the mean time from application submission to first-cycle approval. [35] Because only 11 Program applications have been resubmitted in from October 1, 2012 to June 30, 2016, of which 9 have received second-cycle actions, data were insufficient to evaluate mean overall time to approval. Therefore, we focus only on mean time from application submission to first-cycle approval.

Based on data on the Program (October 1, 2012 to June 30, 2016) and the baseline (FYs 2008-2012), ERG's analyses revealed that first-cycle reviews for Program applications were longer those for baseline applications—an unsurprising result given that there is a 2-month difference between the review clocks. Nevertheless, based on the descriptive statistics, ERG's observations, and feedback from post-action interviews, we conclude that the Program has created conditions that enhance the ability of applicants and FDA reviewers to work toward application approval in the first review cycle. Ultimately, it is possible that this might lead to a decrease in mean overall time to approval (due to avoidance of the significant amount of time required for resubmission and additional review cycles), but this possibility cannot be evaluated at this time. On the other hand, in theory the need to implement Program milestone communications could hamper FDA's ability to approve Priority applications as early as desired.

It is important to note that applicants viewed the Program as having value in terms of enhanced review transparency, communication, predictability, and efficiency regardless of its impact on mean time to first-cycle approval.

[35] As noted previously, first-cycle approval rate can only be as high as the percent of applications received that are of sufficient quality to be approved in the first review cycle. Similarly, time to first-cycle approval can be shortened only if applications are of sufficient quality.

2a. What is the relationship between review process attributes and NME NDA/original BLA first-cycle regulatory outcomes?

From October 1, 2012 to June 30, 2016, most review process attributes showed no statistically significant relationship to first-cycle approval rate. The main exception was time from application submission to primary review completion: Longer than average primary review completion time was associated with a lower first-cycle approval rate. Possible reasons include: (1) a disproportionate number of applications that are challenging and have more review issues, and (2) less time remaining in the review clock to address any identified deficiencies. Conversely, with Program applications that address a compelling public health need—and lack major deficiencies—FDA review teams often aim for early action (and thus early resolution of issues and early completion of primary reviews).

Unlike applications in the baseline, Program applications with a major amendment that triggered a goal extension were associated with a high first-cycle approval rate. This finding aligns with the expectation that reviewing a major amendment can lead to approval in the first cycle rather than requiring resubmission and a second cycle of review.

2b. What is the relationship between review process attributes and time to NME NDA/original BLA first-cycle regulatory outcomes?

From October 1, 2012 to June 30, 2016, two review process attributes were associated with a longer mean time from application submission to first-cycle approval: an above-average time from application submission to primary review completion, and a major amendment that triggered a goal extension. Later primary review completion times, sometimes due to a desire to incorporate AC feedback into the review, could lead to a later identification of issues, with late attempts at resolving those issues potentially delaying the approval.

3a. What is the relationship between application attributes and NME NDA/original BLA first-cycle regulatory outcomes?

From October 1, 2012 to June 30, 2016, Program applications with certain application attributes (Rolling Review, Breakthrough Therapy designation, Orphan Drug designation, Fast Track designation) were associated with higher first-cycle approval rates than those without the attributes, but the differences were not statistically significant or could not be assessed statistically. The difference did reach statistical significance for one application attribute: Priority review. Priority review is granted when the drug/biologic under review will be indicated for a serious condition and has the potential to offer a significant improvement in safety or effectiveness. A majority of Priority applications received and acted on in the Program were related to oncology, infectious diseases/viruses, and congenital/genetic disorders—disease areas that are often life-threatening and where there are significant unmet medical needs. Many FDA review teams for Priority applications maintained frequent communications with the applicants during the review, and even before application submission to gain an initial understanding of the data and assess readiness for application submission.

3b. What is the relationship between application attributes and time to NME NDA/original BLA first-cycle regulatory outcomes?

From October 1, 2012 to June 30, 2016, the review priority of an application was correlated with a statistically significant difference in mean time from application submission to first-cycle approval. As one would expect given the 4-month difference in review clocks, mean time to first-cycle approval was significantly shorter for Priority applications than for Standard applications in the Program. The overall review clock is 2 months longer in the Program than it was in the baseline, so it is also unsurprising that mean time to first-cycle approval was significantly longer for Priority applications in the Program than in the baseline—but the difference was slightly less than 2 months.

Another measure of interest is overall mean time from original submission to approval – which includes approvals achieved in second or additional review cycles. As of June 30, 2016, few applications had been resubmitted (n=11) and acted on (n=9) in a second review cycle, so the data were insufficient to compare overall mean time to approval in the Program versus the baseline.

4a. How do applicants and FDA review staff characterize enhanced communication under the Program?

Applicants

From October 1, 2012 to June 30, 2016, applicant feedback on enhanced communication under the Program was overwhelmingly positive. A large majority of interviewees (including those receiving CR as well as those receiving Approval) characterized communication under the Program as follows:

- ***Overall***—Excellent communication, very constructive, with a spirit of cooperation. In general, communication was excellent for most of the review process, outside of as well as within the new Program milestone communications.
- ***New Program milestone communications (MCC and LCM)***—Valuable opportunities to communicate with FDA. In contrast to routine day-to-day emails and telephone calls, the new communications facilitated a more holistic discussion of the application, broader FDA input (both horizontally and vertically), greater understanding of each party's perspectives, and more efficient resolution of questions and issues. Whether there were no issues or several, these multidisciplinary communications gave applicants greater confidence in their understanding of application status, and a greater confidence that they would not face "surprises" later on.
- ***RPMs and other FDA review team members***—Responsive, constructive, and flexible. FDA staff responded to inquiries promptly, made themselves available to hold impromptu teleconferences to address/clarify application issues, were willing to establish and negotiate reasonable due dates for IRs, were willing to accept amendments, etc. Some applicants noted that they had previously had positive experiences with FDA review staff as well, though many applicants perceived the experience to be even more positive under the Program.
- ***21st Century Review Process Desk Reference Guide***[36]—Invaluable resource for understanding the review process, expectations, and timelines under the Program.

[36] http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM218757.htm

Some applicants identified two areas for improvement in FDA-applicant communications:

- Status and results of inspections
- Review status and activities after the LCM

Applicants characterized the first of these two areas for improvement as most problematic, as addressing issues in time for first-cycle action can be challenging if inspection status updates occur too late in the review cycle.

FDA Review Staff

From October 1, 2012 to June 30, 2016, FDA review staff feedback on enhanced communication under the Program varied, with a few at either extreme and many in a middle range:

- ***FDA-applicant communications in Program***—Most review staff affirmed with varying degrees of enthusiasm that Program elements contributed to enhanced communication, though some believed that the Program offered no additional value to existing communication practices in certain divisions.
- ***Value added of new Program milestone communications (MCC and LCM)***—Many but not all review staff believed that the new Program communications provided further value by ensuring that FDA staff bring together all their inputs to consider the application as a whole, prioritize issues, plan for review milestones, involve leadership, and review the status of the overall application with the applicant.
- ***Workload***—Most reviewers believed that the new Program communications imposed additional workload on staff, including additional time required for scheduling meetings, preparing for meetings, speeding primary reviews in order to provide a more meaningful update at the MCC, dealing with additional work after primary review completion to review and document further amendments and AC meeting feedback, and preparing the LCM background package. Most reviewers believed that the additional burden was manageable. Some reviewers expressed concern that any additional new burdens might introduce a risk of missed deadlines or affect the thoroughness of reviews.

4b. How do applicants and FDA review staff characterize application reviews under the Program?

Applicants

From October 1, 2012 to June 30, 2016, applicant feedback on application reviews under the Program was overwhelmingly positive. Though some applicants commented that there was still room for improvement, most characterized reviews under the Program as follows:

- ***Very transparent***—Due to the big-picture multidisciplinary status updates provided during the new Program milestone communications as well as more focused updates provided during other routine day-to-day communications.

  As noted in Question 4a, applicants identified inspections as an exception to the rule due to a lack of availability of information about status and issues. They described inspections as a "black

box" because they could not discern who was in charge, who to communicate with, what progress was being made, etc.

A smaller number of applicants also commented that identification of significant issues late in the review (e.g., at the LCM) might reflect a lack of transparency; they sometimes wondered whether FDA had been aware of the issues earlier but waited until later to tell the applicant.

- ***Very predictable***—Due to the new Program communications that "anchor" the review with predictable milestones, communicate anticipated future review process dates, and facilitate planning and work to advance the review.

  Both applicants and FDA review staff recognize some inherent unpredictability in the review process. For example, it is sometimes impossible to know early that a reviewer will discover a deficiency until the applicant has responded to several IRs.

  For some applicants, uncertainties about early approval or goal extensions caused action dates to seem somewhat unpredictable. Applicants were uniformly appreciative of early approval, and they understood that FDA could not provide an early approval date in advance; they noted that not knowing how early the approval would be issued made it challenging to prepare for scale up and launch. Similarly, a small number of applicants felt unable to predict when an amendment would be deemed "major" and trigger a goal extension.

- ***Very efficient***—Due to the FDA review team's commitment to ongoing review progress and the Program's new milestone communications that helped propel the review forward efficiently.

FDA Review Staff

Like applicants, most FDA review staff characterized application reviews under the Program as transparent and predictable to the applicant. Many reviewers attributed these achievements at least in part to the Program, while a few felt that the Program's impact was minimal. Many reviewers suggested that the Program might be most beneficial for applications that require substantive discussion and issue resolution throughout the review.

Nearly all FDA review staff agreed that the new Program communications imposed additional workload/burden/pressure on staff, including additional time required for scheduling, preparing for, conducting, and documenting meetings; completing primary reviews early (by the MCC) and performing additional work after primary review completion to review and document further amendments and AC meeting feedback; and preparing the LCM background package. Most reviewers believed that the additional burden was manageable.

Other Aspects of Application Reviews

Both applicants and FDA review staff cited other aspects of application reviews that they considered to be lessons learned or good practices (see findings in next section).

5. Findings and Recommendations

Based on data collected for Program applications received and acted on between October 1, 2012 and June 30, 2016, ERG developed a set of findings and recommendations (Table 5-1) organized in two categories: overarching (related to the Program overall) and specific (related to particular aspects of the Program or review process).

In the Interim Report, the interim findings and recommendations were based on data from the first two years of the Program. In 2014, FDA implemented refined guidelines to address some of the issues raised. Assessment data collected since then suggest that these aspects of the Program are running smoothly and no longer belong in the findings and recommendations for this Final Report:

- ***Mid-Cycle Communication (MCC) procedures.*** In the Interim Report, ERG observed that MCCs were most efficient and productive when FDA reviewers (1) selected FDA attendees based on anticipated need rather than including the entire review team, (2) provided applicants with an informal (telephone, email) "heads-up" about meeting topics, and (3) permitted two-way communication to clarify questions. These practices have become nearly universal in the Program, and feedback has been positive.

- ***Early involvement of signatory authority.*** Early involvment of the signatory authority can help ensure that all parties at FDA are knowledgeable about the application and can foster early agreement, thereby facilitiating timely labeling decisions and avoiding late surprises if the review Office identifies concerns that the review Division did not. FDA has reminded review Offices and Divisions that early involvement of the signatory authority is a Program expectation, and this practice has become more consistent.

- ***Flexibility for expedited reviews.*** Early in the Program, a few reviewers expressed concern that implementation of Program milestone communications might hamper FDA's ability to approve certain Priority applications as early as desired—particularly when the reviewers are working toward early action to help address unmet medical needs for serious diseases and already have well-established practices for open, "real-time" communication with applicants. In September 2014, FDA responded with refined guidelines[37] providing greater flexibility for applications receiving expedited review (defined as a review where FDA anticipates acting at least one month before the PDUFA goal date and communicates this anticipation in the filing letter).

[37] CDER 21st Century Review Process Desk Reference Guide: http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM218757.pdf

Table 5-1. Findings and recommendations based on Program data from October 1, 2012 to June 30, 2016

Type	No.	Finding	Recommendation(s)
Overarching	O1	Overall, the Program has been successful in enhancing review transparency and communication.	No action needed.
	O2	Overall, new Program milestone communications (mid-cycle communications [MCCs] and late-cycle meetings [LCMs]) have enhanced the predictability of reviews by: • Serving as "anchor" points for applicant and FDA planning and work. • Providing a forum for holistic, multi-disciplinary discussion of application status and paths forward to resolve approvability issues promptly, if possible.	No action needed.
	O3	By providing more opportunity to identify, discuss, and resolve substantive issues during the review, the Program has created conditions that enhance the ability of applicants and FDA reviewers to work toward application approval in the first review cycle where possible. This is especially true for applications with substantive but resolvable issues where the full review clock is needed.	No action needed.
	O4	Program implementation has not been resource-neutral as assumed during PDUFA V negotiations. Implementation of new Program milestone communications has increased the burden on FDA's primary reviewers, diverting effort from review work to meeting preparation and sometimes resulting in a need for additional primary review addenda (to document additional work after primary review completion). FDA review teams have been able to manage this burden, but have noted that any additional new burdens might in some cases introduce a risk of missed deadlines or compromise the thoroughness of reviews.	If/when new review process requirements are added as part of a new authorization of the PDUFA program, analyze the associated burden to determine whether additional staff or other resources will be needed to maintain the timeliness and thoroughness of reviews.

Type	No.	Finding	Recommendation(s)
Specific	S1	Regardless of sponsor size and experience, many sponsors need more information on the format and structure of an application to meet FDA expectations by review division/team and indication/therapeutic area. To meet this need, sponsors sometimes request an additional Type C meeting many months prior to a data-oriented pre-submission meeting (PSM). Some FDA review teams believe that existing guidelines should be sufficient and that holding an earlier meeting without data is premature.	Evaluate efficient options for when and how to communicate information about the format and structure of applications by therapeutic area or division. Options could include but are not limited to internal reviewer aids and increased use of Type C Written Responses Only (WROs).
	S2	For some Priority applications where early action is expected / desired, holding an Application Orientation Meeting within a month or so after application receipt has helped (1) acquaint FDA disciplines with application datasets and (2) establish early communication between applicants and FDA about review expectations and perspectives.	Consider the value of providing information about Application Orientation Meetings to FDA review teams, along with the option to conduct such meetings at the review team's discretion (e.g., for certain Priority / Breakthrough Therapy / expedited review applications).* **FDA is proposing this option for PDUFA VI.*
	S3	Given the high volume of information requests, providing target dates for responses is a good practice. Applicants would also benefit from receiving confirmation that their responses are complete.	First, adopt inclusion of target dates for information request responses as a good practice. Second, develop a simple optional approach for tracking information requests and amendments that can be shared between review teams and applicants.
	S4	Providing explanations/rationales for proposed label changes is a good practice for applicants and FDA review teams. This practice has helped both parties understand the others' reasoning, enabling them to respond effectively – which then reduces the amount of back-and-forth required and the time required to complete negotiations.	Include explanations/rationales for proposed label changes (either in written form or by telephone) as a good practice.
	S5	Inconsistent availability/communication of information about the status and results of inspections has hindered review transparency and predictability, both internally at FDA and between FDA and applicants.* **In January 2015, FDA launched the CDER Office of Pharmaceutical Quality (OPQ) to consolidate product quality activities into a unified office. Comments about inspection transparency have not changed since that time.*	Examine inspection information flows and communication channels, with the aim of identifying improvements. **FDA is undertaking such an examination.*

Appendix A. Acronyms and Glossary

Acronym	Term
AC	Advisory Committee
AP	Approval
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDTL	Cross Discipline Team Leader
CMC	Chemistry, Manufacturing, and Controls
CR	Complete Response
DARRTS	Document Archiving, Reporting, and Regulatory Tracking System
DR	Discipline Review
ERG	Eastern Research Group, Inc.
FDA	Food and Drug Administration
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
IND	Investigational New Drug
IR	Information Request
LCM	Late-Cycle Meeting
MCC	Mid-Cycle Communication
MCM	Mid-Cycle Meeting

NDA	New Drug Application
NME	New Molecular Entities
ODE	Office of Drug Evaluation
OPQ	Office of Pharmaceutical Quality
OPSA	Office of Program and Strategic Analysis
OSE	Office of Surveillance and Epidemiology
PDUFA	Prescription Drug User Fee Act
PETT	Program Evaluation Tracking Tool
PSM	Pre-Submission Meeting
RMS-BLA	Regulatory Management System – Biologics License Application
REMS	Risk Evaluation and Mitigation Strategies
RPM	Regulatory Project Manager
RTF	Refuse To File
SOP	Standard Operating Procedure
WD	Withdrawal after Filing
WF	Withdrawal before Filing

Glossary

Advisory Committee (AC): Group of outside experts that provide independent advice to FDA on scientific, technical and policy issues; meetings serve as a forum for public hearing on important matters related to a drug's approval.

> **PDUFA V Commitment Letter**
>
> - Day 74 letter will include preliminary plans on whether to hold an AC meeting to discuss the application.
> - Mid-cycle communications (MCCs) should provide an update on plans for an AC meeting.
> - Late-cycle meetings (LCMs) should adhere to certain scheduling and pre-meeting package requirements relative to the AC meeting (if planned).

Applicant: Individual or corporate entity that has submitted an application to FDA for premarket review. Also see "Sponsor".

Appropriate Review Team Members: Presence of FDA staff needed to answer questions from the applicant during a mid-cycle communication (MCC) or late-cycle meeting (LCM), plus other staff identified in the Commitment Letter (i.e., for LCM, the signatory authority for the application or the assigned alternate/deputy).

Approval (AP): FDA regulatory action on an application (in this case, for a New Molecular Entity [NME] NDA or original BLA) that allows the applicant to commercially market the product in the U.S.; communicated in an approval letter.

Baseline Cohort: All New Molecular Entity (NME) NDAs and original BLAs received in FDA CDER and CBER under PDUFA IV (FYs 2008-2012). Data from the baseline cohort serves as the baseline from which to measure impacts of FDA's new review model for NME NDAs and original BLAs under the PDUFA V Program.

Biologic: A type of drug isolated from natural sources (e.g., human, other animal, microorganism). Biologics include vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins.

Biologics License Application (BLA): A request for permission to introduce, or deliver for introduction, a biologic product into interstate commerce. FDA regulations and policies have established that biological products include blood-derived products, vaccines, in vivo diagnostic allergenic products, immunoglobulin products, products containing cells or microorganisms, and most protein products. Both CDER and CBER have regulatory responsibility for therapeutic biological products, including premarket review and oversight.

Breakthrough Therapy Designation: Designation intended to expedite development and review of drugs for serious or life-threatening conditions. The criteria for Breakthrough Therapy designation require preliminary clinical evidence that demonstrates the drug might have substantial improvement on at least one clinically significant endpoint over available therapy. A Breakthrough Therapy designation

conveys all Fast Track designation program features, more intensive FDA guidance on an efficient drug development program, an organizational commitment involving senior managers, and eligibility for Rolling Review and Priority review.

Center for Biologics Evaluation and Research (CBER): FDA organization that regulates biological products for human use (e.g., blood-derived products, vaccines, allergenics, tissues, and cellular and gene therapies) and ensures that these products are safe, effective, and available to those who need them. Original BLAs received by CBER are reviewed under the Program.

Center for Drug Evaluation and Research (CDER): FDA organization that regulates over-the-counter and prescription drugs for human use and ensures that these products are safe, effective, and available to those who need them. NME NDAs and original BLAs received by CDER are reviewed under the Program.

[PDUFA V] Commitment Letter: Document that summarizes the performance goals and procedures agreed to for the fifth authorization of PDUFA; defines and delineates requirements and recommendations for FDA's new review model for New Molecular Entity (NME) NDAs and original BLAs under PDUFA V ("the Program"). ERG's Program evaluation metrics, protocols, and instruments are based on this document.

Complete Response (CR): FDA regulatory action on an application (in this case, a New Molecular Entity [NME] NDA or Original BLA) that an application will not be approved in its present form. To obtain marketing approval, the applicant must resubmit an application that addresses deficiencies cited.

Cross Discipline Team Leader (CDTL): The FDA staff member responsible for providing day-to-day leadership to the review team and oversight of the review, and resolving conflicts that arise within and across disciplines and to ensure efficient and timely reviews. The CDTL is expected to attend all team meetings and write a CDTL Review to bring together highlights and perspectives of all disciplines.

Day 74 Letter: See "Filing Letter."

Delayed Application Component: Minor component of a Program NDA or BLA (not expected to materially impact the ability of the review team to begin its review) that the applicant and FDA have agreed may be submitted within 30 calendar days of submission of original application. *Synonyms: minor application component, late submission* (when referring to components that applicants and FDA have agreed may be submitted late).

PDUFA V Commitment Letter

- Any agreement on delayed application components will be summarized at the conclusion of the pre-submission meeting and reflected in FDA's meeting minutes.
- Examples of application components that may be appropriate for delayed submission include updated stability data or the final audited report of a preclinical study where the final draft report is submitted with the original application.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission.

Discipline: A scientific review team responsible for specific aspects of an application. For the purpose of the Program evaluation, ERG recognizes eight disciplines in CDER and seven disciplines in CBER:

CDER

- Clinical
- Nonclinical
- Product Quality
- Clinical Pharmacology
- Statistics
- Office of Surveillance and Epidemiology
- Clinical Microbiology
- Other

CBER

- Clinical
- CMC
- Non-clinical
- Pharm/Tox
- Human Pharmacokinetics
- Bioavailability
- Other

Discipline Review (DR) Letter: Formal correspondence that the FDA review team sends to an applicant to convey early thoughts on possible application deficiencies identified within specific sections of the application.

> **PDUFA V Commitment Letter**
>
> - In general, FDA intends to send Discipline Review letters before the late-cycle meeting.
> - Since the application is expected to be complete at the time of submission, FDA intends to complete primary and secondary discipline reviews of the application in time to issue DR letters before the late-cycle meeting.

Document Archiving and Regulatory Reporting Tracking System (DARRTS): CDER's internal database for storing and managing official NDA and BLA records. DARRTS serves as a source of application history and regulatory information for ERG's Program evaluation.

Drug: A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. When used broadly, this term includes biologics. When used more specifically (as in this report), the term refers to non-biologic substances.

Eastern Research Group, Inc. (ERG): Independent contractor enlisted to design and conduct the interim and final assessments of FDA's Program for Enhanced Review Transparency and Communication for New Molecular Entity (NME) NDAs and Original BLAs in PDUFA V.

Evaluation Metrics: Measurements used to evaluate the activities, performance, or impacts of a program. For this evaluation, ERG's evaluation metrics serve as a basis for statistical analysis of "drivers" of Program outcomes; when combined with context-based qualitative analysis, these enable ERG to answer assessment questions about associations and correlations between Program, review process, and application attributes and review timeliness and outcomes.

Expedited Review: Beginning in September 2014, applications that are intended to treat serious and life threatening diseases where there is an unmet medical need, or for which a meaningful clinical benefit to existing therapies has been demonstrated in clinical trials, may receive an expedited review at the discretion of the FDA review team. If the review team determines that a first-cycle approval of such an application is likely, then the team may strive to take an action at least one month prior to the PDUFA

goal date, provided that no significant unexpected review issues arise, and the review team does not experience an unexpected shift in work priorities or team staffing.

Fast Track Designation: Designation is intended to facilitate development and expedite review of drugs to treat serious conditions and fill an unmet medical need; designation may be granted on the basis of preclinical data. A sponsor of a drug that receives Fast Track designation will typically have more frequent interactions with FDA during drug development. In addition, products that have been designated as Fast Track can obtain Rolling Review.

Filing Date: In the Program evaluation, date when FDA considers the application filed, according to the filing letter.

Filing Issue: Substantive deficiency or concern identified by FDA during the initial filing review of an application; issue that appears to have been inadequately addressed in the application and might affect FDA's ability to complete the review of the application. Unlike an application deficiency that may result in a Refuse to File action (RTF), a filing issue does not preclude filing of the application. *Synonym: review issue* (when used in a filing communication).

Filing Letter: Formal correspondence that the FDA review team sends to an applicant within 74 calendar days of original application submission (the "Day 74 goal") to communicate FDA's filing decision, review priority of application, planned review timeline, filing issues, and preliminary plans on whether to hold an Advisory Committee (AC) meeting.

Synonym: Day 74 letter.

> **PDUFA V Commitment Letter**
>
> - The planned review timeline Program Day 74 letters will include the planned date for the internal mid-cycle review meeting.
> - Day 74 letter will include preliminary plans on whether to hold an AC meeting to discuss the application.

First-Cycle Action: Regulatory decision (Approval [AP], Complete Response [CR], or Withdrawal after Filing [WD]) on an application that concludes FDA's first review cycle and closes the PDUFA goal date; includes decisions on applications that previously received a Refuse to File (RTF) or Withdrawal before Filing (WF), but not decisions on Class 1 or Class 2 resubmissions.

Fiscal Year (FY): October 1 of previous calendar year through September 30 of current calendar year. FY quarters are:

- Quarter 1: October 1 –December 31
- Quarter 2: January 1 – March 31
- Quarter 3: April 1 –June 30
- Quarter 4: July 1 – September 30

[The United States] Food and Drug Administration (FDA): Agency within the Department of Health and Human Services that is responsible for:

- Protecting the public health by assuring the safety, efficacy and security of products that the Agency regulates.
- Advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medicines and foods to maintain and improve their health.
- Regulating the manufacturing, marketing and distribution of tobacco products.
- Ensuring the nation's counterterrorism capability by the security of the food supply and by fostering development of medical products to respond to public health threats.

Food and Drug Administration Safety and Innovation Act (FDASIA): Enacted on July 9, 2012, law that expands FDA's authorities and strengthens the agency's ability to safeguard and advance public health. The law includes the fifth authorization of PDUFA that provides steady and reliable funding to maintain and support a staff of trained reviewers to determine whether a proposed new product is safe and effective for patients.

Good Clinical Practice (GCP): Standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials or studies.

Good Laboratory Practice (GLP): A regulation for conducting nonclinical laboratory studies that support or are intended to support applications for research or marketing permits for human drugs and biological products regulated by the FDA, among other products. Compliance is intended to assure the quality and integrity of the safety data.

Good Manufacturing Practice (GMP): A regulation containing minimum requirements for the methods, facilities, and controls used in manufacturing, processing, and packing of a drug product. Compliance is intended to ensure that a product is safe for use, and that it has the ingredients and strength it claims to have.

Information Request (IR): FDA communication to an applicant to request data, analysis, or clarification needed to allow completion of application review. FDA can issue IRs during meetings with the applicant, in filing and Discipline Review (DR) letters to the applicant, and as separate communications. For the purpose of the Program evaluation, ERG counts IRs issued during meetings, in filing and DR letters, and other tracked correspondences between FDA and applicants. ERG also counts individual items requested within each IR document and categorizes these by FDA Discipline.

Inspections: FDA conducts inspections to evaluate the compliance of nonclinical and clinical investigators, and of drug manufacturers to established FDA regulations. The outcome of an inspection can decide the regulatory action taken on an application. For this Program evaluation, inspections are considered complete on the date when both Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP) inspections have been completed.

> **GCP Inspections** – Assessment by CDER's Office of Scientific Investigations (OSI) or CBER's Office of Compliance and Biologics Quality (OCBQ) of clinical sites for compliance with GCP.
>
> **GLP Inspections** – Assessment of nonclinical sites for compliance with GLP. For the purpose of the Program evaluation, GLP inspection dates were not collected due to the infrequency of these inspections being conducted in support of a marketing application.

GMP Inspections – Assessment by CDER/CBER or the Office of Regulatory Affairs (ORA) of manufacturing sites for compliance with GMP.

> **PDUFA V Commitment Letter**
>
> Complete all GCP, GLP, and GMP inspections 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.

Interim Assessment: In accordance with Section II Part B.1 of the Commitment Letter, ERG will publish an interim assessment of the Program based on applications received on or after October 1, 2012 and acted on by September 30, 2014. The interim assessment will be available for public comment.

Investigational New Drug Application (IND): Current federal law requires that a new drug be the subject of an approved marketing application before it is transported or distributed across state lines. The IND is the means through which the sponsor obtains an exemption from the FDA to ship the investigational drug to clinical investigators in many states. The data gathered during the animal studies and human clinical trials of an IND become part of the NDA. See also "New Drug Application".

Issue/Deficiency (Major, Significant, Substantive): In the context of application review, an insufficiency within the marketing application, identified by FDA staff, that might need resolution from the applicant to continue review or affect approvability. The FDA review team may describe issues/deficiencies as "major", "significant", and/or "substantive" if they believe it might materially affect the review process. Some topics (labeling, risk management/Risk Evaluation and Mitigation Strategies [REMS], Post-marketing Commitments [PMCs]/Post-marketing Requirements [PMRs], updates on regulatory milestones) are not considered major, significant, or substantive unless specifically designated as such for the purposes of this evaluation.

Late-Cycle Meeting (LCM): Meeting held late in the review cycle between members of the FDA review team and the applicant to discuss the status of the review.

> **PDUFA V Commitment Letter**
>
> - FDA review staff will prepare and send a late-cycle briefing package with a detailed update on the current status of the review and any remaining issues or points of discussion.
> - Potential topics for discussion include major deficiencies identified to date, issues to be discussed at the Advisory Committee meeting (if planned), current assessment of the need for REMS or other risk management actions, information requests from the review team to the applicant, and additional data or analyses the applicant might wish to submit.

Late-Cycle Meeting Briefing Package: Prior to the late-cycle meeting with the applicant, FDA will issue a briefing package to the applicant that will consist of the agency's background package for the Advisory Committee (AC) meeting, any Discipline Review (DR) letters issued to date, current assessments on Risk Evaluation and Mitigation Strategies (REMS) or other risk management and a brief memo outlining substantive application issues.

Major Amendment: Submission of significant data that could address outstanding deficiencies in the application and lead to approval in the current review cycle. Receipt and review by FDA of a major amendment extends the PDUFA goal date by three months.

Major Safety Concern: A safety concern with the drug that could result in death or serious injury to the user, or could indirectly result in death or serious injury if used incorrectly, in the absence of timely information, or through the action of a care provider. In the context of mid-cycle communications (MCCs), any safety signal, serious adverse events, suggestions for restriction to certain patient populations, or references to potential inclusion of additional warnings, precautions, or contraindications to labeling. See also "Mid-cycle Communication (MCC)".

Medical Dictionary for Regulatory Activities (MedDRA): Clinically validated medical terminology dictionary used by pharmaceutical regulatory authorities. Entries are organized hierarchically, with five levels ranging from very general, like System Organ Class (SOC), to very specific. MedDRA categories referenced in this report are at the SOC level.

Mid-Cycle Communication (MCC): Teleconference with FDA review staff, including the Regulatory Project Manager (RPM) and Cross Discipline Team Leader (CDTL), and applicant generally held within two weeks following the Agency's internal mid-cycle meeting (MCM) to provide an update on the status of the review.

PDUFA V Commitment Letter

FDA's update to the applicant should include:

- Any significant issues identified by the review team to date
- Any information requests
- Information regarding major safety concerns
- Preliminary review team thinking regarding risk management
- Proposed date(s) for the late-cycle meeting, updates regarding plans for the Advisory Committee meeting (if anticipated)
- Other projected milestones dates for the remainder of the review cycle.

Mid-Cycle Meeting (MCM): Internal FDA meeting about an application held by month 5 (Standard review) or month 3 (Priority review) of the review cycle to provide an opportunity for management to review the work of the review team thus far. Meeting objectives are to:

- Present status and key findings of all reviews, consults, and inspections.
- Confirm the decision that was made regarding the need for an Advisory Committee (AC) meeting.
- Identify any issues that could preclude an Approval (AP) action.
- Begin high-level discussion of labeling and need for post-marketing requirements and/or commitments.
- Determine if a Risk Evaluation and Mitigation Strategies (REMS) is needed (if not already determined) and, if so, the goals and the elements of the REMS.
- Revise the review plan and interim timelines, if needed.
- Solicit feedback from the signatory authority and other discipline directors.

Also see "Mid-Cycle Communication (MCC)".

New Drug Application (NDA): Application through which drug applicants formally propose that the FDA approve a new pharmaceutical for sale and marketing in the U.S. The goals of the NDA are to provide enough information to permit FDA reviewers to reach the following key decisions:

- Whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks.
- Whether the drug's proposed labeling (package insert) is appropriate, and what it should contain.
- Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity.

New Molecular Entity (NME): Drug product that contains an active moiety that has not been approved by FDA, or marketed in the United States, either as a single ingredient drug or as part of a combination product.

Office of Compliance (OC): During the first half of the Program (October 2012 to January 2015), FDA CDER organization responsible for conducting and coordinating surveillance and pre-approval inspections of manufacturing and other facilities as well as ensuring compliance with current Good Clinical Practice (cGCP) and current Good Laboratory Practice (cGLP) related to a marketing application under review. A report is issued to the review team summarizing the findings. After being launched in January 2015, the Office of Pharmaceutical Quality assumed responsibility for pre-approval and surveillance inspection activities.

Office of Management and Budget (OMB): Federal government agency that evaluates, formulates, and coordinates management procedures and program objectives within and among departments and agencies of the Executive Branch. It also controls the administration of the Federal Budget, while providing the president with recommendations regarding budget proposals and relevant legislative enactments.

Office of New Drugs (OND): Office at FDA within the CDER responsible for providing regulatory oversight for investigational studies during drug development and making decisions regarding marketing approval for new drugs, including decisions related to changes to already marketed products. Its reviewing offices include Office of Drug Evaluation I/II/III/IV, Office of Antimicrobial Products, and Office of Hematology and Oncology Products.

Office of Pharmaceutical Quality (OPQ): Office at FDA within CDER responsible for product quality functions, including review, inspection, and research. After being launched in January 2015, OPQ has assumed responsibility for pre-approval and surveillance inspection activities from the Office of Compliance.

Office of Surveillance and Epidemiology (OSE): Office at FDA within CDER responsible for maintaining a system of post-marketing surveillance and risk assessment programs to identify adverse events that did not appear during the drug development process. OSE staff identify drug safety concerns and recommend actions to improve product safety and protect the public health. Other activities include

updating drug labeling, providing information to the community, implementing or revising a risk management program, and reevaluating approval or marketing decisions.

Prescription Drug User Fee Act (PDUFA): Enacted in 1992, law that provided added funds through user fees that enabled FDA to hire additional reviewers and support staff and upgrade its information technology systems. In exchange, FDA agreed to review performance goals, such as completing application reviews for NDAs and BLAs in a predictable timeframe. PDUFA has been reauthorized every five years since its passage, with the most recent reauthorization (for FYs 2013-2017) occurring in 2012 under Food and Drug Administration Safety and Innovation Act (FDASIA). New changes and performance goals/commitments are explained in detail in the PDUFA V Commitment letter.

The PDUFA V Commitment Letter introduces a new review model (known as "the Program") for New Molecular Entity (NME) NDAs and original BLAs in PDUFA V to promote greater review transparency and improve communication between FDA and applicants on these complex applications. The Program provides increased communication during FDA review by incorporating mid-cycle communications (MCCs) and late-cycle meetings (LCMs) between FDA and applicants and begins the review clock (6 months for Priority applications and 10 months for Standard applications) 60-days after receipt of the application. This Program is the subject of ERG's assessment and evaluation.

PDUFA Goal Date: The goal date for when FDA expects to issue a regulatory decision on an application. The PDUFA Goal date is determined by the review priority designation. Under the Program, Standard applications receive a 10-month review clock that officially begins on the filing date of the original submission; Priority applications, generally reserved for drugs aimed at serious or unmet medical needs, receive a 6-month review clock. See also "Prescription Drug User Fee Act (PDUFA)".

Post-Action Interview: Face-to-face or telephone interview that ERG conducts with either applicant representatives or the FDA review team after the first review cycle action (Approval [AP], Complete Response [CR], or Withdrawal after Filing [WD]). The purpose of the interview is to gather applicant and FDA review team opinions and experiences (including good practices, challenges, and lessons learned) with application reviews under the Program.

Post-Marketing Commitment (PMC): Study or clinical trial that an applicant has agreed to conduct, but are not required by a statute or regulation.

Post-Marketing Requirement (PMR): Study or clinical trial that an applicant is required to conduct under one or more statutes or regulations.

Pre-Approval Inspections: Product quality inspections of facilities involved in the manufacture of a drug product as part of an NDA.

Pre-License Inspections: Product quality inspections of facilities involved in the manufacture of a biologic product as part of a BLA.

Pre-Submission Meeting (PSM): Meeting requested by a sponsor who intends to submit a marketing application. Strongly encouraged, but not required under the Program. Also known as Pre-NDA or Pre-BLA meetings.

For the purpose of the Program evaluation, ERG considers Program PSMs to be Type B multidisciplinary PSMs. If an application received multiple PSMs, ERG considers the last Type B multi-disciplinary meeting to be the official Program PSM and any other meetings, multidisciplinary or discipline-specific, to be follow-up meetings or complementary meetings.

> **PDUFA V Commitment Letter**
>
> Pre-submission meetings should:
>
> - Be scheduled sufficiently in advance of the planned application submission to allow for meaningful response to FDA feedback (generally at least 2 months before planned submission).
> - Generate agreement on the content of a complete application for the proposed indication(s), including preliminary discussions on the need for REMS or other risk management actions.
> - Generate agreement on submission of a limited number of delayed application components.
> - Include a summary of discussions and agreements (to be reflected in FDA's meeting minutes).

Primary Reviews: Reviews conducted by specified CDER discipline review teams, such as:

- Clinical (Medical)
- Pharmacology/Toxicology
- Product Quality (formerly Chemistry, Manufacturing and Controls)
- Biometrics (Statistical)
- Clinical Pharmacology and Biopharmaceutics
- Clinical Microbiology
- Medication Error
- Risk Management Analyst for Risk Evaluation and Mitigation Strategies (REMS) submissions
- Office of Scientific Investigations (OSI)
- Office of Manufacturing Product Quality (OMPQ)

After primary reviews are completed, secondary reviews are conducted by the discipline team leaders; tertiary reviews are typically conducted by the office or division director, who also takes action on the application. See also "Discipline". *Note: Not all applications require all of these primary review disciplines.*

[The] Program: Implemented on October 1, 2012, the Program is a new review model established by FDA under the PDUFA V intended to improve review transparency and communications between FDA review teams and applicants. Applications subject to Program provisions include all New Molecular Entity (NME) NDAs and original BLAs received between October 1, 2012 and September 30, 2017. ERG is the independent contractor tasked with evaluating the Program. See also "Prescription Drug User Fee Act (PDUFA)".

Program Evaluation Tracking Tool (PETT): A tool used by ERG to consolidate and monitor quantitative, qualitative, observational, and calculated data on Program attributes, characteristics, and regulatory outcomes. The PETT stores and houses primary data collected by ERG as well as additional data drawn from internal FDA databases.

Refuse To File (RTF): A regulatory decision issued on an application that does not meet FDA's standards for submission. RTF decisions do not constitute a review cycle or a first-cycle action. Applications that are filed over protest after receiving a RTF decision are not reviewed in the Program. See "Regulatory Action / Regulatory Outcome."

Regulatory Action / Regulatory Outcome: The regulatory decision that FDA issues on an application in the Program. This includes an action that closes the PDUFA goal (Approval [AP], Complete Response [CR], Withdrawal after Filing [WD]) and an action issued before complete review of the application (Refuse To File [RTF], Withdrawal before Filing [WF]). ERG's assessment of the Program focuses primarily on the former actions, while also tracking the latter.

Regulatory Management System - Biologics License Application (RMS-BLA): An internal data management system that supports the Managed Review Process for review and approval of applications for biologically derived drugs, blood products, and other entities regulated by CBER. ERG extracted data from RMS-BLA to support the baseline analysis and the Program evaluation.

Regulatory Project Manager (RPM): The FDA staff member responsible for coordinating communication between FDA and the applicant and serving on the review team as one of the regulatory leaders.

Review Priority (Priority, Standard): Designation that dictates the length of application review, based on whether the drug product provides safe and effective therapy where no satisfactory alternative therapy exists or represents a significant improvement compared to marketed products in treating, preventing or diagnosing disease. FDA communicates an application's review priority to the applicant in the filing communication. See "Filing Letter" and "PDUFA Goal Date".

> **Priority review** – Applications that have a regulatory action completion date of 6 months after the filing date.
>
> **Standard review** – Applications that have a regulatory action completion date of 10 months after the filing date.

Review Cycle: Period from application receipt to regulatory action. In the Program, the review cycle consists of a 60-day filing review period followed by a 10-month (Standard review) or 6-month (Priority review) review of the application.

Risk Evaluation and Mitigation Strategy (REMS): A formal risk management strategy to ensure that the benefits of a drug or biological product outweigh its risks.

Sponsor: Individual or corporate entity who takes responsibility for and initiates a marketing application; the term "sponsor" is used before NDA/BLA submission. Also see "Applicant."

Signatory Authority: Generally an Office of Drug Evaluation (ODE) Director or Division Director who takes the action on the application. For applications signed off at the office level, tertiary review includes participation of the Office of New Drugs (OND) Associate Director for Pharmacology/Toxicology, Office of Pharmaceutical Quality (OPQ) or Office of Biotechnology Products Division Director, Office of Clinical Pharmacology (OCP) Division Director, and Biometrics Office Director.

Splitting Applications: Administrative split of an application by the review division into two or more applications, either at the time of filing or prior to the action. Applications are split, for example, when multiple indications in different review divisions are submitted under one application; or if different regulatory actions must be taken on separate indications or dosages submitted under one application. When applications are split, they are denoted by Original-1/Original-2.For the Program evaluation, ERG considers applications split into Original-1 and Original-2 as separate applications.

Top-line results: In clinical trials supporting a marketing application to FDA, analysis of clinical trial data that show whether the endpoints (target outcomes) were met.

Withdrawal (before and after Filing): An action by the applicant to withdraw an application from FDA review.

> **Withdrawal before Filing (WF)** – Withdrawal of an application after submission but before FDA completes its filing review; not considered a review cycle action because application review (and the PDUFA review clock) begins when FDA files an application.
>
> **Withdrawal after Filing (WD)** – Withdrawal of an application after FDA has issued a filing communication and closed the Day 74 goal; considered a review cycle action because application review (and the PDUFA review clock) begins when FDA files an application.

Appendix B. Evaluation Metrics

Regulatory Outcomes Metrics

Table B-1 presents values for regulatory outcomes metrics in the baseline (received in FYs 2008-2012, acted on by June 30, 2016) and Program (October 1, 2012 to June 30, 2016). ERG used these metrics to:

- Describe regulatory outcomes in the Program.
- Identify associations and correlations between Program, review process, and application attributes and regulatory outcomes.
- Compare regulatory outcomes between the Program and the baseline.

Table B-1. Regulatory outcomes metrics*

			Baseline	Program
AP	RO1	Percent of applications that received AP	82.6%	84.2%
	RO2	Percent of applications that received AP in the first review cycle	54.8%	79.5%
	RO3	Percent of approved applications that received AP in the first review cycle	66.3%	94.4%
	RO4	Number of review cycles to AP: mean	1.4	1.1
	RO4	Number of review cycles to AP: median	1	1
	RO4	Number of review cycles to AP: range	3 [1, 4]	1 [1, 2]
CR	RO5	Percent of applications that received CR	42.0%	17.0%
	RO6	Percent of applications that received CR where efficacy was cited as an approvability issue	50.0%	58.6%
	R06	Percent of applications that received CR where product quality was cited as an approvability issue	56.5%	27.6%
	RO6	Percent of applications that received CR where safety was cited as an approvability issue	68.5%	24.1%
	R06	Percent of applications that received CR where inspections were cited as an approvability issue	34.8%	24.1%
	R06	Percent of applications that received CR where FDA requested additional data be submitted	77.2%	34.5%
	R06	Percent of applications that received CR where FDA requested additional clinical trials be conducted	51.1%	27.6%
	R06	Percent of applications that received CR where FDA requested additional analyses be performed	46.7%	24.1%
	RO7	Percent of applications that received CR and were resubmitted	70.7%	37.9%
WD	RO8	Percent of applications that were WD	3.2%	3.5%
	RO9	Percent of applications that were WD and were resubmitted	0.0%	0.0%

Time (AP, CR, and WD)	RO10	Time from FDA receipt of original application submission to first-cycle action: mean	9.4 mos.	10.2 mos.
	RO10	Time from FDA receipt of original application submission to first-cycle action: median	9.9 mos.	11.0 mos.
	RO10	Time from FDA receipt of original application submission to first-cycle action: range	17.5 mos. [2.6, 20.1]	13.3 mos. [2.5, 15.8]
	RO11	Time from FDA receipt of original application submission to AP: mean	16.6 mos.	10.9 mos.
	RO11	Time from FDA receipt of original application submission to AP: median	10.0 mos.	11.0 mos.
	RO11	Time from FDA receipt of original application submission to AP: range	95.0 mos. [2.6, 97.6]	31.4 mos. [2.5, 33.9]
	RO12	Time from first-cycle CR to resubmission: mean	13.3 mos.	9.3 mos.
	RO12	Time from first-cycle CR to resubmission: median	10.1 mos.	7.8 mos.
	RO12	Time from first-cycle CR to resubmission: range	52.5 mos. [0.2, 52.7]	23.8 mos. [2.0, 25.8]
	RO13	Time from WD to resubmission: mean	N/A	N/A
	RO13	Time from WD to resubmission: median	N/A	N/A
	RO13	Time from WD to resubmission: range	N/A	N/A
RTF	RO14	Percent of all submitted applications that received RTF as their latest status	5.0%	2.8%
	RO15	Percent of applications that received RTF and were eventually filed	29.4%	16.7%
	RO16	Percent of applications that received RTF as an initial action where the reason was documentation	88.2%	N/A
	RO16	Percent of applications that received RTF as an initial action where the reason was efficacy	41.2%	83.3%
	RO16	Percent of applications that received RTF as an initial action where the reason was safety	17.7%	66.7%
	RO16	Percent of applications that received RTF as an initial action where the reason was product quality	11.8%	50.0%
	RO16	Percent of applications that received RTF as an initial action where FDA requested additional data be submitted	58.8%	83.3%
	RO16	Percent of applications that received RTF as an initial action where FDA requested additional clinical trials be conducted	41.2%	50.0%
	RO16	Percent of applications that received RTF as an initial action where FDA requested additional analyses be conducted	0.0%	83.3%
WF	RO17	Percent of all submitted applications that were WF as their latest status	2.9%	0.0%
	RO18	Percent of applications that were WF and were eventually filed	30.0%	N/A

Time (RTF & WF)	RO19	Time from RTF to resubmission: mean	4.3 mos.	5.1 mos.
	RO19	Time from RTF to resubmission: median	4.7 mos.	5.1 mos.
	RO19	Time from RTF to resubmission: range	8.0 mos. [0.8, 8.8]	0 mos. [5.1, 5.1]
	RO20	Time from WF to resubmission: mean	3.1 mos.	N/A
	RO20	Time from WF to resubmission: median	1.9 mos.	N/A
	RO20	Time from WF to resubmission: range	4.5 mos. [1.5, 6.0]	N/A

**Data encompass NME NDAs and original BLAs received during FYs 2008-2012 and acted on by June 30, 2016 (baseline) or received and acted on from October 1, 2012 to June 30, 2016 (Program).*

Pre-Submission Meeting Metrics

Table B-2 presents values for Program PSM metrics. In the baseline cohort, most applications also had PSMs, but these were PSMs that did not incorporate new recommendations instituted with the Program. Since Program PSMs were not conducted during that time, we provide no values for the baseline cohort. ERG used these metrics to:

- Identify associations and correlations between PSM attributes and regulatory outcomes.
- Identify good practices and lessons learned that might be useful in refining Program implementation.

B-2. Program PSM metrics*

		Baseline	Program
PS1	Percent of Program PSMs that led to marketing applications		78.2%
PS2	Percent of applications that had a Type B multidisciplinary Program PSM		69.0%**
PS3	Percent of applications with a Program PSM that have all five Program attributes		22.0%
PS4	Percent of applications with a Program PSM that held the meeting at least 2 months before submission		79.7%
PS5	Time from Program PSM to original application submission: mean		4.3 mos.
PS5	Time from Program PSM to original application submission: median		3.6 mos.
PS5	Time from Program PSM to original application submission: range		19.2 mos. [0.5, 19.7]
PS6	Percent of applications with a Program PSM where FDA and sponsor agreed on content of complete application		52.5%
PS7	Percent of applications with a Program PSM where FDA and sponsor agreed on delayed application components		53.4%
PS8	Number of agreed-upon delayed application components per application: mean		0.4
PS8	Number of agreed-upon delayed application components per application: median		0.0
PS8	Number of agreed-upon delayed application components per application: range		6 [0, 6]
PS9	Percent of agreed-upon delayed application components related to product quality		21.4%
PS9	Percent of agreed-upon delayed application components related to clinical pharmacology		11.9%
PS9	Percent of agreed-upon delayed application components not specified by a discipline		7.1%

B-2. Program PSM metrics*		Baseline	Program
PS9	Percent of agreed-upon delayed application components related to nonclinical		2.4%
PS9	Percent of agreed-upon delayed application components in "other" category		4.8%
PS9	Percent of agreed-upon delayed application components related to clinical		7.1%
PS9	Percent of agreed-upon delayed application components related to statistics		2.4%
PS9	Percent of agreed-upon delayed application components related to OSE		0.0%
PS9	Percent of agreed-upon delayed application components related to clinical microbiology		0.0%
PS10	Percent of applications with a Program PSM that include preliminary discussion on need for REMS or other risk management actions		55.9%
PS11	Percent of applications with a Program PSM where agreements and discussions were summarized		55.1%

**Data encompass NME NDAs and original BLAs received and acted on from October 1, 2012 to June 30, 2016 (Program).*

***This value is artificially low because 24 applications submitted early in PDUFA V had PSMs before the Program became effective, and these are not counted (i.e., these applications had a PSM, but not a* Program *PSM).*

Original Application Metrics

Table B-3 presents values for original application metrics based on data for NME NDAs and original BLAs received during FYs 2008-2012 and acted on by June 30, 2016 (baseline) or received and acted on from October 1, 2012 to June 30, 2016. ERG used these metrics to:

- Characterize Program applications.
- Identify associations and correlations between application attributes and first-cycle review times and outcomes.

Table B-3. Original application information metrics*		Baseline	Program
AI1	Percent of applications that were complete on original submission		86.0%
AI2	Percent of applications with comprehensive and readily located lists of all clinical and manufacturing sites on original submission		97.2%
AI3	Percent of applications with agreement that there would be no late components		14.3%
AI4	Number of IRs issued per application outside of Program milestone meetings / communications during the first-cycle review**: mean	14.7	21.7
AI4	Number of IRs issued per application outside of Program milestone meetings / communications during the first-cycle review**: median	13.0	19.0
AI4	Number of IRs issued per application outside of Program milestone meetings / communications during the first-cycle review**: range	68 [0, 68]	85 [0, 85]
AI5	Number of requested items in IRs per application**: mean	45.6	65.0
AI5	Number of requested items in IRs per application**: median	39.0	52.0
AI5	Number of requested items in IRs per application**: range	194 [0, 194]	291 [0, 291]
AI6	Number of received amendments per application: mean	32.9	40.9
AI6	Number of received amendments per application: median	29.0	42.0
AI6	Number of received amendments per application: range	135 [0, 135]	118 [1, 119]
AI7	Percent of applications with a major amendment	27.4%	22.8%

AI8	Percent of applications with GCP, GLP, and GMP inspections conducted within Program timetables***		46.1%

**Data encompass NME NDAs and original BLAs received during FYs 2008-2012 and acted on by June 30, 2016 (baseline) or received and acted on from October 1, 2012 to June 30, 2016 (Program).*

***Does not include CDER BLAs due to limitations in baseline source data, so were excluded from both values for comparability.*

****Metric values exclude Good Laboratory Practice (GLP) inspections.*

Filing Letter Metrics

Table B-4 presents values for filing letter metrics based on based on data for NME NDAs and original BLAs received and acted on during FYs 2008-2012 (baseline) or FYs 2013-2016 (Program).

ERG identified five attributes, based on the PDUFA V Commitment Letter, that are required of filing letters for applications in the Program. Filing letters will include:

1) Issuance of the filing letter within 74 days of the date FDA received the application.
2) Notification of issues identified during the filing review.
3) Notification of planned review timelines.
4) Notification of the planned date for the internal mid-cycle review meeting.
5) Preliminary plans on whether to hold an Advisory Committee (AC) meeting to discuss the application.

ERG used these metrics to:

- Characterize review issues identified early in the review cycle.
- Identify associations and correlations between Program, review process, and application attributes/issues and first-cycle review times and outcomes.

Table B-4. Filing letter metrics*

		Baseline	Program
FL1	Percent of applications with a filing letter sent	100.0%	100.0%
FL2	Percent of applications with a filing letter that has all five Program attributes		92.4%
FL3	Percent of applications with a filing letter sent within 74 days of FDA receipt of original application submission	95.4%	98.8%
FL4	Percent of applications with a filing letter that states whether potential review issues have been identified	92.2%	100.0%
FL5	Percent of applications with a filing letter that states that no review issues have been identified	32.0%	52.6%
FL6	Percent of applications with a filing letter that lists one or more review issues	59.4%	46.8%
FL7	Number of potential review issues listed in filing letter per letter: mean	3.7	4.1
FL7	Number of potential review issues listed in filing letter per letter: median	2	0
FL7	Number of potential review issues listed in filing letter per letter: range	40 [0, 40]	76 [0, 76]
FL8	Percent of applications with a filing letter with potential review issues related to clinical**	16.9%	29.2%
FL8	Percent of applications with a filing letter with potential review issues related to product quality**	15.1%	25.7%

Table B-4. Filing letter metrics*		Baseline	Program
FL8	Percent of applications with a filing letter with potential review issues related to clinical pharmacology**	7.8%	13.5%
FL8	Percent of applications with a filing letter with potential review issues related to statistics**	7.8%	6.4%
FL8	Percent of applications with a filing letter with potential review issues related to nonclinical**	6.8%	4.7%
FL8	Percent of applications with a filing letter with potential review issues in "other" category **	37.0%	3.5%
FL8	Percent of applications with a filing letter with potential review issues related to OSE **	1.4%	2.9%
FL8	Percent of applications with a filing letter with potential review issues related to clinical microbiology **	0.5%	0.0%
FL9	Percent of applications with a filing letter that contains an internal MCM date		97.7%
FL10	Percent of applications with a filing letter that contains a planned review timeline	81.3%	98.2%
FL11	Percent of applications with a filing letter that states whether or not an AC meeting was likely	2.3%	94.7%
FL12	Percent of applications with a filing letter that states that an AC meeting was likely	1.8%	26.3%
FL13	Percent of applications with a filing letter that clearly identifies communication type, date, subject, author and recipient	99.1%	100.0%
FL14	Percent of applications with a filing letter that contains IRs	42.5%	46.2%
FL15	Number of IRs per filing letter: mean	2.6	3.3
FL15	Number of IRs per filing letter: median	5	0
FL15	Number of IRs per filing letter: range	23 [1, 24]	76 [0, 76]
FL16	Percent of applications with a filing letter that contains IRs related to product quality	13.7%	30.4%
FL16	Percent of applications with a filing letter that contains IRs related to clinical pharmacology	11.0%	17.0%
FL16	Percent of applications with a filing letter that contains IRs related to clinical	7.8%	16.4%
FL16	Percent of applications with a filing letter that contains IRs related to statistics	5.5%	11.1%
FL16	Percent of applications with a filing letter that contains IRs related to nonclinical	2.3%	7.0%
FL16	Percent of applications with a filing letter that contains IRs related to OSE	0.9%	4.1%
FL16	Percent of applications with a filing letter that contains IRs related to other disciplines	27.9%	4.7%
FL16	Percent of applications with a filing letter that contains IRs related to clinical microbiology	0.0%	0.6%

**Data encompass NME NDAs and original BLAs received during FYs 2008-2012 and acted on by June 30, 2016 (baseline) or received and acted on from October 1, 2012 to June 30, 2016 (Program).*

***Filing letters that contain potential review issues from multiple disciplines are counted once per applicable discipline.*

MCC Metrics

Table B-5 presents values for MCC metrics based on based on data for NME NDAs and original BLAs received during FYs 2008-2012 and acted on by June 30, 2016 (baseline) or received and acted on from October 1, 2012 to June 30, 2016 (Program).

ERG identified seven attributes, based on the PDUFA V Commitment Letter, that are required of MCCs for applications in the Program. MCCs will include:

1) Attendance of the RPM and appropriate review team members.
2) Calling the applicant within 2 weeks of the internal mid-cycle meeting to provide an update on the status of the review of the application.
3) Any significant issues identified by the review team to date.
4) Information regarding major safety concerns.
5) Preliminary review team thinking regarding risk management.
6) Updates regarding plans for the AC meeting (if an AC meeting is planned).
7) Other projected milestones for the remainder of the review cycle.

ERG used these metrics to:

- Identify associations and correlations between MCC attributes and regulatory reviews and outcomes.
- Identify good practices and lessons learned that might be useful in refining Program implementation.

Table B-5. MCC metrics*

		Baseline	Program
MC1	Percent of applications with an MCC		99.4%
MC2	Percent of applications with an MCC that has all seven Program attributes		43.5%
MC3	Percent of applications with an MCC with the RPM and appropriate review team members present		90.6%
MC4	Percent of applications with an MCC held within 2 weeks of FDA's internal MCM		80.0%
MC5	Percent of applications with an MCC where FDA stated whether the review team had identified significant issues		97.6%
MC6	Percent of applications with an MCC where FDA stated that the review team had identified no significant issues to date		24.7%
MC7	Percent of applications with an MCC where FDA stated that the review team had identified one or more significant issues		72.9%
MC8	Number of significant issues identified per MCC: mean		2.7
MC8	Number of significant issues identified per MCC: median		2.0
MC8	Number of significant issues identified per MCC: range		20 [0, 20]
MC9	Percent of applications with an MCC with significant issues related to product quality**		41.8%
MC9	Percent of applications with an MCC with significant issues related to clinical**		44.7%
MC9	Percent of applications with an MCC with significant issues related to clinical pharmacology**		28.2%

Table B-5. MCC metrics*		Baseline	Program
MC9	Percent of applications with an MCC with significant issues related to statistics**		12.9%
MC9	Percent of applications with an MCC with significant issues related to nonclinical**		9.4%
MC9	Percent of applications with an MCC with significant issues in "other" category**		7.6%
MC9	Percent of applications with an MCC with significant issues related to OSE**		2.4%
MC9	Percent of applications with an MCC with significant issues related to clinical microbiology**		1.2%
MC9	Percent of applications with an MCC with significant issues related to labeling/PMR/PMC**		0.6%
MC10	Percent of applications with an MCC in which FDA issued IRs		23.5%
MC11	Percent of applications with an MCC that contains IRs related to product quality		6.5%
MC11	Percent of applications with an MCC that contains IRs related to clinical pharmacology		9.4%
MC11	Percent of applications with an MCC that contains IRs related to clinical		3.5%
MC11	Percent of applications with an MCC that contains IRs related to statistics		2.4%
MC11	Percent of applications with an MCC that contains IRs related to labeling/PMR/PMC		1.2%
MC11	Percent of applications with an MCC that contains IRs related to nonclinical		1.2%
MC11	Percent of applications with an MCC that contains IRs related to OSE		0.0%
MC11	Percent of applications with an MCC that contains IRs related to clinical microbiology		0.0%
MC11	Percent of applications with an MCC that contains IRs related to other disciplines		0.0%
MC12	Percent of applications with an MCC with discussion of major safety concerns and risk management		70.0%
MC13	Percent of applications with an MCC with an update on plans for an AC meeting		88.8%
MC14	Percent of applications with an MCC in which FDA identified projected milestone dates		75.3%

**Data encompass NME NDAs and original BLAs received and acted on from October 1, 2012 to June 30, 2016. Metrics MC2-MC14 reflect data for the 170 Program applications with MCCs; 1 application did not have an MCC due to an early CR.*

***MCCs that contain significant review issues from multiple disciplines are counted once per applicable discipline.*

DR Letter Metrics

Table B-6 presents DR letter metrics based on data for NME NDAs received during FYs 2008-2012 and acted on by June 30, 2016 (baseline) or received and acted on from October 1, 2012 to June 30, 2016 (Program). ERG used these metrics to:

- Identify associations and correlations between DR letter attributes and regulatory reviews and outcomes.
- Identify good practices and lessons learned that might be useful in refining Program implementation.

Table B-6. DR letter metrics *

		Baseline	Program
DR1	Percent of DR letters that were issued before an LCM		100.0%
DR2	Percent of DR letters that combine multiple disciplines into a single letter	6.1%	27.3%
DR3	Percent of applications with at least one DR letter	13.2%	7.6%
DR4	Number of DR letters issued per application: mean	0.2	0.1
DR4	Number of DR letters issued per application: median	0	0
DR4	Number of DR letters issued per application: range	7 [0, 7]	1 [0, 1]
DR5	Percent of applications with DR letters related to clinical	1.4%	4.1%
DR5	Percent of applications with DR letters related to product quality	6.8%	3.5%
DR5	Percent of applications with DR letters related to statistics	1.8%	1.8%
DR5	Percent of applications with DR letters related to OSE	0.5%	1.2%
DR5	Percent of applications with DR letters related to nonclinical	1.4%	0.6%
DR5	Percent of applications with DR letters related in "other" category	1.4%	0.6%
DR5	Percent of applications with DR letters related to clinical pharmacology	1.8%	0.0%
DR5	Percent of applications with DR letters related to clinical microbiology	0.0%	0.0%

**Data encompass NME NDAs and original BLAs received during FYs 2008-2012 and acted on by June 30, 2016 (baseline) or received and acted from October 1, 2012 to June 30, 2016 (Program).*

LCM Metrics

Table B-7 presents values for LCM metrics based on based on data for NME NDAs and original BLAs received and acted on during FYs 2008-2012 (baseline) or FYs 2013-2014 (Program). LC1 excludes applications that were withdrawn by the applicant before the LCM took place. LC2-LC22 includes only those applications with LCMs.

ERG identified two attributes, based on the PDUFA V Commitment Letter, that are required of LCMs for applications in the Program. LCMs will include:

1) Attendance of the signatory authority for the application, appropriate review team members, and appropriate team leaders and/or supervisors from disciplines which substantive issues have been identified to date.
2) Hold the LCM
    a. if an AC meeting is planned, not less than 12 calendar days before the date of the AC meeting, or no later than 3 months (standard review) or no later than 2 months (priority review) prior to the PDUFA goal date, and sending the LCM briefing package to the applicant not less than 20 calendar days before the AC meeting.
    b. if no AC meeting is planned, no later than 3 months (standard review) or no later than 2 months (priority review) prior to the PDUFA goal date, and sending the LCM briefing package to the applicant not less than 12 calendar days before the LCM.

ERG used these metrics to:

- Identify associations and correlations between LCM attributes and regulatory reviews and outcomes.
- Identify good practices and lessons learned that might be useful in refining Program implementation.

Table B-7. LCM and AC meeting metrics*		Baseline	Program
LC1	Percent of applications with an LCM		92.8%
LC2	Percent of applications with an LCM that has both Program attributes		63.2%
LC3	Percent of applications with an LCM scheduled in accordance with Program timelines		72.3%
LC4	Percent of applications with an LCM with the FDA signatory authority and appropriate review team members present		89.7%
LC5	Percent of applications with an LCM in which FDA identified major deficiencies or substantive review issues		69.7%
LC6	Number of major deficiencies or substantive review issues identified per LCM: mean		2.2
LC6	Number of major deficiencies or substantive review issues identified per LCM: median		1
LC6	Number of major deficiencies or substantive review issues identified per LCM: range		9 [0, 9]
LC7	Percent of applications with an LCM with major deficiencies or substantive review issues related to clinical		40.0%
LC7	Percent of applications with an LCM with major deficiencies or substantive review issues related to product quality		31.6%
LC7	Percent of applications with an LCM with major deficiencies or substantive review issues related to statistics		10.3%
LC7	Percent of applications with an LCM with major deficiencies or substantive review issues related to clinical pharmacology		12.9%
LC7	Percent of applications with an LCM with major deficiencies or substantive review issues related to OSE		2.6%
LC7	Percent of applications with an LCM with major deficiencies or substantive review issues in “other” category		3.9%
LC7	Percent of applications with an LCM with major deficiencies or substantive review issues related to nonclinical		4.5%
LC7	Percent of applications with an LCM with major deficiencies or substantive review issues related to labeling/PMR/PMC		5.8%
LC7	Percent of applications with an LCM with major deficiencies or substantive review issues related to clinical microbiology		0.6%
LC8	Percent of applications with an LCM in which FDA identified issues for AC meeting (if planned)**		25.8%
LC9	Percent of applications with an LCM in which FDA discussed whether or not there was a need for REMS or risk management actions		43.9%
LC10	Percent of applications with an LCM in which FDA issued IRs		18.7%
LC11	Percent of applications with an LCM that contains IRs related to product quality		3.2%
LC11	Percent of applications with an LCM that contains IRs related to statistics		0.6%
LC11	Percent of applications with an LCM that contains IRs in “other” category		0.6%
LC11	Percent of applications with an LCM that contains IRs related to labeling/PMR/PMC		1.3%
LC11	Percent of applications with an LCM that contains IRs related to clinical		0.0%
LC11	Percent of applications with an LCM that contains IRs related to nonclinical		1.3%
LC11	Percent of applications with an LCM that contains IRs related to clinical pharmacology		0.6%

Table B-7. LCM and AC meeting metrics*

		Baseline	Program
LC11	Percent of applications with an LCM that contains IRs related to OSE		0.0%
LC11	Percent of applications with an LCM that contains IRs related to clinical microbiology		0.0%
LC12	Percent of applications with an LCM in which the applicant identified additional data/analyses they wish to submit		17.4%
LC13	Percent of applications with an LCM in which the applicant identified additional data/analyses they wish to submit and FDA discussed whether these would be reviewed in current cycle and constitute a major amendment		12.3%
LC14	Percent of applications with an AC meeting held in accordance with Program timelines**		11.6%
LC15	Percent of applications with an LCM briefing package that has all Program attributes (time and content)		63.2%
LC16	Percent of applications with an LCM briefing package sent in accordance with Program timelines		70.3%
LC17	Percent of applications with an LCM briefing package that has Program content		91.0%
LC18	Percent of applications with an LCM briefing package that includes or references DR letters issued to date		98.1%
LC19	Percent of applications with an LCM briefing package that includes an assessment of need for REMS or other risk management		94.2%
LC20	Percent of applications with an LCM briefing package that includes brief memorandum outlining major deficiencies or substantive review issues		98.1%
LC21	Percent of applications with an LCM briefing package that includes or references to AC meeting briefing package**		23.9%
LC22	Percent of applications with an LCM briefing package that includes questions or discussion points for AC meeting**		24.5%

**Data encompass NME NDAs and original BLAs received during FYs 2008-2012 and acted on by June 30, 2016 (baseline) or received and acted on from October 1, 2012 to June 30, 2016 (Program).*

***The denominator for this value includes all applications with a late-cycle meeting, regardless if an AC was held or not.*

Appendix C. Evaluation Protocols

Protocol for Evaluating FDA Interactions (Meetings) with Applicants

Eastern Research Group, Inc. (ERG) is conducting an independent assessment of the impact of FDA's PDUFA V Program on NME NDA and original BLA reviews. As part of the assessment, ERG is evaluating three types of FDA interactions with applicants:

- Pre-submission meetings
- Mid-cycle communications
- Late-cycle meetings

Assigning ERG Staff to FDA-Applicant Interactions

ERG has assigned Patrick Zhou to serve as ERG's meeting coordinator, with Chris Sese serving as backup as needed. Upon receipt of a notification, the meeting coordinator will:

1) Record the date of notification receipt, point of contact, office, division, meeting/communication topic, application number, reference application, applicant, scheduled date and time, and meeting/communication type in the "Meeting Schedule" worksheet of ERG's Program Evaluation Workbook.

2) Work with Kimberly Taylor in the Office of Program and Strategic Analysis to determine whether the scheduled interaction is within the scope of ERG's assessment (for a detailed decision tree to determine Program applications, see Appendix). ERG staff will record whether the meeting/communication was accepted for assessment, reason for acceptance/decline, person who made the meeting determination, and date of determination in the "Meeting Schedule" worksheet of ERG's Program Evaluation Workbook.

3) Assign the in-scope interactions to ERG staff using the following decision trees (Figures 1 and 2) and record the assigned ERG staff in the "Meeting Schedule" worksheet of ERG's Program Evaluation Workbook.

Figure 1: Number of Staff Decision

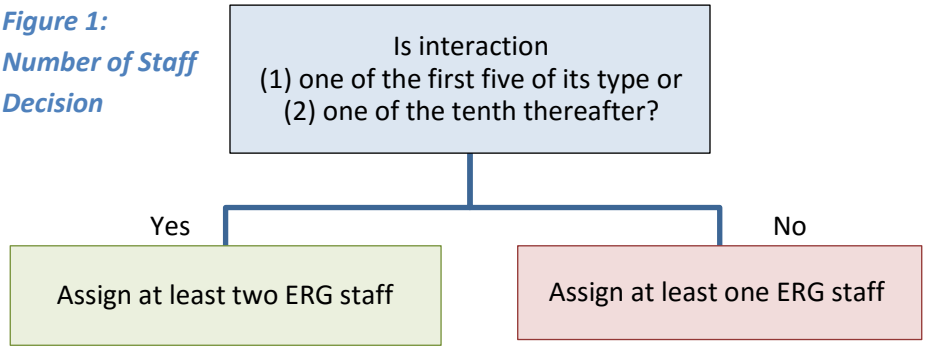
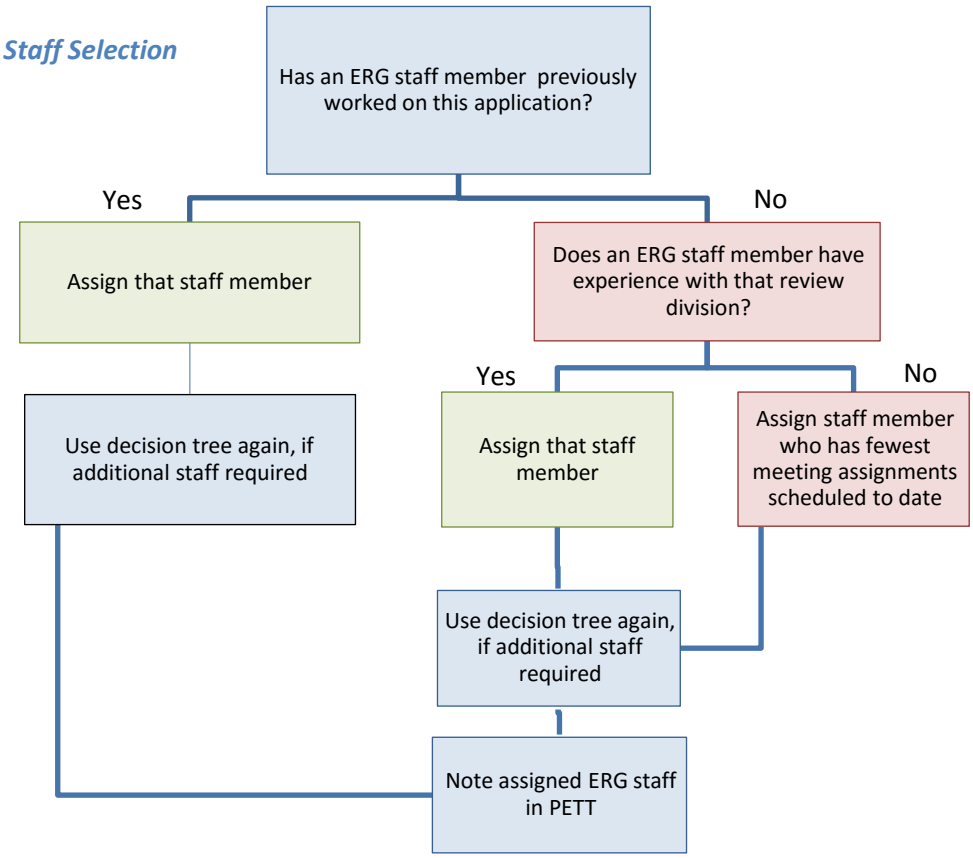


Figure 2: Staff Selection



Evaluating the Interaction

The ERG staff member(s) assigned to the interaction will:

1) Accept the scheduled interaction as directed by the meeting coordinator.

2) Review any materials (e.g., preliminary meeting comments, briefing packages, etc.) associated with the FDA-applicant interaction to understand the context for the interaction, and to fill in any pre-meeting content in the instruments when applicable.

   Kimberly Taylor will ensure that ERG staff have access to relevant materials. When confidential materials, such as meeting briefing packages, are provided by Kimberly Taylor, ERG staff will return materials to her or shred them as directed. When materials are obtained from DARRTS, CBER-EDR, or provided by the RPM/point-of-contact via invitation to the interaction (e.g., FDA's meeting preliminary comments), materials may be kept in a secure filing cabinet at the onsite ERG office along with the hard copy interaction instruments.

3) Send an email to the RPM (or FDA staff who scheduled the interaction) one business day before the meeting reminding him or her of ERG's presence at the meeting. The email will include the following introductory statement:

> *I am a member of the independent contractor team tasked with assessing "the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs in PDUFA V". As part of our assessment, we are objectively observing major elements of the Program, including [pre-submission meetings / mid-cycle communications / late-cycle meetings], to learn and see how they contribute to the overall process.*

Once an RPM has received this introductory statement on three separate occasions, it is not necessary to include it in subsequent emails unless a significant amount of time has elapsed since the last communication.

4) Attend the interaction using the information provided in the meeting/communication notification or call in from a neutral, closed-door location.

   If meeting participants are waiting outside meeting room, ERG staff will wait some distance away until the meeting room becomes available. ERG staff will enter the meeting room quietly, sit away from meeting participants, and refrain from making eye contact or interacting with meeting participants verbally or nonverbally. ERG staff will sign in with their name and "independent assessor, ERG" in all meetings they attend. If introductions are requested by all parties at the start of the meeting, ERG staff will say, "[Name], independent assessor, Eastern Research Group".

   If FDA and applicant introductions are being made, but ERG is not introduced separately, ERG staff may introduce themselves after FDA has completed their introductions.

   If a meeting participant addresses ERG staff directly, ERG staff will state:

My name is _____. As a member of the independent contractor team assigned to this meeting, I am a silent observer. I am not permitted to interact with meeting participants.

   In cases where ERG staff do not receive the call-in number for teleconference interactions at least one hour before the scheduled meeting/communication time, the ERG staff member who is assigned to the teleconference will contact Kimberly Taylor or the RPM to request the information.

5) Use the corresponding instrument and coding guide to evaluate the FDA-applicant interaction (e.g. use the "Pre-submission meeting evaluation instrument" for pre-submission meetings).

   If conditions (e.g., small meeting room) enable meeting participants to view ERG's evaluation instrument, ERG staff will use a clipboard cover to ensure privacy.

6) Record interaction evaluation data from the instrument into the corresponding Program Evaluation Tracking Tool (PETT) worksheet of the Program Evaluation Workbook, Evaluation Log, and Discipline Tally, as the instruments indicate. Transfer the data in the instrument to a digital copy, save the digitized instrument into the application's folder, and place the hard copy instrument in a secure filing cabinet at the onsite ERG office.

   Note: ERG will not share interaction-specific evaluation content with FDA staff or applicants involved in the communication or anyone else outside of our project team.

QA/QC

To ensure the quality and consistency of our FDA-applicant interaction assessments, ERG will assign multiple staff to at least each of the first five interactions (of each type) and every tenth thereafter. ERG staff assigned to an interaction will:

1) Conduct their interaction assessments separately (i.e., fill in the instrument independently).

2) After the interaction, compare responses/notes to identify any differences.

3) Discuss any differences with the ERG Program Evaluation team, decide on a resolution, record the agreed-upon set of responses/ratings in in the QA/QC comment section of the digital instrument and date it with the internal discussion date. Enter the agreed-upon set of responses/ratings into the appropriate PETT worksheet, and save the finalized digital copy into the appropriate folder. Clarify the coding guide accordingly if necessary.

4) Note any differences found and resolution agreed upon in a Comments field in PETT.

As an additional quality check, ERG will provide two completed instruments of each type to the Office of Program and Strategic Analysis (OPSA) for comment by an Associate Director of Regulatory Affairs (ADRA) of each review office. OPSA will return ADRA comments (if any) to enable ERG to identify any differences in interpretation and resolve them as appropriate.

Appendix: Program Application Decision Tree

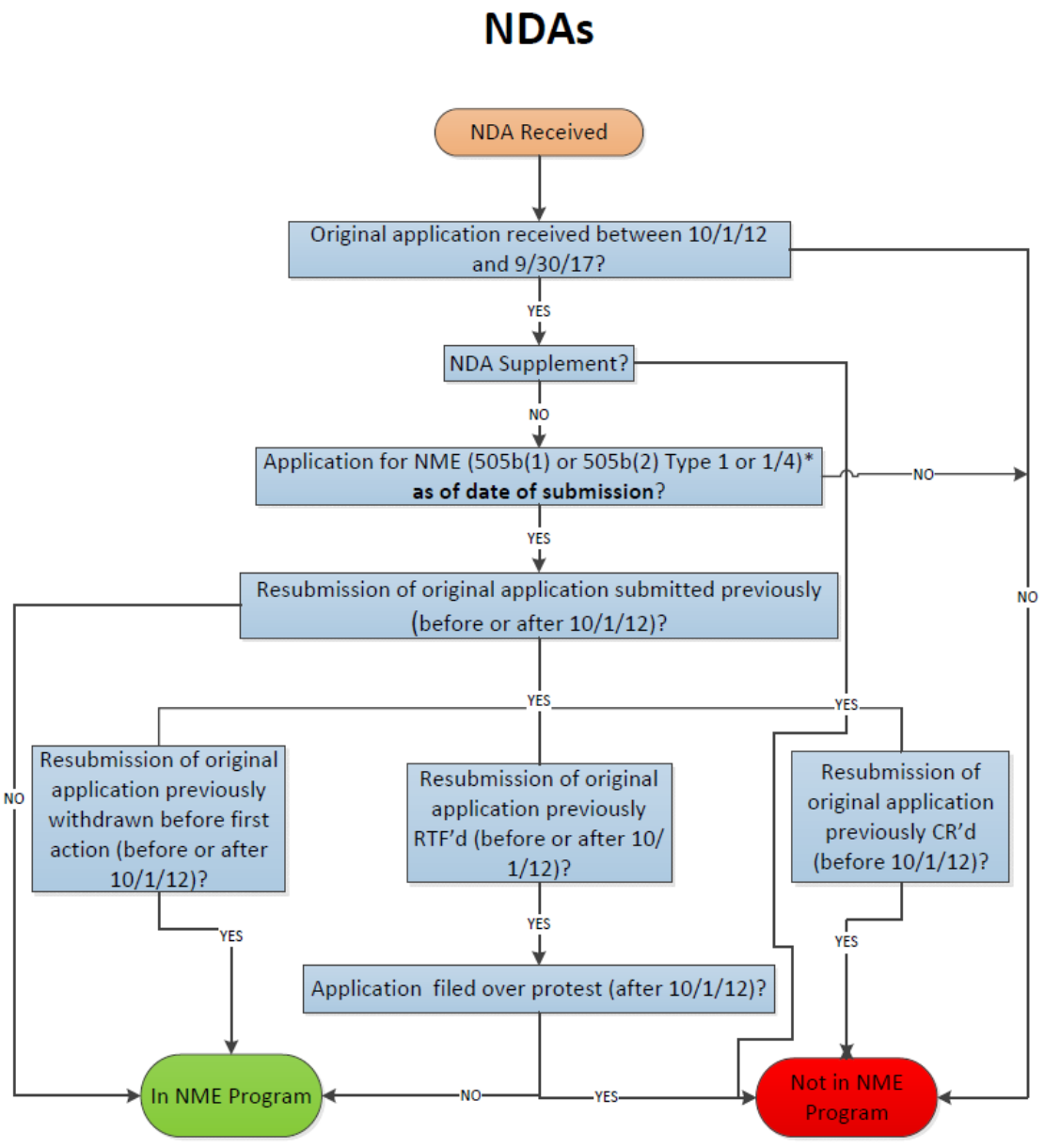
DEFINITIONS:

NDA505(b)(1): Application for approval of a new drug product that includes full reports of data generated by the applicant or for which the applicant has right of reference (ROR)

NDA505(b)(2): Application for approval of a new drug product that replies at least in part on data not generated by the applicant or for which the applicant does not have ROR

Type 1: Submission classification code for an NDA for a new drug product whose active moiety has not previously been approved in the U.S.

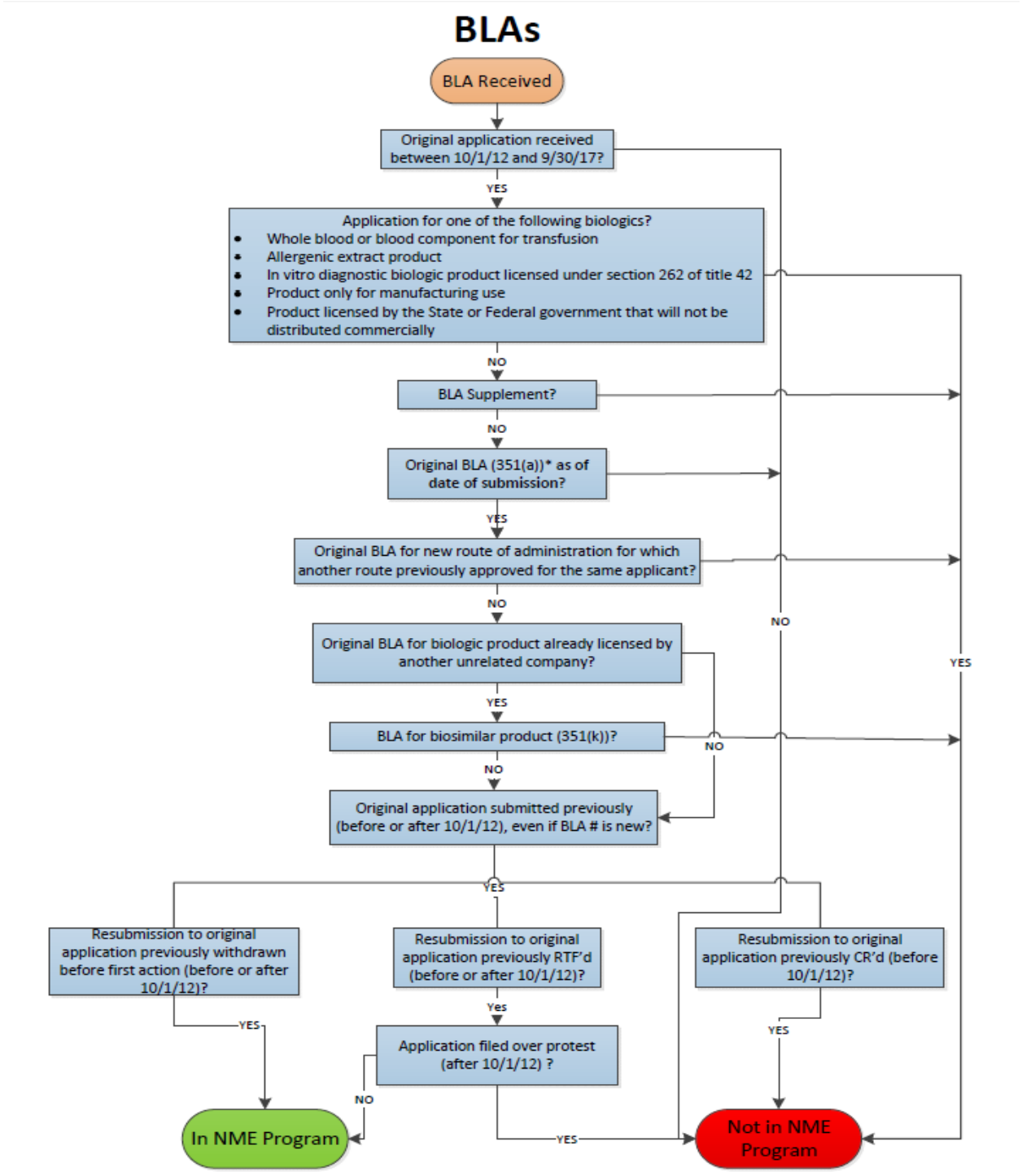
Type 1/4: Submission classification code for an NDA for a new combination drug product that contains at least one active moiety that has not previously been approved in the U.S.



DEFINITIONS:

BLA351(a): An application for licensing a biological product

BLA351(k): An application for licensing a biological product under an abbreviated approval pathway for biological products that propose to be "highly similar" (biosimilar) to or (interchangeable" with an FDA-approved biological product as described under the Biologics Price Competition and Innovation Act of 2009 (BPCI Act). The BPCI Act was enacted as part of the Affordable Care Act on March 23,2010.



Protocol for Conducting Post-Action Interviews with FDA

Eastern Research Group, Inc. (ERG) is conducting an independent assessment of the impact of the PDUFA V Program for Enhanced Review Transparency and Communication on NME NDA and original BLA reviews ("the Program"). As part of the assessment, ERG is conducting interviews with FDA after Program applications have been reviewed and receive a first-cycle action. For each in-scope application, ERG will conduct interviews with FDA review team members, such as the Regulatory Project Manager (RPM), Cross Discipline Team Leader (CDTL) or Committee Chair, Division/Office Director, CMC Branch Chief, and/or any other appropriate discipline team leaders.

ERG Pre-Work

ERG has assigned Patrick Zhou to serve as ERG's task coordinator, with Chris Sese serving as backup coordinator as needed. The task coordinator will maintain a list of Program applications that have received a first-cycle action of Complete Response (CR), Approval (AP) or a withdrawal after filing (WD). A separate list of applications will be kept for applications that have received an action of Refuse-To-File (RTF) or withdrawal prior to filing (WF) without a resubmission. ERG will confirm the accuracy of our list of in-scope applications in two ways:

- Via weekly status checks with the Office of Program and Strategic Analysis (OPSA).
- By consulting the Document Archiving, Reporting and Regulatory Tracking System (DARRTS) and the Regulatory Management System for Biologics License Applications (RMS-BLA) within three days of the end of each month to verify that all in-scope applications have been accounted for in ERG's Program Evaluation Tracking Tool (PETT).

After the review team holds the late-cycle meeting for an application, the task coordinator will assign an ERG staff member to schedule/conduct a post-action interview for that application, and one or more additional ERG staff member(s) to act as note-taker(s) during the interview. To the extent possible, the task coordinator will assign the interview to ERG staff with knowledge of the application (i.e., the ERG staff responsible for observing and evaluating application meetings and milestones).

ERG will conduct interviews after the first-cycle action date. During the post-action interview, ERG will ask RPMs and other key staff about their experience with the review process for the application, focusing on the review transparency and communication under PDUFA V. ERG will not expect FDA staff interviewees to prepare in advance.

FDA Pre-Work

After each late-cycle meeting, staff from FDA's Office of Program and Strategic Analysis will inform the RPM that ERG will be in contact to schedule an interview and suggest potential interviewees. The following statement and information will be issued:

Notice of Contractor Request for Interview

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct independent interim and final assessments of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ("the Program"). The PDUFA V Commitment Letter[1] states that these assessments will include interviews with FDA review team staff following the first-cycle action on applications reviewed in the Program. The purpose of the interview is to better understand review team experiences with the Program and its ability to improve transparency and communication during FDA review.

You will be contacted by ERG after the late-cycle meeting to schedule the interview following action on your application. Your responses during the interview will be confidential. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Applicants will be interviewed by ERG separately. Your participation and feedback during the interview will be helpful to these assessments.

Post-Action Interview Scheduling

To schedule post-action interviews, ERG's assigned staff will:

1) Alert the Office of Program and Strategic Analysis at least one day before contacting the RPM to allow time for internal FDA discussion about potential interviewees.

2) Contact the RPM within seven business days after the late-cycle meeting has been held to schedule an interview (depending on the proximity of the PDUFA goal date, RPMs can be contacted sooner or later):

   - ✓ Summarize purpose of interview and topics to be covered.
   - ✓ Plan date, time, and location for a 90-minute face-to-face interview after the action goal date for the application. If necessary, ERG will conduct the interview by telephone.
   - ✓ Based on input from the RPM, identify FDA representatives to be present.
   - ✓ Send a formal meeting invitation via Outlook to interviewee(s).
   - ✓ Complete a Post-Action Interview Information Sheet for the interview.
   - ✓ Send a meeting reminder 1-2 business day(s) before the interview.

[1] http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf

Conducting the Interviews

ERG staff members assigned to the interview will implement the interview as follows:

Interviewer: Conduct the interview in accordance with the script for post-action interviews with FDA – and in accordance with good interview practices for engaging interviewees while remaining neutral and objective. This includes probing for insights about the underlying reasons for specific interviewee feedback.

Note: The interviewer will read food-for-thought rating-scale statements as written. For open-ended questions, the interviewer may use discretion in following up on interviewee statements, so the interview might not proceed linearly as scripted.

Note-taker(s): Record interviewee responses throughout the interview. After the interview, review this documentation with the interviewer and additional note-taker (where applicable) to ensure the adequacy and accuracy of the notes. Record rating-scale responses in the Program Evaluation Tracking Tool (PETT) and enter open-ended discussion notes into the Post-Action Interview Log. Place hard copy instrument/notes in a secure filing cabinet at the onsite ERG office.

ERG will not share identifying information or application-specific interview content outside the internal project team. . ERG will report only anonymized results and findings in the interim and final assessments. Interviews should last no longer than ninety minutes.

QA/QC

To ensure the quality and consistency of our post-action interviews, notes, and conduct, ERG will assign two note-takers to the first ten interviews and every tenth thereafter, in addition to the interviewer. ERG staff assigned to an interview will:

1) Designate an interviewer and observers/note-takers.

2) After the interview, compare notes on responses to identify any differences.

3) Discuss any differences with the ERG Program Evaluation team, decide on a resolution, and enter an agreed-upon set of responses into PETT.

4) Note any differences found and resolution agreed upon in a Comments field in PETT.

Attachment

ERG will send this request to schedule interviews with RPMs. If there is no response after seven calendar days, ERG will send the same message again with "Second request" appended to the subject line.

FDA Interview Request [by email, using FDA email address]

Subject line: PDUFA V Program: Post-action interview request regarding [established name]

Dear [first and last name of contact person],

I am contacting you to request a post-action interview to discuss your experience regarding [established name], NDA/BLA [application #], currently being reviewed under the PDUFA V Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs ("The Program"). We would like to schedule the interview now so we can meet as soon after the action (Approval, Complete Response, or Withdrawal). No preparation on your part is expected.

Eastern Research Group, Inc. (ERG) is the contractor conducting an independent assessment of the Program. An important part of the assessment, as outlined in the PDUFA V Commitment Letter, is feedback from the FDA review team and applicants regarding the Program. In analyzing and reporting on feedback, ERG will keep identifying information of interviewees strictly confidential.

During the interview, we will ask about your experience with the review process for your application, practices that improved review transparency and communication, and challenges experienced during the review of the application in the Program. Your responses will help identify how the Program works well and how it could be improved.

Please identify FDA staff to be included in the interview. [If CDER, "We encourage you to include you as the RPM, the CDTL, and the signatory authority"; if CBER, "Please refer to JA 900.12, **After Action Activities for BLAs and NDAs in the PDUFA V Program.**"] If you wish, you might also include others who were instrumental in the review process such as the Division Director, CMC Branch Chief, and/or discipline team leaders:

1. _____(Name, title/role)
2. _____(Name, title/role)
3. _____(Name, title/role)
4. _____(Name, title/role)
5. _____(Name, title/role)
6. _____(Name, title/role)

Thank you for your attention. I will follow up with a meeting confirmation with a proposed date, time, and location of the interview for you to confirm. If you have any questions in the meantime or need to reschedule, please feel free to contact me.

Best regards,
[Name]
[Contact information: email and phone]

When needed, ERG will use this script to request FDA interviews by phone.

FDA Interview Request [by phone]

My name is [name] and I am following up on the emails I sent requesting an interview to discuss your experience regarding [established name] reviewed under the PDUFA V Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs.

Did the RPM acknowledge prior emails?

Yes: When would be a good time for an interview?

[If the RPM does not suggest times, ERG will propose three sets of dates and times.]

No: Eastern Research Group, Inc. (ERG) is the contractor conducting an independent assessment of the Program for reviewing NME NDAs and original BLAs under PDUFA V. We are interviewing FDA review team members after FDA issues first-cycle actions. ERG keeps identifying information of interviewees strictly confidential. During the interview, we will ask you about your experience with the review process, practices that improved review transparency, practices that improved communication, and any challenges experienced during review of your application in the Program. Your responses will help identify practices that could improve the likelihood of success of the Program. When would be a good time for an interview?

Is the RPM willing to participate in an interview with ERG?

Yes: Thank you very much.

What other review team members should be included in the interview? We would like to interview you all as a group for up to 90 minutes.

Can you please provide the interviewees' contact information? I will follow up with a meeting invitation with the date, time, and location of our interview. If you have any questions in the meantime or need to reschedule, please feel free to contact me. [Contact information: email and phone]

No: Contact Patrick Frey or Kim Taylor to discuss how to proceed.

ERG will send this meeting confirmation after the interview scheduling details have been established.

Meeting Confirmation [by email, using FDA email address]

Subject line: Confirmation: PDUFA V Program Interview regarding [established name]

Dear [first and last name of interviewee(s)],

This is a confirmation for our interview about the review of [established name], NDA/BLA [application #], reviewed under the PDUFA V Program. The purpose of the interview is described below.

When: [Day], [Date], [Time]

Where: [Confirmed location]

Who: [Name(s), Title(s)]

Thank you for your participation. We look forward to speaking with you.

Best regards,
[Name]
[Contact information: email and phone]

Eastern Research Group, Inc. (ERG) is the contractor conducting an independent assessment of the Program. An important part of the assessment, as outlined in the PDUFA V Commitment Letter, is feedback from the FDA review team and applicants regarding the Program. During the interview, we will ask about your experience with the review process for your application, practices that improved review transparency and communication, and challenges experienced during the review of the application in the Program. Your responses will help identify how the Program works well and how it could be improved. You are not expected or required to prepare any material in advance. In analyzing and reporting on feedback, ERG will not be reviewing your work or anyone else's work and will keep identifying information of interviewees strictly confidential.

ERG will send a meeting reminder 24-48 hours before the interview.

Meeting Reminder [by email, using FDA email address]

Subject line: Reminder: PDUFA V Program Interview regarding [established name]

Dear [first and last name of interviewee(s)],

This is a reminder for our upcoming interview about the review of [established name], NDA/BLA [application #], reviewed under the PDUFA V Program. The purpose of the interview is described below.

When: [Day], [Date], [Time]

Where: [Confirmed location]

Who: [Name(s), Title(s)]

Thank you for your participation. We look forward to speaking with you.

Best regards,
[Name]
[Contact information: email and phone]

Eastern Research Group, Inc. (ERG) is the contractor conducting an independent assessment of the Program. An important part of the assessment, as outlined in the PDUFA V Commitment Letter, is feedback from the FDA review team and applicants regarding the Program. During the interview, we will ask about your experience with the review process for your application, practices that improved review transparency and communication, and challenges experienced during the review of the application in the Program. Your responses will help identify how the Program works well and how it could be improved. You are not expected or required to prepare any material in advance. In analyzing and reporting on feedback, ERG will not be reviewing your work or anyone else's work and will keep identifying information of interviewees strictly confidential.

If FDA staff request the interview questions, ERG will attach the prepared PDF file with general interview questions and include the following statement in the response:

FDA Request for Interview Questions

[Attach the "Post-action Interview questions – FDA Request" document]

"Please note that we do not ask or expect you to spend time preparing for this interview. Nevertheless, we can provide our interview questions (see attachment) upon request."

Post-action Interview Questions

Note: Eastern Research Group, Inc. (ERG) does not ask or expect you to spend time preparing for this interview. We provide interview questions as a courtesy upon request.

I am going to read a series of statements about steps in the NDA/BLA review process. For each statement, please tell me if you strongly disagree, disagree, neither agree nor disagree, agree, or strongly agree. You can also say "Don't know" or "Not applicable". These questions are intended to serve as food for thought for the open-ended discussion.

Step in Review Process	Statement	Agreement Rating						
		Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree	Don't know	Not Applicable
Pre-submission meeting	The pre-submission meeting was an effective forum for discussing questions and issues with the applicant prior to application submission.							
	The review team had enough information about the application to communicate a preliminary stance on the need for REMS or other risk management strategies.							
	The pre-submission meeting resulted in a clear and shared understanding of expectations regarding the content of the complete application prior to submission.							
	The applicant addressed the issues discussed in the pre-submission meeting in the application.							
Day 74 letter	(If applicable) The applicant addressed review issues identified in the Day 74 or filing letter in a timely manner.							
	(If applicable) The applicant responded to information requests identified in the Day 74 or filing letter in a timely manner.							

Step in Review Process	Statement	Agreement Rating						
		Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree	Don't know	Not Applicable
Mid-cycle communication	The mid-cycle communication was an effective forum for updating the applicant on: • The current status of the application.							
	• Significant review issues.							
	• Major safety concerns identified thus far and preliminary thinking on risk management.							
	• The timeline for the remainder of the review.							
	The mid-cycle communication was an effective forum for clarifying any outstanding or new information requests.							
	The mid-cycle communication contributed to enhanced: • Communication with the applicant.							
	• Review transparency.							
Discipline Review letters	(If applicable) Discipline Review letter(s) were an effective method of delineating application deficiencies.							
	(If applicable) The applicant addressed those deficiencies that could be addressed in the first review cycle.							
	(If applicable) Issuing Discipline Review letters before the late-cycle meeting facilitated FDA's preparation for discussing deficiencies at that meeting.							
Late-cycle meeting	The late-cycle meeting was an effective forum for: • Discussing questions and issues with the applicant.							

Step in Review Process	Statement	Agreement Rating						
		Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree	Don't know	Not Applicable
	• Discussing the need for REMS or other risk management actions.							
	• Planning for the remainder of the review process.							
	• (If applicable) Discussing and planning for the Advisory Committee meeting.							
	(If applicable) The late-cycle meeting was held far enough in advance of the Advisory Committee meeting to allow sufficient time to prepare.							
	The late-cycle meeting was held far enough in advance of the PDUFA goal date to allow adequate time to address any deficiencies outlined.							
Process as a whole	Meetings and communications with the applicant enabled the review team to convey review issues and deficiencies as early as possible in the review process.							
	The applicant responded to review issues and information requests early enough to enable the review team to review the information in a timely manner (that is, to meet internal review timelines and goals during this review cycle).							
	The meetings and communications established by the Program were effective in contributing to review transparency.							

Now I'd like to ask you about any experiences that you would consider either good practices or challenges during the review of the application for [established name].

Q1. As part of our evaluation, we're trying to learn more about what constitutes a complete application upon submission. To the best of your recollection, of the amendments submitted by the applicant during the filing period, were any of these necessary to consider the application complete for filing purposes? That is, without the amendment(s), would you have needed to RTF the application?

Q2. What types of practices did you find helpful in the review?

Q3. What types of challenges did you encounter in the review?

Q4. Can you comment on your experience in the Program with respect to the transparency, efficiency, and predictability of the review process?

Q5. Have you identified any "lessons learned" that might help you or other FDA staff with future application reviews? Or sponsors with their applications?

Q6. Is there anything else you'd like to add about your review experience with [established name]?

Protocol for Conducting Post-Action Interviews with Applicants

Eastern Research Group, Inc. (ERG) is conducting an independent assessment of the impact of the PDUFA V Program for Enhanced Review Transparency and Communication on NME NDA and original BLA reviews ("the Program"). As part of the assessment, ERG is conducting interviews with applicants after Program applications have been reviewed by FDA and receive a first-cycle action. For each in-scope application, ERG will conduct interviews with applicant designees, such as the Regulatory Program Lead, Clinical Lead, and/or Global Project Lead. No more than three individuals will be interviewed per application.

ERG Pre-Work

ERG has assigned Patrick Zhou to serve as ERG's task coordinator, with Chris Sese serving as backup coordinator as needed. The task coordinator will maintain a list of Program applications that have received a first-cycle action of Complete Response (CR), Approval (AP) or a withdrawal after filing (WD). A separate list of applications will be kept for applications that have received an action of Refuse-To-File (RTF) or withdrawal prior to filing (WF) without a resubmission. ERG will confirm the accuracy of our list of in-scope applications in two ways:

- Via weekly status checks with the Office of Program and Strategic Analysis (OPSA).
- By consulting the Document Archiving, Reporting and Regulatory Tracking System (DARRTS) and the Regulatory Management System for Biologics License Applications (RMS-BLA) within three days of the end of each month to verify that all in-scope applications have been accounted for in ERG's Program Evaluation Tracking Tool (PETT).

When an application receives a first-cycle action, the task coordinator will assign an ERG staff member to offer/schedule a post-action interview with the applicant and one or more additional ERG staff member(s) to act as note-taker(s) during the interview. To the extent possible, the task coordinator will assign the interview to ERG staff with previous knowledge of the application (i.e., the staff responsible for observing and evaluating application meetings and milestones).

FDA Pre-Work

FDA will inform applicants that ERG will contact them after first-cycle actions under the Program to schedule an interview. This will be done systematically by placing the text box below in the official action letter:

Notice of Contractor Request for Interview

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ("the Program"). The PDUFA V Commitment Letter[1] states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

You will be contacted by ERG to schedule the interview following this action on your application. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

Post-Action Interview Scheduling

To schedule post-action interviews, ERG's assigned staff will:

1) Identify the addressee of the action letter as the contact person for the applicant.

2) Contact the applicant within seven calendar days of the action letter date (or within seven calendar days of ERG being notified that the application has received an FDA action) to schedule an interview:

   - ✓ Summarize purpose of interview and topics to be covered.
   - ✓ Plan date, time, and location for face-to-face interview. If necessary (e.g., if applicant is not local or unable to travel), ERG will conduct the interview by telephone.
   - ✓ Identify up to three applicant representatives to be present, such as the Regulatory Program Lead, Clinical Lead, and/or Global Project Lead.
   - ✓ Complete a Post-Action Interview Information Sheet for the interview.
   - ✓ Send a formal meeting invitation to interviewee(s) from the ERG email account.
   - ✓ Send a meeting reminder 24-48 hours before the interview.

[1] http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf

Conducting the Interviews

ERG staff members assigned to the interview will implement the interview as follows:

Interviewer: Conduct the interviews in accordance with the guide/script for interviewing applicants – and in accordance with good interview practices for engaging interviewees while remaining neutral and objective. This includes probing for insights about the underlying reasons for specific interviewee feedback.

Note: The interviewer will read rating-scale questions as written. For open-ended questions, the interviewer may use discretion in following up on interviewee statements, so the interview might not proceed linearly as scripted.

Note-taker(s): Record interviewee responses throughout the interview. After the interview, review this documentation with the interviewer and additional note-taker (where applicable) to ensure the adequacy and accuracy of the notes. Record rating-scale responses in the Program Evaluation Tracking Tool (PETT) and enter open-ended discussion notes in the Post-Action Interview log, then place the hard copy instrument in a secure filing cabinet at the onsite ERG office.

ERG will not share identifying information or application-specific interview content with the FDA review staff or anyone else outside of ERG's internal assessment team. ERG will report only anonymized results and findings in the interim and final assessments. Interviews should last no longer than ninety minutes.

QA/QC

To ensure the quality and consistency of our post-action interviews, ERG will assign two note-takers to the first ten interviews and one thereafter, in addition to the interviewer. ERG staff assigned to an interview will:

1) Designate an interviewer and observers/note-takers.

2) After the interview, compare notes on responses to identify any differences.

3) Discuss any differences with the ERG Program Evaluation team, decide on a resolution, clarify the coding guide accordingly (if necessary), and enter an agreed-upon set of responses into PETT.

4) Note any differences found and resolution agreed upon in a Comments field in PETT.

Attachment

ERG will send this request to schedule interviews with applicants using their ERG email account. If there is no response after seven calendar days, ERG will send the same message again with "Second request" appended to the subject line.

Applicant Interview Request [by email, using ERG email address]

Subject line: PDUFA V Program: Interview request regarding [trade name]

Dear [first and last name of contact person],

I am contacting you to request an interview to discuss your experience regarding [trade name], NDA/BLA [application #], reviewed under the PDUFA V Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs ("The Program").

Eastern Research Group, Inc. (ERG) is the contractor conducting an independent assessment of the Program. An important part of the assessment, as outlined in the PDUFA V Commitment Letter, is feedback from the FDA review team and applicants regarding the Program. These separate interviews are scheduled after FDA issues a first-cycle action for applications reviewed under the Program. [If the application was withdrawn after filing, include this sentence: "FDA considers withdrawals after filing as first-cycle actions that close the PDUFA goal."] Your participation in an interview is voluntary. ERG will keep identifying information of individual responses strictly confidential.

During the interview, you will be asked about your experience with the review process for your application, practices that improved review transparency and communication, and challenges experienced during the review of the application in the Program. Your responses will help identify how the Program works well and how it could be improved.

Please choose an interview date and time (in 90-minute blocks):

1. [Date/time block 1]
2. [Date/time block 2]
3. [Date/time block 3]
4. [Date/time block 4]
5. Other (please specify): _____

Please choose location from the following:

1. FDA's White Oak Campus in Silver Spring, MD (we will reserve a conference room)
2. [TBD: "Neutral" off-campus location or applicant's office if local]
3. Other local location (please specify): _____
4. Telephone interview (please specify telephone number): _____

Please identify the people (up to three) who will participate in the interview:

1. _____(Name, title/role)
2. _____(Name, title/role)

3. _____(Name, title/role)

Thank you for your attention. I will follow up with a meeting invitation with the date, time, and location of our interview. If you have any questions in the meantime or need to reschedule, please feel free to contact me.

Best regards,
[Name]
[Contact information: email and phone]

Public reporting burden for this collection of information is estimated to average 60-90 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other suggestions for reducing this burden to Ila S. Mizrachi, Office of Information Management, Food and Drug Administration, 1350 Piccard Drive, PI50-400B, Rockville, MD 20850, 301-796-7726 Ila.Mizrachi@fda.hhs.gov.

Notwithstanding any other provisions of the law, no person is required to respond to, nor shall any person be subjected to a penalty for failure to comply with, a collection of information subject to the requirements of the Paperwork Reduction Act, unless that collection of information displays OMB Control Number 0910-0746.

When needed, ERG will use this script to request applicant interviews by phone.

Applicant Interview Request [by phone]

My name is [name] and I am following up on the emails I sent requesting an interview to discuss your experience regarding [trade name] reviewed under the PDUFA V Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs.

Does applicant acknowledge emails?

Yes: When would be a good time for an interview?

[If the applicant does not suggest times, ERG will propose three sets of dates and times.]

No: Eastern Research Group, Inc. (ERG) is the contractor conducting an independent assessment of the Program for reviewing NME NDAs and original BLAs under PDUFA V. We are interviewing applicants after FDA issues first-cycle actions. Participation is voluntary, and ERG keeps identifying information for individual responses strictly confidential. During the interview, I will ask you about your experience with the review process, practices that improved review transparency, practices that improved communication, and any challenges experienced during review of your application in the Program. Your responses will help identify practices that could improve the likelihood of success of the Program. When would be a good time for an interview?

Is applicant willing to schedule an interview?

Yes: Thank you very much. Would it be convenient to meet in or around Silver Spring, Maryland, or shall we talk by phone?

Would you like me to include anyone else from your company in the interview? To ensure the efficiency of the interview, we are interested in interviewing up to three individuals as a group for up to 90 minutes.

Yes: Can you please provide the interviewees' contact information? I will follow up with a meeting invitation with the date, time, and location of our interview. If you have any questions in the meantime or need to reschedule, please feel free to contact me. [Contact information: email and phone]

No: I will follow up with a meeting invitation with the date, time, and location of our interview. If you have any questions in the meantime or need to reschedule, please feel free to contact me. [Contact information: email and phone]

I'd like to read the standard government statement about the voluntary nature of this interview:

Public reporting burden for this collection of information is estimated to average 60-90 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other suggestions for reducing this burden to Ila S. Mizrachi, Office of Information Management, Food and Drug Administration, 1350 Piccard Drive, PI50-400B, Rockville, MD 20850, 301-796-7726 Ila.Mizrachi@fda.hhs.gov.

Notwithstanding any other provisions of the law, no person is required to respond to, nor shall any person be subjected to a penalty for failure to comply with, a collection of information subject to the requirements of the Paperwork Reduction Act, unless that collection of information displays OMB Control Number 0910-0746.

No: Thanks anyway. I appreciate your time.

ERG will send this meeting confirmation after the interview scheduling details have been established.

Meeting Confirmation [by email, using ERG email address]

Subject line: Confirmation: PDUFA V Program Interview regarding [trade name]

Dear [first and last name of interviewee(s)],

This is a confirmation for our upcoming interview about the review of [trade name], NDA/BLA [application #], reviewed under the PDUFA V Program. The purpose of the interview is described below.

When: [Day], [Date], [Time]

Where: [Confirmed location]

Who: [Name(s), Title(s)]

Thank you for your participation. We look forward to speaking with you.

Best regards,
[Name]
[Contact information: email and phone]

Eastern Research Group, Inc. (ERG) is the contractor conducting an independent assessment of the Program. An important part of the assessment, as outlined in the PDUFA V Commitment Letter, is feedback from the FDA review team and applicants regarding the Program. During the interview, we will ask about your experience with the review process for your application, practices that improved review transparency and communication, and challenges experienced during the review of the application in the Program. Your responses will help identify how the Program works well and how it could be improved. You are not expected or required to prepare any material in advance. In analyzing and reporting on feedback, ERG will not be evaluating your application or the work of any individual FDA staff and will keep identifying information of interviewees strictly confidential.

Public reporting burden for this collection of information is estimated to average 60-90 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other suggestions for reducing this burden to Ila S. Mizrachi, Office of Information Management, Food and Drug Administration, 1350 Piccard Drive, PI50-400B, Rockville, MD 20850, 301-796-7726 Ila.Mizrachi@fda.hhs.gov.

Notwithstanding any other provisions of the law, no person is required to respond to, nor shall any person be subjected to a penalty for failure to comply with, a collection of information subject to the requirements of the Paperwork Reduction Act, unless that collection of information displays OMB Control Number 0910-0746.

ERG will send this meeting reminder 24-48 hours before the interview.

Meeting Reminder [by email, using ERG email address]

Subject line: Reminder: PDUFA V Program Interview regarding [trade name]

Dear [first and last name of interviewee(s)],

This is a reminder for our upcoming interview about the review of [trade name], NDA/BLA [application #], reviewed under the PDUFA V Program. The purpose of the interview is described below.

When: [Day], [Date], [Time]

Where: [Confirmed location]

Who: [Name(s), Title(s)]

Thank you for your participation. We look forward to speaking with you.

Best regards,
[Name]
[Contact information: email and phone]

Eastern Research Group, Inc. (ERG) is the contractor conducting an independent assessment of the Program. An important part of the assessment, as outlined in the PDUFA V Commitment Letter, is feedback from the FDA review team and applicants regarding the Program. During the interview, we will ask about your experience with the review process for your application, practices that improved review transparency and communication, and challenges experienced during the review of the application in the Program. Your responses will help identify how the Program works well and how it could be improved. You are not expected or required to prepare any material in advance. In analyzing and reporting on feedback, ERG will not be evaluating your application or the work of any individual FDA staff and will keep identifying information of interviewees strictly confidential.

Public reporting burden for this collection of information is estimated to average 60-90 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other suggestions for reducing this burden to Ila S. Mizrachi, Office of Information Management, Food and Drug Administration, 1350 Piccard Drive, PI50-400B, Rockville, MD 20850, 301-796-7726 Ila.Mizrachi@fda.hhs.gov.

Notwithstanding any other provisions of the law, no person is required to respond to, nor shall any person be subjected to a penalty for failure to comply with, a collection of information subject to the requirements of the Paperwork Reduction Act, unless that collection of information displays OMB Control Number 0910-0746.

If applicants request the interview questions, ERG will attach the prepared PDF file with general interview questions and include the following statement in the response:

Applicant Request for Interview Questions

[Attach the "Post-action Interview questions – Applicant Request" document]

"Please note that we do not ask or expect you to spend time preparing for this interview. Nevertheless, we can provide our interview questions (see attachment) upon request."

Post-action Interview Questions

Note: Eastern Research Group, Inc. (ERG) does not ask or expect you to spend time preparing for this interview. We provide interview questions as a courtesy upon request.

I am going to read a series of statements about steps in the NDA/BLA review process. For each statement, please tell me if you strongly disagree, disagree, neither agree nor disagree, agree, or strongly agree. You can also say "Don't know" or "Not applicable".

Step in Review Process	Statement	Agreement Rating						
		Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree	Don't know	Not Applicable
Pre-submission meeting	The pre-submission meeting took place far enough in advance of application submission to allow for incorporation of FDA feedback in the NDA/BLA.							
	The pre-submission meeting was an effective forum for discussing questions and issues with FDA prior to submission.							
	The pre-submission meeting was attended by the appropriate FDA staff to allow sufficient discussion of questions and issues at the meeting.							
	The pre-submission meeting provided insight into FDA's preliminary stance on the need for REMS or other risk management actions based on the information provided to the agency to date.							
	The pre-submission meeting resulted in a clear and shared understanding of expectations regarding the content of the complete application prior to submission.							
	Discussion of the content of the complete application and delayed submission of minor components: • Allowed for planning of application-related activities prior to submission.							

Step in Review Process	Statement	Agreement Rating						
		Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree	Don't know	Not Applicable
	• Resulted in an earlier submission of the original application. (That is, without agreement on late components, you would have needed to delay the original submission.)							
	• Resulted in a later-than-planned submission of the original application.							
Day 74 letter	FDA's preliminary thinking on the need for an Advisory Committee meeting provided in the Day 74 letter was helpful for planning purposes.							
	The Day 74 letter provided transparent information about potential NDA/BLA review issues.							
Mid-cycle communication	The mid-cycle communication provided transparent information about: • The current status of the application.							
	• Significant issues identified by the review team.							
	• Major safety concerns identified thus far and preliminary thinking on risk management.							
	Information provided in the mid-cycle communication allowed for efficient: • Responses to information requests.							
	• Preparation of other items such as labeling language and PMC plans.							
Discipline Review letters	The Discipline Review letter(s) clearly delineated application deficiencies.							
	The Discipline Review letter(s) included a path forward to address the deficiencies communicated in the letter.							

Step in Review Process	Statement	Agreement Rating						
		Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree	Don't know	Not Applicable
	(*If applicable*) Receiving Discipline Review letters in advance of the late-cycle meeting allowed time to prepare for discussing the deficiencies at the late-cycle meeting.							
Late-cycle meeting	The late-cycle meeting provided transparent information about: • The current status of the application.							
	• Remaining application deficiencies.							
	• FDA's assessment of the need for REMS or other risk management actions.							
	The late-cycle meeting was an effective forum for: • Discussing questions and issues with FDA.							
	• Discussing FDA information needs.							
	• Planning for the remainder of the review process.							
	• Discussing the Advisory Committee meeting.							
	The late-cycle meeting was held far enough in advance of the Advisory Committee meeting to allow sufficient time to prepare.							
Process as a whole	I felt well-informed about the status of my NDA/BLA as a result of interactions with FDA during the agency's review of the application.							
	I was not surprised by the action letter I received.							
	Interactions with FDA allowed sufficient planning for manufacturing scale-up and launch activities (approvals) or resubmission of the application (for CRs).							

Now I'd like to ask you about any experiences that you would consider either good practices or challenges during the review of the application for [established name].

Q1. What types of practices did you find helpful in the review?

Q2. What types of challenges did you encounter in the review?

Q3. Can you comment on your experience in the Program with respect to the transparency, efficiency, and predictability of the review process?

Q4. Have you identified any "lessons learned" that might help you or FDA with future application reviews?

Q5. Is there anything else you'd like to add about your review experience with [established name]?

Pre-Submission Meeting Evaluation Instrument

Meeting Information

	Fill in this section before the meeting or while assessing the minutes.
Evaluator	
In-person / Phone	
If phone, was F2F offered to sponsor?	
IND #	
Established name	
Sponsor	
Emerging sponsor?	
Planned submission date / timeframe	
Reference NDA/BLA	
Pre-submission meeting date	
Observed / Minutes only	

Program Requirements

Fill in this section after the meeting or while assessing the minutes.			
	Discussed	Agreement	Comments
Content of complete application	Y / N / Narrow	Y / N / NA	☐ Addressed in preliminary comments
Delayed application components	Y / N / Narrow	Y / N / NA	☐ Addressed in preliminary comments
Preliminary discussion on need for REMS or other risk management	Y / N		☐ Addressed in preliminary comments

Agreed-upon Delayed Application Components

Fill-in this section after the meeting or while assessing the minutes.			
#	Discipline	Delayed Component	Additional notes or context
1.			
2.			
3.			
4.			

Meeting Summary

Fill in this section after the meeting.		
Meeting duration	____ minutes	Start time: End time:
Meeting Moderator	FDA / Sponsor	Comments:
Discussions and agreements summarized	Y / N / P	
Who summarized	FDA / Sponsor / NA	
Discussions summarized at end of	Meeting / Topic / NA	

Fill in this section after the meeting or while reviewing the minutes.
# of anticipated topics for discussion: Anticipated topics for discussion *(reference the questions/comments in the preliminary meeting comments)*: Comments on any of the documents associated with this pre-submission meeting (briefing package, preliminary comments, meeting request/granted letters, etc.):

Meeting Discussion Table

FDA / Sponsor	Discussion Reference #	Time Start	Time End	Discipline	Issue Overview	Dialogue Tally	Discussion Summary / Observations

Program Topics

Issue	Time Start	Time End	Who introduces topic? (FDA / Sponsor)	Discussed? (Y / N/ Narrow)	Dialogue Tally	Discussion Summary / Observations
Content of a Complete Application						
Delayed Application Components						
Risk Evaluation, REMS or other risk management						

General Notes	Observations
☐ Sponsor appeared well versed in Program requirements discussed in meeting ☐ FDA staff appeared well versed in Program requirements discussed in meeting ☐ Sponsor raised topics/questions not in written list ☐ Discussion generally constructive/collaborative ☐ Discussion generally contentious ☐ Rushed at the end ☐ Office Director present ☐ Division Director present	

Pre-Submission Meeting Evaluation Instrument – Coding Guide

Meeting Information

	Fill in this section before the meeting.
Evaluator	*Write your name.*
In-person / Phone	*Write "In-person" if meeting took place in person.* *Write "Phone" if by teleconference.*
If phone, was F2F offered to sponsor?	*Write "Yes" if FDA offered F2F meeting to sponsor, but was changed to teleconference in the review of preliminary meeting documents.* *Otherwise, write "No".*
IND #	*Write the IND application number.*
Established name	*Write the established name of the drug.*
Sponsor	*Write the name of the sponsor as identified in the "Meeting Granted Letter".*
Emerging sponsor?	*Write "Yes" if the sponsor meets the definition of emerging sponsor. Otherwise, write "No".*
Planned submission date / timeframe	*Write the date the sponsor expects to submit the application, whether stated in the meeting or in preliminary meeting documents.* *Write "Unknown" if the month of a planned submission is unknown.*
Reference NDA/BLA	*Write the reference NDA/BLA application number indicated at the time of pre-submission.* *Write "N/A" if this is unavailable.*
Pre-submission meeting date	*Write the meeting date.*
Observed / Minutes only	*Write "Observed" if the meeting was attended by ERG staff.* *Write "Minutes only" if the meeting was assessed using meeting minutes.*

Program Requirements

Fill in this section after the meeting or while assessing the minutes.			
	Discussed	Agreement	Comments
Content of complete application	*Refer to the responses given in the "Program Topics" table.*	*Circle "Y" if agreement was reached and confirmed by both sides.* *Circle "N" if agreement was not reached and confirmed openly by both sides.* *Circle "NA" if it was not discussed thus no agreement was made.*	☐ Addressed in preliminary comments *Check the box if the topic was discussed in the preliminary comments for the meeting.* *Record any comments / observations regarding this discussion.*
Delayed application components	*Refer to the responses given in the "Program Topics" table.*	*Circle "Y" if agreement was reached; agreement on zero components is considered agreement made.* *Circle "N" if agreement was not reached.* *Circle "NA" if it was not discussed thus no agreement was made.*	☐ Addressed in preliminary comments *See above.*

Preliminary discussion on need for REMS or other risk management	*Refer to the responses given in the "Program Topics" table.*		☐ Addressed in preliminary comments *See above.*

Agreed-upon Delayed Application Components

Fill-in this section after the meeting or while assessing the minutes			
#	Discipline	Delayed Component	Additional notes or context
1.	*Identify the review discipline associated with this submission component.*	*List the delayed component that FDA and sponsor agreed upon.*	*Provide or note any additional information or context regarding the delayed component.*
2.	*Same as above.*	*Same as above.*	*Same as above.*
3.	*Same as above.*	*Same as above.*	*Same as above.*
4.	*Same as above.*	*Same as above.*	*Same as above.*

Meeting Summary

Fill in this section after the meeting.		
Meeting duration	*Subtract the end time from the start time.*	*Start time: Time meeting begins* *End time: Time meeting closed*
Meeting Moderator	*Circle "FDA" if FDA facilitates the meeting.* *Circle "Sponsor" if the sponsor facilitates the meeting*	Comments: *Record any comments / observations regarding this discussion.*
Discussions and agreements summarized	*Circle "Y", if discussion on all meeting topics was summarized.* *Circle "N", if discussion on meeting topics was not summarized.* *Circle "P", if discussion on some meeting topics was summarized.*	
Who summarized	*Circle "FDA" if FDA summarized. Circle "Sponsor" if applicant summarized.* *Circle "NA" if no summary took place.*	
Discussions summarized at end of	*Circle "Topic" if summarized at end of each topic.* *Circle "Meeting" if summarized at the end of meeting.* *Circle "NA" if no summary took place.*	

Fill in this section after the meeting or while assessing the minutes.
# of anticipated topics for discussion: *Count and write the total number of anticipated discussion topics as indicated by the preliminary meeting comments/discussion, if available.* Anticipated topics for discussion *(reference the question in the preliminary meeting comments)*: *Write the reference question/discussion number (as indicated in the preliminary meeting comments) and/or discipline. If question/discussion number is not assigned, paraphrase/copy the original topic. This information is often found in the email sent from the RPM.* Comments on any of the documents associated with this pre-submission meeting (briefing package, preliminary comments, meeting request/granted letters, etc.): *Record any comments/notes regarding the documents associated with the pre-submission meeting. Comments like these should include anything relevant to Program requirements, such as agreements made on delayed components.*

Meeting Discussion Table

FDA / Sponsor	Discussion Reference #	Time Start	Time End	Discipline	Issue Overview	Dialogue Tally	Discussion Summary / Observations
Circle "FDA" if the topic was initiated by FDA staff. *Circle "Sponsor" if it was initiated by sponsor.* *Write "N/A" if the minutes are assessed.*	*Identify a reference number for the issue in the pre-meeting documentation (e.g., preliminary comments, agenda) when possible; for example, "Agenda Item #2" or "Preliminary Responses #15". If the topic is an additional or unplanned discussion, write "Additional".* *Write "N/A" if the minutes are assessed.*	*Record when discussion started.* *Write "N/A" if the minutes are assessed.*	*Record when discussion ended.* *Write "N/A" if the minutes are assessed.*	*Write the discipline of the topic/issue if it is labeled or readily identified by FDA, either in the meeting or in pre-meeting documents, or the meeting minutes, if assessed; otherwise, write "Unspecified".*	*If the meeting is observed, summarize the elaboration of the issue communicated.* *If the minutes are assessed, summarize issue that is marked by "Discussion:" (distinguishing topics that were covered in the preliminary comments) in the meeting minutes.*	*Tally the total number of instances when FDA and applicant take turns speaking. End discussion courtesies (i.e. "Thank you") will not be tallied. For example, if the FDA asks the applicant if they intend to submit a complete application, and the applicant says "Yes, we intend to submit a complete application." The tally is 2. If the FDA subsequently responded "Thank you." The tally is still 2.* *Write "N/A" if the minutes are assessed.*	*Summarize the main points of the discussion at a high-level, making additional qualitative observations on this point as necessary.*
Same as above.	*Same as above.*	*Same as above.*	*Same as above.*	*Same as above.*	*Same as above.*	*Same as above.*	*Same as above.*
Same as above.	*Same as above.*	*Same as above.*	*Same as above.*	*Same as above.*	*Same as above.*	*Same as above.*	*Same as above.*

Program Topics

Issue	Time Start	Time End	Who introduces topic? (FDA / Sponsor)	Discussed? (Y / N/ Narrow)	Dialogue Tally	Discussion Summary / Observations
Content of a Complete Application	*Write discussion start time.* *Write "N/A" if the minutes are assessed.*	*Write discussion end time.* *Write "N/A" if the minutes are assessed.*	*Write "FDA" if the topic was initiated by FDA staff.* *Write "Sponsor" if it was initiated by sponsor.* *Write "N/A" if the minutes are assessed.*	*Write "Y" if application completeness was an explicit topic of discussion.* *Write "N" if a complete application's content is not discussed or raised at all.* *Write "Narrow" if a few components of an application are discussed but the notion of application completeness is not discussed explicitly* *If the minutes are assessed,* *Write "Y" if there is an indication in the minutes that the topic was discussed at the meeting (e.g., "Discussion at meeting" header, different font).* *Write "N" if it was not discussed at all. Write "Narrow" if it was only partially discussed or was not an explicit topic of discussion.*	*Tally the total number of instances when FDA and applicant take turns speaking. End discussion courtesies (i.e. "Thank you") will not be tallied. For example, if the FDA asks the applicant if they intend to submit a complete application, and the applicant says "Yes, we intend to submit a complete application." The tally is 2. If the FDA subsequently responded "Thank you", the tally is still 2.* *Write "N/A" if the minutes are assessed.*	*Summarize the main points of the discussion at a high-level, making additional qualitative observations on this point as necessary.* *Write "N/A" if the minutes are assessed*
Delayed Application Components	*Same as above.*	*Same as above.*	*Same as above.*	*Write "Y" if delayed application components or acceptable late submissions are an explicit topic of discussion.* *Write "N" if it was not discussed at all.* *Write "Narrow" if only specific components were addressed rather than all potential delayed components, including none, being an explicit topic of discussion.* *If the minutes are assessed,* *Write "Y" if there is an indication in the*	*Same as above.*	*Same as above.*

				minutes that the topic was discussed at the meeting (e.g., 'Discussion at meeting' header, different font). *Write "N" if it was not discussed at all. Write "Narrow" if it was only partially discussed or was not an explicit topic of discussion.*		
Risk Evaluation, REMS or other risk management	*Same as above.*	*Same as above.*	*Same as above.*	*Write "Y" if any aspect of REMS or post-market risk management was discussed or mentioned.* *Write "N" otherwise.*	*Same as above.*	*Same as above.*

General Notes	Observations
☐ Sponsor appeared well versed in Program requirements discussed in meeting ☐ FDA staff appeared well versed in Program requirements discussed in meeting ☐ Sponsor raised topics/questions not in written list ☐ Discussion generally constructive/collaborative ☐ Discussion generally contentious ☐ Rushed at the end ☐ Office Director present ☐ Division Director present *Check all boxes that apply.* *Identify other items that might be suitable for checkbox list.*	*Write observations of meeting as a whole.* *Write "N/A" if the minutes are assessed.*

Day 74 Letter Evaluation Instrument

Communication Information

Evaluator	
NDA# / BLA#	
Multiple applications?	Y / N
If duplicate, application #	
Established name	
Applicant	
Communication date	

Program Requirements

Clearly identified communication type, date, subject(s), author(s), and recipient(s)?	Y / N
Planned date of the internal mid-cycle meeting?	Y / N
Planned review timeline?	Y / N
Preliminary plans on whether or not to hold an Advisory Committee meeting?	Y / N
If communicated in filing letter, is the preliminary plan to hold an Advisory Committee meeting?	Y / N / NA
PDUFA Goal date	

Communication Content

Number of amendments submitted prior to filing	
Did FDA notify the applicant of potential review issues?	Y / N
Number of review issues	

#	*Identify the review issue*	*Discipline*
1.		
2.		
3.		
4.		
5.		
6.		
7.		

Additional Content

Does FDA make information requests?	Y / N
Number of information requests	

#	*Identify the information requested*	*Discipline*
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		

Notes	
Observations:	QA/QC Comments:

Day 74 Letter Evaluation Instrument – Coding Guide

Communication Information

Evaluator	*Write your name.*
NDA# /BLA#	*Write the NDA or BLA number.*
Duplicate application?	*Circle "Y" if the communication applies to more than one application.* *Circle "N" if the communication applies to only one application.*
If duplicate, application #	*Write the NDA or BLA application number of the other application for which this communication applies.*
Established name	*Write the established name of the drug.*
Applicant	*Write the name of the applicant as addressed in the communication.*
Communication date	*Record the date of the electronic signature at the end of the letter.*

Program Requirements

Clearly identified communication type, date, subject(s), author(s), and recipient(s)?	*Circle "Y" if each of these items is readily found in the letter.* *Circle "N" If any of these items are missing from the letter.*
Planned date of the internal mid-cycle meeting?	*Circle "Y" if FDA provides a date to the applicant for the internal mid-cycle meeting.* *Circle "N" if no date is provided for the internal mid-cycle meeting.*
Planned review timeline?	*Circle "Y" if FDA communicates any future milestone date to the applicant for the upcoming review, not including the internal mid-cycle meeting and PDUFA goal date.* *Circle "N" if FDA does not communicate any other dates other than the internal mid-cycle meeting and PDUFA goal.*
Preliminary plans on whether or not to hold an Advisory Committee meeting?	*Circle "Y" if FDA explicitly communicates their thinking on the potential for an Advisory Committee meeting, including whether FDA anticipates holding one, not holding one, or is undecided.* *Circle "N" if there is no mention of current plans or preliminary thinking on Advisory Committee.*
Is the preliminary plan to hold an Advisory Committee meeting?	*Circle "Y" if FDA communicates their intent to hold an Advisory Committee.* *Circle "N" if FDA communicates that they do not intend to hold an Advisory Committee.* *Circle "N/A" if there was no mention of current plans or preliminary thinking on Advisory Committee above.*
PDUFA Goal date	*Write the date of the PDUFA goal.* *Write "N/A" if not indicated.*

Communication Content

Number of amendments submitted prior to filing	*Write the total number of amendments FDA acknowledges having received from the applicant in the letter.* *If the letter does not acknowledge any received amendments, write "0".*
Did FDA notify the applicant of potential review issues?	*Circle "Y" If FDA explicitly notifies the applicant of review issues and clearly lists the issues under a header or leading statement (i.e. "We identified the following potential review issues") or if no issues exist and FDA notifies the applicant. Issues under a heading of labeling or labeling format should not be included here.* *Circle "N" if FDA does not clearly identify or list any potential review issues or does not notify the applicant that no issues have been identified thus far.*
Number of review issues	*Count the total number of potential review issues or write "N/A" only if it was not discussed (i.e., if answered "N" above). Do not include issues under a heading of labeling or labeling format.* *If the header or leading statement combines review issues and information requests (e.g., "we identified the following potential review issues and request that you submit the following information"), treat each item in the list as a potential review issue unless expressly identified as an information request or labeling format issue.*

#	*Identify the review issue*	*Discipline*
1.	*Summarize the review issue identified in the letter.* *If the header does not clearly distinguish between potential review issues or information requests, summarize the issue/request and also write the reference the "Additional Content" table of this document.*	*Write the header which identifies the discipline concerning this review issue.* *If there is no header, contact the RPM for clarification.*
2.	*See above.*	*See above.*
3.	*See above.*	*See above.*
4.	*See above.*	*See above.*
5.	*See above.*	*See above.*
6.	*See above.*	*See above.*
7.	*See above.*	*See above.*

Additional Content

Does FDA make information requests?	*Circle "Y" if FDA explicitly notifies the applicant of information requests and clearly lists the requests under a header or leading statement (i.e. "We request that you submit the following information"). Information requests under a heading of labeling or labeling format should not be included here.* *Circle "N" if no information was requested or if the information requested is expressly identified as a labeling format issue.*
Number of information requests	*Count number of information requests and write number, or write "0" only if it was not discussed (i.e., if answered "N" above). Do not include information requests under a heading of labeling or labeling format.* *If the header or leading statement combines review issues and information requests (e.g., "we identified the following potential review issues and request that you submit the following information"), treat each item in the list as an information request unless expressly identified as a review issue or labeling format issue.*

#	*Identify the information requested*	*Discipline*
1.	*Summarize the information request identified in the letter.* *If the header does not clearly distinguish between potential review issues or information requests, summarize the issue/request and also write the reference the "Communication Content" table of this document.*	*Write the header which identifies the discipline concerning this information request.* *If there is no header, contact the RPM for clarification.*
2.	*See above.*	*See above.*
3.	*See above.*	*See above.*
4.	*See above.*	*See above.*
5.	*See above.*	*See above.*
6.	*See above.*	*See above.*
7.	*See above.*	*See above.*
8.	*See above.*	*See above.*
9.	*See above.*	*See above.*
10.	*See above.*	*See above.*

Notes

Observations:	QA/QC Comments:
Record any additional comments.	*Record any disagreements/reconciliations between evaluator decisions.*

Mid-Cycle Communication Evaluation Instrument

Communication Information

	Fill-in this section before the meeting or while assessing the minutes.
Evaluator	
NDA# / BLA#	
Multiple applications?	Y / N
If yes above, application number(s)	
Established name	
Applicant	
Communication Date	
Mid-cycle meeting date	
Meeting agenda sent	Y / N / Unknown
Observed / Minutes only	

Communication Content

Fill-in this section after the meeting or while assessing the minutes.		
Meeting duration	____ minutes	Start time: End time:
Discussion of potential major safety concerns identified by review team to date	Y / N	Reference:
Preliminary thinking on risk management	Y / N	Comments:
Proposed dates for late-cycle meeting	Y / N	
Update on whether Advisory Committee meeting is planned	Y / N	
Projected milestone dates in remainder of review cycle	Y / N	
Were all appropriate FDA members present?*	Y / N	Discipline / Staff not available:

*At this time, ERG is measuring this item solely on the basis of whether the RPM, CDTL and other review staff present can answer all applicant questions during the meeting. If so, we enter "Y". If not, we enter "N" and note the discipline that was needed to answer the applicant's question.

Discussion Table

Significant issues identified by review team to date? Y / N

Number of significant issues raised during communication ____

Total time of significant issues discussion: _____

Time Start	Time End	Discipline	Issue Overview	Dialogue Tally	Discussion Summary / Observations	Significant Issues

IRs identified by review team? Y / N

# of information requests issued during communication _____

Discipline	Information Request	Notes / Observations

Additional Topics Raised by Applicant

Issue	Time Start	Time End	Issue Overview	Dialogue Tally	Discussion Summary / Observations

General Notes / Observations

Mid-Cycle Communication Evaluation Instrument – Coding Guide

Communication Information

	Fill-in this section before the meeting or while assessing the minutes.
Evaluator	*Write your name.*
NDA# / BLA#	*Write the NDA or BLA number.*
Multiple applications?	*Circle "Y" if the communication applies to more than one application.* *Circle "N" if the communication applies to only one application.*
If yes above, application number(s)	*Write the NDA or BLA application number of the other application for which this communication applies.*
Established name	*Write the established name of the drug.*
Applicant	*Write the name of the applicant as introduced during the meeting.*
Communication Date	*Write the date of mid-cycle communication.*
Mid-cycle meeting date	*Write the date of the FDA internal mid-cycle meeting.*
Meeting agenda sent	*Circle "Y" if a meeting agenda or any pre-meeting information is sent to the applicant prior to the communication regarding the communication content/format, and indicate the location (email/DARRTS).* *Circle "N" if no communication or notice was issued to the applicant regarding the content/format or agenda of the meeting.* *Circle "Unknown" if it is unclear whether or not an agenda was sent.*
Observed / Minutes only	*Write "Observed" if the meeting was attended by ERG staff.* *Write "Minutes only" if the meeting was assessed using meeting minutes.*

Communication Content

Fill-in this section after the meeting or while assessing the minutes.		
Meeting duration	*Subtract the end time from the start time.* *Write "N/A" if the minutes are assessed.*	*Start time: Time meeting begins* *End time: Time meeting closed* *Write "N/A" if the minutes are assessed.*
Discussion of potential major safety concerns identified by review team to date	*If the meeting is observed,* *Circle "Y" if FDA explicitly introduces major safety concerns or discusses safety signals, the potential need to include additional warnings, precautions or contraindications in the labeling, serious adverse events, or suggests that the use of the drug should be restricted to certain populations; or if FDA explains that no major safety concerns were identified by the review team thus far.* *Circle "N" if none of the above issues were raised or discussed during the*	

	meeting. *If the minutes are assessed,* *Circle "Y" if the minutes document or reference a discussion regarding safety signals, the potential need to include additional warnings, precautions or contraindications in the labeling, serious adverse events, or there are suggestions that the use of the drug should be restricted to certain populations; or if the minutes state that no major safety concerns were identified.* *Circle "N" if none of the above issues were recorded in the minutes.*
Preliminary thinking on risk management	*Circle "Y" if FDA communicates, or includes in the minutes, any current thoughts about risk management or REMS.* *Circle "N" if FDA does not mention any current thoughts on risk management or REMS at all at the meeting or in the minutes.*
Proposed dates for late-cycle meeting	*Circle "Y" if FDA communicates, or includes in the minutes, proposed dates for the late-cycle meeting.*
Update on whether Advisory Committee meeting is planned	*Circle "Y" if an Advisory Committee meeting is anticipated or not anticipated and FDA communicates its plans at the meeting or in the minutes.* *Circle "N" if the status of the Advisory Committee is yet undecided or if no mention is made of the Advisory Committee.*
Projected milestone dates in remainder of review cycle	*Circle "Y" if FDA communicates, or includes in the minutes, an update on projected milestone dates for remainder of review cycle (in addition to the late-cycle meeting and Advisory Committee).* *Circle "N" if no projected milestone dates are provided, or if the only projected milestone dates provided are the late-cycle meeting and Advisory Committee.*
Were all appropriate FDA members present?*	*If the meeting is observed,* *Circle "Y" if all questions asked by the applicant during the meeting were answered by the FDA.* *Circle "N" if FDA has to delay a full response to an applicant's question because the requested staff member or discipline was not in attendance.* *If the minutes are assessed,* *Circle "Y" if the RPM and CDTL are included in the attendee list, and all questions asked by the applicant in the minutes were answered by the FDA.* *Circle "N" if the RPM or CDTL are not included in the attendee list, or if the minutes record the applicant asking a question that FDA has to defer answering due to the absence of a discipline.*

Discussion Table

Significant issues identified by review team to date?	*Circle "Y" if significant issues exist and FDA communicates these to the applicant or if no significant issues exist and FDA communicates this to the applicant. If FDA does not specify whether an identified review issue is significant or not, ERG will assume that it is a significant issue.* *Circle "N" if no review issues are brought up or discussed.*	Number of significant issues updates raised during communication	*Sum the total number of check marks in the "Significant Issues" column.*	Total time of significant issues discussion:	*Sum the total number of minutes from the rows which are indicated as "significant issues". Write "N/A" if minutes are assessed.*

Time Start	Time End	Discipline	Issue Overview	Dialogue Tally	Discussion Summary / Observations	Significant Issues
Record when meeting started. *Write "N/A" if minutes are assessed.*	*Record when meeting ended.* *Write "N/A" if minutes are assessed.*	*Identify the discipline if possible.* *Write "Unspecified" if unknown.*	*Summarize / paraphrase the issue discussed* *If the minutes are assessed, write the subheading if available, or discussion topic to locate the discussion.*	*Tally the total number of instances when FDA and applicant take turns speaking. End discussion courtesies (i.e. "Thank you") will not be tallied. For example, if the FDA asks the applicant if they intend to submit a complete application, and the applicant says "Yes, we intend to submit a complete application." The tally is 2. If the FDA subsequently responded "Thank you", the tally is still 2.* *Write "N/A" if the minutes are assessed.*	*Summarize general observations of the overall discussion of this topic/issue.*	*Make a check in this box if the issue discussed in this row is not related to labeling, risk management/post-marketing, REMS, updates on late-cycle meetings, Advisory Committees or other remaining milestone dates, or an explicitly introduced update on Major Safety Concerns.*

Information Requests

IRs identified by review team?	*Circle "Y" if FDA identifies and requests new information to be submitted by the applicant.* *Circle "N" if FDA only references previously issued information requests or does not mention information requests at all.*
# of information requests issued during communication	*Sum number of information requests issued during the meeting.* *Write "0" if FDA identifies new information requests to be sent, but does not issue them during the meeting, or if the minutes state that FDA has no new IRs.* *Write "N/A" only if it was not discussed (i.e., if circled "N" above).*

Discipline	Information Request	Notes / Observations
Identify the discipline of the information request.	*Summarize the information that is requested in the meeting or minutes.*	*Record any comment/observation regarding any of the information requests.*
Same as above.	*Same as above.*	

Additional Topics Raised by Applicant

Time Start	Time End	Issue Overview	Dialogue Tally	Discussion Summary / Observations
Record when discussion started. *Write "N/A" if minutes are assessed.*	*Record when discussion ended.* *Write "N/A" if minutes are assessed.*	*Summarize / paraphrase the issue discussed.* *Write "N/A" if minutes are assessed.*	*Tally the total number of instances when FDA and applicant take turns speaking. End discussion courtesies (i.e. "Thank you") will not be tallied. For example, if the FDA asks the applicant if they intend to submit a complete application, and the applicant says "Yes, we intend to submit a complete application." The tally is 2. If the FDA subsequently responded "Thank you", the tally is still 2.* *Write "N/A" if minutes are assessed.*	*Summarize general observations of the overall discussion of this topic/issue.* *Write "N/A" if minutes are assessed.*
See above.	*See above.*	*See above.*	*See above.*	*See above.*

General Notes / Observations
Add any additional notes of interest or comments about the collection of data for the original application that are not captured elsewhere.

Discipline Review Letter Evaluation Instrument

Communication Information

Evaluator	
NDA# / BLA#	
Established name	
Applicant	
Communication date	

Discipline

Discipline(s) clearly identified?	Y / N
CDER Disciplines (circle all that apply)	CBER Disciplines (circle all that apply)
Clinical	Clinical
Nonclinical	CMC
Product Quality	Non-Clinical
Clinical Pharmacology	Pharm / Tox
Statistics	Human Pharmacokinetics
OSE	Bioavailability
Clinical Microbiology	Other
Other	
Comments	

Deficiencies

#	Brief summary of deficiency	Comments
1.		
2.		
3.		
4.		
5.		

6.		
7.		
8.		
9.		
10.		

Notes/Observations:	QA/QC comments and notes:

Discipline Review Letter Evaluation – Coding Guide

Communication Information

Evaluator	*Write your name.*
NDA# / BLA#	*Write the NDA or BLA number.*
Established name	*Write the established name of the drug.*
Applicant	*Write the name of the applicant as addressed in the communication.*
Communication date	*Record the date of the electronic signature at the end of the letter.*

Discipline

Discipline(s) clearly identified?	*Circle "Y' if disciplines are clearly identified by header or text.* *Circle "N" if disciplines are not identified.*
CDER Disciplines (circle all that apply) *(Circle all the disciplines below that are clearly identified by header as it appears in the Discipline Review letter; even if the discipline category can be inferred without a clear header, select "other" and include a note in the comments section)*	CBER Disciplines (circle all that apply) *(Circle all the disciplines below that are clearly identified by header as it appears in the Discipline Review letter; even if the discipline category can be inferred without a clear header, select "other" and include a note in the comments section)*
Clinical	Clinical
Nonclinical	CMC
Product Quality	Non-Clinical
Clinical Pharmacology	Pharm / Tox
Statistics	Human Pharmacokinetics
OSE	Bioavailability
Clinical Microbiology	Other
Other	
Comments	
Identify the disciplines that are classified as "Others", and add anything else noteworthy (for example, if a discipline is identified in the DR letter but notes that there are no deficiencies).	

Deficiencies

#	Brief summary of deficiency	Comments
1.	*Briefly summarize the deficiency identified in the letter.*	*Include any additional comments or observations about this deficiency if necessary.*
2.	*See above.*	*See above.*

Notes/Observations:	OA/QC comments and notes:
Record any additional comments.	*Record any differences between evaluators and how the differences were resolved.*

Late-Cycle Meeting Evaluation Instrument

Meeting Information

	Fill-in this section before the meeting or while assessing the minutes.
Evaluator	
NDA# / BLA#	
Multiple applications?	Y / N
If yes above, application number(s)	
Established name	
Applicant	
F2F / Phone	
If phone, was F2F offered to applicant?	
Late-cycle meeting date	
Meeting Time	
PDUFA Goal date	
Briefing Package sent date	
Observed / Minutes only	

Briefing Package

Fill-in this section before the meeting and assessing the minutes.		
Discipline review letters issued to date	Included / Referenced / Not included / None	*# of letters:*
Substantive review issues identified	Y / N	*# of issues:*
Number of substantive review issues to be discussed in meeting agenda		Comments:
Assessment of need for REMS or other risk management	Y / N	Comments:
Post-marketing (PMRs or PMCs) issues	Y / N	
Labeling Issues	Y / N	
Advisory Committee Date		Comments:
Background package for Advisory Committee	Y / N / NA	
Date AC Briefing package sent (if not included)		
Potential questions and points of discussion for the Advisory Committee	Y / N /NA	

Meeting Content

Fill-in this section after the meeting or while assessing the minutes.		
Meeting duration	____ minutes	Start time: End time:
Were all appropriate FDA members present?*	Y / N	Discipline / Staff not available:
Potential discussion topics		
Whether issues for an AC meeting have been identified to date	Y / N / NA / Referenced	Comments:
Need for REMS or other risk management	Y / N	
Reminder or discussion of outstanding information requests?	Y / N	
Does applicant wish to submit additional data or analyses?	Y / N / NA	Comments:
If yes above, did FDA discuss whether or not the submission would constitute a major amendment?	Y / N / NA	

*At this time, ERG is measuring this item solely on the basis of whether the RPM and other review staff present can answer all applicant questions during the meeting. If so, we enter "Y". If not, we enter "N" and note the discipline that was needed to answer the applicant's question.

General Notes / Observations
☐ Applicant sent written response to the LCM briefing package ☐ Applicant appeared well versed in Program requirements discussed in meeting ☐ FDA staff appeared well versed in Program requirements discussed in meeting ☐ Discussion generally constructive/collaborative ☐ Discussion generally contentious ☐ Rushed at the end ☐ Office Director present ☐ Division Director present

Discussion Table

Total number of issues discussed: _____

Number of substantive/significant issues or major deficiencies raised during meeting _____

Substantive/significant review issues or major deficiencies identified to date? Y / N

Time of discussion on substantive or significant review issues: _____

FDA / Applicant	Substantive / significant issue	Time Start	Time End	Discipline	Issue Overview	Dialogue Tally	Discussion Summary / Observations

Information Requests

IRs identified by review team? Y / N

# of information requests issued during communication _____

Discipline	Information Request	Notes / Observations

Late-Cycle Meeting Evaluation Instrument – Coding Guide

Meeting Information

	Fill-in this section before the meeting or while assessing the minutes.
Evaluator	*Write your name.*
NDA# / BLA#	*Write the NDA or BLA number.*
Multiple applications?	*Circle "Y" if the communication applies to more than one application.* *Circle "N" if the communication applies to only one application.*
If yes above, application number(s)	*Write the NDA or BLA application number of the other application for which this communication applies.*
Established name	*Write the established name of the drug.*
Applicant	*Write the name of the applicant as stated in the briefing package.*
In-person / Phone	*Write "In-person" if meeting took place in person.* *Write "Phone" if by teleconference.*
If phone, was F2F offered to applicant?	*Write "Yes" if FDA offered F2F meeting to applicant but it was changed to teleconference in the review of preliminary meeting documents.* *Circle "No" if a face-to-face meeting was not offered to the applicant.*
Late-cycle meeting date	*Write the date of late-cycle meeting.*
Meeting Time	*Record the time that the meeting is scheduled to begin and end.*
PDUFA Goal date	*Write the PDUFA goal date.*
Briefing Package sent date	*Write the date that the briefing package was sent.*
Observed / Minutes only	*Write "Observed" if the meeting was attended by ERG staff.* *Write "Minutes only" if the meeting was assessed using meeting minutes.*

Briefing Package

Fill-in this section before the meeting and assessing the minutes.		
Discipline review letters issued to date	*Circle "Included" if the briefing package includes the discipline review letters issued for this application to date.* *Circle "Referenced" if one or more discipline review letters are referenced by date; include more details in the adjacent space.* *Circle "Not Included" if the briefing package does not include or reference discipline review letters that have been issued to date.* *Circle "None" if no discipline review letters were issued for this application.*	*# of letters: Write the number of discipline review letters included/referenced.*
Substantive review issues identified	*Circle "Y" if the briefing package includes review issues identified as substantive or major deficiencies or if FDA states that there are no substantive review issues.* *Circle "N" if there are no review issues identified as substantive or major deficiencies.*	*# of issues: Write the number of substantive review issues or major deficiencies explicitly identified.*
Number of substantive review issues to be discussed in meeting	*Write the number of substantive review issues planned to be discussed in meeting agenda*	Comment: *Record any comment / observation regarding these*

agenda	*(typically at the end of the briefing package).* *Write "N/A" if FDA does not clearly specify which identified issues are to be discussed in the meeting.*	*review issues.*
Assessment of need for REMS or other risk management	*Circle "Y" if the briefing package includes FDA's current stance on the need for REMS or other risk management.* *Circle "N" if there is no mention of REMS or risk management.*	Comment: *Same as above.*
Post-marketing (PMRs or PMCs) issues	*Circle "Y" if the briefing package includes comments or updates regarding post-marketing issues.* *Circle "N" if there is no mention of post-marketing commitments or requirements.*	
Labeling Issues	*Circle "Y" if the briefing package includes an update on labeling issues or discussions.* *Circle "N" if there is no mention on labeling issues.*	
Advisory Committee Date	*Write the Advisory Committee meeting date if planned.* *Write "N/A" is no AC meeting is planned.*	Comments: *Same as above.*
Background package for Advisory Committee	*Circle "Y" if FDA includes or makes reference to the Advisory Committee meeting background package in the late-cycle meeting briefing package.* *Circle "N" if an Advisory Committee is planned but no reference to a briefing package is made or included.* *Circle "NA", if there is no Advisory Committee meeting planned.*	
Date AC Briefing package sent (if not included)	*Write the date of the late cycle briefing package if the Advisory Committee briefing package is included or write the date that the FDA intends to send the Advisory Committee briefing package.* *Write "N/A", if there is no Advisory Committee meeting planned.*	
Potential questions and points of discussion for the Advisory Committee	*Circle "Y" if FDA includes potential questions and/or points for discussion for the Advisory Committee meeting.* *Circle "N" if an Advisory Committee is expected but no points of discussion or potential questions are included.* *Circle "NA", if there is no Advisory Committee meeting planned.*	

Meeting Content

Fill-in this section after the meeting or while assessing the minutes.		
Meeting duration	*Subtract the end time from the start time.* *Write "N/A" if the minutes are assessed.*	*Start time: Time meeting begins.* *End time: Time meeting closed.*
Were all appropriate FDA members present?*	*If the meeting is observed,* *Circle "Y", if the signatory authority or the signatory proxy is present and FDA staff did not need to defer answering an anticipated meeting topic due to absence of a review team member.* *Circle "N" if no questions needed to be deferred and or if the signatory authority was not present.* *If the minutes are assessed,* *Circle "Y", if the signatory authority and RPM are included on the attendee list for the communication and if the minutes do not record the applicant asking a question that FDA has to defer answering due to the absence of a discipline.* *Circle "N" if questions needed to be deferred or if the signatory authority or RPM are not included in the attendee list.*	Discipline / Staff not available: *Record the discipline / staff unavailable to field the question.*
Potential discussion topics		
Whether issues for an AC meeting have been identified to date	*Circle "Y" if topics or issues for an Advisory Committee meeting are discussed by FDA.* *Circle "N" if an Advisory Committee is expected and Advisory Committee meeting topics are not discussed by FDA.* *Circle "NA" if no Advisory Committee is anticipated.* *Circle "Referenced" if FDA cites or references topics from a previously communicated document without further discussion.*	Comments: *Record any comment/observation regarding this discussion. For example, note if contents were referenced to previous meeting discussion rather than being fully discussed.*
Need for REMS or other risk management	*Circle "Y" if FDA explicitly addresses whether REMS or other risk management is needed, or if FDA references previous discussion regarding the need for REMS or other risk management.* *Circle "N" if REMS or risk management is not addressed/referenced by FDA.*	
Reminder or discussion of outstanding information requests?	*Circle "Y" if FDA discusses or reminds the applicant of previously issued or outstanding*	

	information requests. *Circle "N" if there was no discussion of previously issued or outstanding information requests.*	
Does applicant wish to submit additional data or analyses?	*Circle "Y" if applicant expresses interest in submitting more data, unsolicited by FDA.* *Circle "N" if the applicant has no plans to submit data or the proposed data/analyses was are in response to a request by FDA.*	Comments: *Record any comment/observation regarding this discussion. For example, note if it is unclear whether the information will be submitted formally as an amendment to the application or not.*
If yes above, did FDA discuss whether or not the submission would constitute a major amendment?	*Circle "Y" if FDA discusses with applicant whether the submission would constitute a major amendment.* *Circle "N" If FDA did not discuss, or does not know whether the data constitute a major amendment.* *Circle "NA" if the previous question was answered "N".*	

*At this time, ERG is measuring this item solely on the basis of whether the RPM and other review staff present can answer all applicant questions during the meeting. If so, we enter "Y". If not, we enter "N" and note the discipline that was needed to answer the applicant's question.

General Notes / Observations
☐ Applicant sent written response to the LCM briefing package ☐ Applicant appeared well versed in Program requirements discussed in meeting ☐ FDA staff appeared well versed in Program requirements discussed in meeting ☐ Discussion generally constructive/collaborative ☐ Discussion generally contentious ☐ Rushed at the end ☐ Office Director present ☐ Division Director present *Add any additional notes of interest or comments about the collection of data for the original application that are not captured elsewhere.*

Discussion Table

Total number of issues discussed:	*Sum the total number of rows below in the "Discussion" table.*	Number of substantive/significant issues or major deficiencies raised during meeting	*Sum the total number of rows with a check in the "substantive or significant issue" column.* *Write "N/A" only if topic was not discussed (i.e., if "N" for "Substantive/significant review issues or major deficiencies identified to date").*
Substantive/significant review issues or major deficiencies identified to date?	*Circle "Y" if significant issues or major deficiencies exist and FDA communicates these explicitly to the applicant or if no significant issues / major deficiencies exist and FDA communicates this to the applicant.* *Circle "N" if there is no clear indication as to whether substantive/significant issues have been identified.*	Time of discussion on substantive or significant review issues:	*Sum the total number of minutes from the rows which are indicated as "substantive / significant issues".* *Write "N/A" if minutes are assessed.*

FDA / Applicant	Substantive / significant issue	Time Start	Time End	Discipline	Issue Overview	Dialogue Tally	Discussion Summary / Observations
Circle "FDA" if the topic was initiated by FDA staff. Circle "Applicant" if it was initiated by applicant. *Write "N/A" if minutes are assessed.*	*Make a check in this box if the issue being discussed is explicitly mentioned during the meeting as a significant/substantive issue, or was included in the briefing package LCM agenda under a header identifying significant/substantive issues or major deficiencies.* *Leave this box blank if FDA explicitly mentions that it is not a significant/substantive issue, or if it is not explicitly stated whether the issue is significant/substantive.*	*Record when discussion started.* *Write "N/A" if minutes are assessed.*	*Record when discussion ended.* *Write "N/A" if minutes are assessed.*	*Write the discipline of the topic/issue if it is labeled or readily identified by FDA, either in the meeting or in pre-meeting documents, or the minutes if they are assessed.* *Write "Unspecified" if the discipline is unclear or unknown.*	*Summarize / paraphrase the issue discussed.* *If the minutes are assessed, write the subheading if available, or discussion topic to locate the discussion.*	*Tally the total number of instances when FDA and applicant take turns speaking. End discussion courtesies (i.e. "Thank you") will not be tallied. For example, if the FDA asks the applicant if they intend to submit a complete application, and the applicant says "Yes, we intend to submit a complete application." The tally is 2. If the FDA subsequently responded "Thank you", the tally is still 2.* *Write "N/A" if minutes are assessed.*	*Summarize the main points of the discussion at a high-level, making additional qualitative observations on this point as necessary.*

Information Requests

IRs identified by review team?	*Circle "Y" if FDA identifies and requests new information to be submitted by the applicant.* *Circle "N" if FDA only references previously issued information requests or does not mention information requests at all.*
# of information requests issued during communication	*Sum number of information requests issued during the meeting.* *Write "0" if FDA identifies new information requests to be sent, but does not issue them during the meeting.* *Write "N/A" only if it was not discussed (i.e., if circled "N" above).*

Discipline	Information Request	Notes / Observations
Identify the discipline of the information request.	*Summarize the information that is requested in the meeting.*	*Record any comment/observation regarding any of the information requests.*
Same as above.	*Same as above.*	

Post-Action Interview: Scheduling Information (FDA)

Keep this Scheduling Information sheet with interview information sheet until interview is complete. After interview, record interview response data in PETT and store this sheet in a secure location.

Interviewer: _____

NDA# / BLA#: _____

Contact person: _____

Contact person title: _____

Contact person email: _____

Contact person phone: _____

Date(s) contacted: _____ (MM/DD/YYYY)

Agreed-upon date: _____ (MM/DD/YYYY)

Agreed-upon time: _____ (HH:MM AM/PM)

Agreed-upon location: _____

Interviewee(s):

1. Name _____
   Title/role _____
2. Name _____
   Title/role _____
3. Name _____
   Title/role _____
4. Name _____
   Title/role _____
5. Name _____
   Title/role _____
6. Name _____
   Title/role _____
7. Name _____
   Title/role _____
8. Name _____
   Title/role _____

Post-Action Interview: Interview Information (FDA)

Complete this Interview Information sheet in advance.

Interviewer: _____

Note-taker: _____

NDA# / BLA#: _____

Established name: _____

Applicant: _____

Original application receipt date: _____ (MM/DD/YYYY)

Filing date: _____ (MM/DD/YYYY)

Review priority: Standard / Priority (circle one)

Interview date: _____ (MM/DD/YYYY)

Interview type: In-person / Phone (circle one)

ERG call-in number: Domestic: 888-346-3659
International: 857-288-2638
Passcode: 99213# (Leader: 992139#)

Other call-in number: _____ (xxx-xxx-xxxx)
Passcode: _____(xxxxxxx)

Interviewee(s):

Role of interviewee #1 _____

Role of interviewee #2 _____

Role of interviewee #3 _____

Role of interviewee #4 _____

Role of interviewee #5 _____

Role of interviewee #6 _____

Role of interviewee #7 _____

Role of interviewee #8 _____

Post-Action Interviews with FDA RPM / Review Staff

Beginning the Interview

Thank you for taking the time to talk with us today. I am [name] and this is [name(s)], from Eastern Research Group.

If face-to-face, shake hands.

If multiple interviewees are present and do not spontaneously introduce themselves, prompt:

And you are?

Pleasure to meet you.

Alternative if RPM/review staff are known to interviewer: Good to see you.

As part of our independent assessment of the Program, we would like to ask you about your experiences with the review process for NDA/BLA [application number], [established name].

The purpose of this interview is to obtain your opinions and feedback about the Program's impact on review transparency and communication with the sponsor for [established name], and to identify any good practices or challenges that you encountered. We are not evaluating your work, nor will we ask you to evaluate anyone else's work.

This interview should take about an hour to an hour and a half. I will ask questions, and [name(s)] will take notes. ERG will keep your identifying information confidential. We will share only anonymized results outside our internal project team. Your participation is appreciated.

Do you have any questions before we start?

After any questions have been addressed, proceed to 'Conducting the Interview.'

Conducting the Interview

Please feel free to ask me to clarify if anything is unclear. To start, I'd like to ask you for your quick gut reaction to how key steps in the process contributed to the review of the application for [established name].

Q1. I am going to read a series of statements about steps in the NDA/BLA review process. For each statement, please tell me if you strongly disagree, disagree, neither agree nor disagree, agree, or strongly agree. You can also say "Don't know" or "Not applicable".

Repeat response options after each statement (unless interviewee responds without prompt): "Do you strongly disagree, disagree, neither agree nor disagree, agree, or strongly agree?"

As the interviewee responds, mark the appropriate cell to record the response.

Step in Review Process	Statement	Agreement Rating						
		Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree	Don't know	Not Applicable
Pre-submission meeting	The pre-submission meeting was an effective forum for discussing questions and issues with the applicant prior to application submission.							
	The review team had enough information about the application to communicate a preliminary stance on the need for REMS or other risk management strategies.							
	The pre-submission meeting resulted in a clear and shared understanding of expectations regarding the content of the complete application prior to submission.							
	The applicant addressed the issues discussed in the pre-submission meeting in the application.							
Day 74 letter	(If applicable) The applicant addressed review issues identified in the Day 74 or filing letter in a timely manner.							
	(If applicable) The applicant responded to information requests identified in the Day 74 or filing letter in a timely manner.							
Mid-cycle communication	The mid-cycle communication was an effective forum for updating the applicant on: • The current status of the application.							
	• Significant review issues.							
	• Major safety concerns identified thus far and preliminary thinking on risk management.							
	• The timeline for the remainder of the review.							
	The mid-cycle communication was an effective forum for clarifying any outstanding or new information requests.							
	The mid-cycle communication contributed to enhanced: • Communication with the applicant.							
	• Review transparency.							
Discipline Review letters	(If applicable) Discipline Review letter(s) were an effective method of delineating application deficiencies.							

Step in Review Process	Statement	Agreement Rating						
		Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree	Don't know	Not Applicable
	(If applicable) The applicant addressed those deficiencies that could be addressed in the first review cycle.							
	(If applicable) Issuing Discipline Review letters before the late-cycle meeting facilitated FDA's preparation for discussing deficiencies at that meeting.							
Late-cycle meeting	The late-cycle meeting was an effective forum for: • Discussing questions and issues with the applicant.							
	• Discussing the need for REMS or other risk management actions.							
	• Planning for the remainder of the review process.							
	• (If applicable) Discussing and planning for the Advisory Committee meeting.							
	(If applicable) The late-cycle meeting was held far enough in advance of the Advisory Committee meeting to allow sufficient time to prepare.							
	The late-cycle meeting was held far enough in advance of the PDUFA goal date to allow adequate time to address any deficiencies outlined.							
Process as a whole	Meetings and communications with the applicant enabled the review team to convey review issues and deficiencies as early as possible in the review process.							
.	The applicant responded to review issues and information requests early enough to enable the review team to review the information in a timely manner (that is, to meet internal review timelines and goals during this review cycle).							
	The meetings and communications established by the Program were effective in contributing to review transparency.							

Q2. As part of our evaluation, we're trying to learn more about what constitutes a complete application upon submission. To the best of your recollection, of the amendments submitted by the applicant during the filing period, were any of these necessary to consider the application complete for filing purposes? That is, without the amendment(s), would you have needed to RTF the application?

[Provide the list of amendments submitted during the filing review period for CDER applications if requested.]

Now I'd like all/both of you to think about the review of the application for *[established name]* under the Program, considering all the aspects of the Program review process that we reviewed quickly. I'd like to ask you about any experiences that you would consider either good practices or challenges during the review of this application.

Q3. What types of practices did you find helpful in the review?

Probe about elements of the review process.

Probe for insights on how/why specific practices were helpful.

Q4. What types of challenges did you encounter in the review?

Probe about elements of the review process.

Probe for insights on how/why specific aspects of the review were challenging.

Q5. Can you comment on your experience in the Program with respect to the transparency, efficiency, and predictability of the review process?

Probe for insights about how this experience compared to previous experiences in terms of transparency, efficiency, and predictability of the review process.

Q6. Have you identified any "lessons learned" that might help you or other FDA staff with future application reviews? Or sponsors with their applications?

Q7. Is there anything else you'd like to add about your review experience with [established name]?

Closing the Interview

Thank you very much for taking the time to talk with us. Your feedback is helpful in giving us a sense of how application review processes under the Program are working from a real-world perspective. Thanks again.

Post-Action Interview: Scheduling Information (Applicant)

Keep this Scheduling Information sheet with interview information sheet until interview is complete. After interview, record interview response data in PETT and store this sheet in a secure location.

Interviewer: _____

NDA#/ BLA#: _____

Contact person: _____

Contact person title: _____

Contact person email: _____

Contact person phone: _____

Date(s) contacted: _____ (MM/DD/YYYY)

Agreed-upon date: _____ (MM/DD/YYYY)

Agreed-upon time: _____ (HH:MM AM/PM)

Agreed-upon location: _____

Interviewee(s):

1. Name _____
   Title/role _____
   Phone _____
   Email _____
2. Name _____
   Title/role _____
   Phone _____
   Email _____
3. Name _____
   Title/role _____
   Phone _____
   Email _____

Post-Action Interview: Interview Information (Applicant)

Complete this Interview Information sheet in advance.

Interviewer: _____

Note-taker: _____

NDA# / BLA#: _____

Established name: _____

Applicant: _____

Original application receipt date: _____ (MM/DD/YYYY)

Filing date: _____ (MM/DD/YYYY)

Review priority: Standard / Priority (circle one)

Interview date: _____ (MM/DD/YYYY)

Interview type: In-person / Phone (circle one)

ERG call-in number: Domestic: 888-346-3659
International: 857-288-2638
Passcode: 99213# (Leader: 992139#)

Other call-in number: _____ (xxx-xxx-xxxx)
Passcode: _____(xxxxxxx)

Interviewee(s):

Role of interviewee #1 _____

Role of interviewee #2 _____

Role of interviewee #3 _____

Post-Action Interviews with Applicant

Beginning the Interview

Thank you for taking the time to talk with us today. I am [name] and this is [name], from Eastern Research Group.

If face-to-face, shake hands.

If multiple interviewees are present and do not spontaneously introduce themselves, prompt:

And you are?

Pleasure to meet you.

Alternative if applicant(s) is/are known to interviewer: Good to see you.

As part of our independent assessment of FDA's program for enhanced review transparency and communication under PDUFA V, we would like to ask you about your experiences with the review process for NDA/BLA [application number], [established name].

The purpose of this interview is to obtain your opinions and feedback about review transparency and communication for this application under the PDUFA V NME Program. We are not evaluating your application for [established name] or the performance of any individual FDA staff members.

This interview should take about an hour to an hour and a half. I will ask questions, and [name(s)] will take notes. ERG will keep your identifying information confidential. We will share only anonymized results outside our internal project team. Here is the standard government statement about the voluntary nature of this information collection:

Public reporting burden for this collection of information is estimated to average 60-90 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other suggestions for reducing this burden to ***Ila S. Mizrachi,*** *Office of Information Management, Food and Drug Administration, 1350 Piccard Drive, PI50-400B, Rockville, MD 20850, 301-796-7726, Ila.Mizrachi@fda.hhs.gov****.*** *Notwithstanding any other provisions of the law, no person is required to respond to, nor shall any person be subjected to a penalty for failure to comply with, a collection of information subject to the requirements of the Paperwork Reduction Act, unless that collection of information displays a currently valid OMB Control Number.*

The OMB Control Number for this information collection is OMB Control Number 0910-0746.

Do you have any questions before we start?

After any questions have been addressed, proceed to 'Conducting the Interview.'

Please feel free to ask me to clarify if anything is unclear.

Conducting the Interview

To start, I'd like to ask you, [contact person's name], since you are the contact person for this application, for your quick gut reaction to how key steps (e.g., pre-submission meeting, mid-cycle communication, late-cycle meeting) in the process contributed to the application review. I understand that everyone may have opinions and feedback and I would love to hear about it when we get to open-ended discussion.

Q1. I am going to read a series of statements about steps in the NDA/BLA review process. For each statement, please tell me if you strongly disagree, disagree, neither agree nor disagree, agree, or strongly agree. You can also say "Don't know" or "Not applicable".

Repeat response options after each statement (unless interviewee responds without prompt): "Do you strongly disagree, disagree, neither agree nor disagree, agree, or strongly agree?"

As the interviewee responds, mark the appropriate cell to record the response.

Step in Review Process	Statement	Agreement Rating						
		Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree	Don't know	Not Applicable
Pre-submission meeting	The pre-submission meeting took place far enough in advance of application submission to allow for incorporation of FDA feedback in the NDA/BLA.							
	The pre-submission meeting was an effective forum for discussing questions and issues with FDA prior to submission.							
	The pre-submission meeting was attended by the appropriate FDA staff to allow sufficient discussion of questions and issues at the meeting.							
	The pre-submission meeting provided insight into FDA's preliminary stance on the need for REMS or other risk management actions based on the information provided to the agency to date.							
	The pre-submission meeting resulted in a clear and shared understanding of expectations regarding the content of the complete application prior to submission.							
	Discussion of the content of the complete application and delayed submission of minor components: • Allowed for planning of application-related activities prior to submission.							

Step in Review Process	Statement	Agreement Rating						
		Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree	Don't know	Not Applicable
	• Resulted in an earlier submission of the original application. (That is, without agreement on late components, you would have needed to delay the original submission.)							
	• Resulted in a later-than-planned submission of the original application.							
Day 74 letter	FDA's preliminary thinking on the need for an Advisory Committee meeting provided in the Day 74 letter was helpful for planning purposes.							
	The Day 74 letter provided transparent information about potential NDA/BLA review issues.							
Mid-cycle communication	The mid-cycle communication provided transparent information about: • The current status of the application.							
	• Significant issues identified by the review team.							
	• Major safety concerns identified thus far and preliminary thinking on risk management.							
	Information provided in the mid-cycle communication allowed for efficient: • Responses to information requests.							
	• Preparation of other items such as labeling language and PMC plans.							
Discipline Review letters	The Discipline Review letter(s) clearly delineated application deficiencies.							
	The Discipline Review letter(s) included a path forward to address the deficiencies communicated in the letter.							
	(*If applicable*) Receiving Discipline Review letters in advance of the late-cycle meeting allowed time to prepare for discussing the deficiencies at the late-cycle meeting.							

Step in Review Process	Statement	Agreement Rating						
		Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree	Don't know	Not Applicable
Late-cycle meeting	The late-cycle meeting provided transparent information about: • The current status of the application.							
	• Remaining application deficiencies.							
	• FDA's assessment of the need for REMS or other risk management actions.							
	The late-cycle meeting was an effective forum for: • Discussing questions and issues with FDA.							
	• Discussing FDA information needs.							
	• Planning for the remainder of the review process.							
	• Discussing the Advisory Committee meeting.							
	The late-cycle meeting was held far enough in advance of the Advisory Committee meeting to allow sufficient time to prepare.							
Process as a whole	I felt well-informed about the status of my NDA/BLA as a result of interactions with FDA during the agency's review of the application.							
	I was not surprised by the action letter I received.							
	Interactions with FDA allowed sufficient planning for manufacturing scale-up and launch activities (approvals) or resubmission of the application (for CRs).							

Now I'd like to ask you about any experiences that you would consider either good practices or challenges during the review of the application for [established name].

Q2. What types of practices did you find helpful in the review?

Probe about elements of the Program

Probe for insights on how/why specific practices were helpful.

Q3. What types of challenges did you encounter in the review?

Probe about elements of the Program

Probe for insights on how/why specific aspects were challenging.

Q4. Can you comment on your experience in the Program with respect to the transparency, efficiency, and predictability of the review process?

If applicant has regulatory experience with FDA, probe for insights about how this experience compared to previous experiences in terms of transparency, efficiency, and predictability of the review process.

Q5. Have you identified any "lessons learned" that might help you or FDA with future application reviews?

Q6. Is there anything else you'd like to add about your review experience with [established name]?

Closing the Interview

Thank you very much for taking the time to talk with us. Your feedback is helpful in giving us a sense of how application review processes under the PDUFA V Program for enhanced review transparency and communication are working from a real-world perspective. Thanks again.

Appendix D. Statistical Framework

Overview

In order to provide answers to the Program assessment questions, ERG performed a series of statistical hypothesis tests. The tests involved two types of comparisons:

1. *Within Program differences* – ERG compared outcomes for Program applications that have certain attributes to those that do not have the attributes.

2. *Changes from baseline* – ERG compared outcomes for Program applications to applications in the baseline period.

There are three relevant outcomes for performing these comparisons:

- Approval (AP)
- Complete Response (CR)
- Withdrawal after Filing (WD)

ERG focused on approval in this analysis because the numbers of CRs and WDs are too small for statistical analysis. Approval outcomes can take one of two numerical forms:

- Binary ("yes," the application was approved; "no," the application was not approved)
- Continuous (time to approval)

The attributes are divided into three categories:

- Program attributes
- Review process attributes
- Application attributes

Most of the attributes are binary (yes/no). In some cases, the source metrics are continuous (e.g., number of information request or amendments). ERG converted many of these to binary form by selecting values to define "yes" and "no" categories (e.g., "above average number of information requests" equals "yes", "below average number of information requests" equals "no"). We did this for two reasons: (1) the values for continuous attributes generally cluster around some values rather than form a linear pattern, and (2) the number of data points for each value or cluster of values is too small to achieve statistical significance. Nevertheless, some attributes (e.g., number of amendments) have sufficient variation across applications to allow for meaningful analysis.

Methods

Table D-1 provides a summary of the methods and statistical tests that ERG performed for this report. These tests are described further below.

Statistical methods such as the ones ERG used in this report are more valid with larger numbers of observations. Thus, to avoid erroneous conclusions due to small sample sizes, ERG specified a minimum number of observations to permit meaningful statistical tests. When the number of observations was too small, ERG presented descriptive statistics and noted that statistical testing was not valid.

Statistical Analysis of Program Applications With/Without Attributes (Within Program Differences)

Approval rates. When comparing approval rates within the Program, ERG performed statistical tests to compare proportions between two populations: applications with the attribute that receive first-cycle approval and those without the attribute that receive first-cycle approval. The formula for this test is:

$$Z = (p_A - p_B) / SE$$

where SE is the standards error of the estimate and is defined as:

$$SE = [p * (1 - p) * [(1/n_A) + (1/n_B)]]^{1/2}$$

p is the pooled proportion defined as:

$$p = (p_A * n_A + p_B * n_B) / (n_A + n_B)$$

p_A is the proportion from the sample with the attribute that receive first-cycle approval, p_B is the proportion from the sample without the attribute that receive first-cycle approval, n_A is the sample size for the sample with the attribute, and n_B is the sample size for the sample without the attribute. The resulting value for Z is then compared to a standard normal distribution.

ERG conducted these as two-sided tests, meaning that we looked for whether the approval rate for the sample with the attribute is significantly different than the approval rate for sample without the attribute. Values of Z exceeding 1.645 (in absolute value) indicate a significant difference at the 10-percent level. ERG reported both the estimated Z value and its associated p-statistic (the probability of obtaining a Z value at least as large as the estimated value given the null hypothesis of equality between the two population proportions).

Time to approval. To compare times to approval among Program applications for different attributes, ERG performed a set of simple linear regressions. The regression was specified as follows:

ERG focused on time to first-cycle approval because the number of applications that were resubmitted and acted on in a second review cycle is too small for statistical analysis.

$$Y = \beta_0 + \beta_1 ATT + \beta_2 PRIORITY + e$$

where ATT is the attribute being assessed and PRIORITY is a yes/no measure of whether the application is a Priority application. We use review priority as an overarching control across all attributes because Priority and Standard applications have different review clocks. ERG reported the estimated regression

Table D-1. Descriptions of Methods and Statistical Tests Used in Assessing Impacts of Attributes

Comparison Type	Outcome Type	Description of Comparison Method	Statistical Test
Within Program	First-cycle approval (yes/no)	Compare the proportion of applications with the attribute that attain the outcome to the proportion of applications without the attribute that attain the outcome.	Z test for comparing proportions
	Time to first-cycle approval (months)	Estimate a simple linear regression model that relates time to approval as the dependent variable to attributes, using review priority as a control variable.	t test from a linear regression
Program to baseline – overall	First-cycle approval (yes/no)	Compare the proportion of Program applications that attain the outcome to the proportion of baseline applications that attain the outcome.	Z test for comparing proportions
Program to baseline – associations of Program components with overall success	First-cycle approval (yes/no)	Use a logistic regression analysis to determine whether Program applications have higher approval rates compared to baseline applications while controlling for different attributes that occur in both the Program and baseline (e.g., review priority).	Z test from a logistic regression
	Time to first-cycle approval (months)	Use a linear regression analysis to determine whether Program applications have shorter time to first-cycle approval compared to baseline applications while controlling for different attributes that occur in both the Program and baseline (e.g., review priority).	t test from a linear regression

coefficients and associated t-statistics for each variable included in the model, as well as the R^2 values and adjusted R^2 values for each model. Given that these are linear regression models, the units for the estimated regression coefficients reflect the units of the dependent variables, in this case months. Furthermore, coefficients for attributes that are binary in nature will reflect the impact of the attribute on the mean value for time to approval.

Statistical Analysis of Program versus Baseline Applications (Changes from Baseline)

ERG assessed changes from the baseline using multivariate regression modeling to assess whether the Program has led to higher first-cycle approval rates and shorter times to first-cycle approval while controlling for relevant attributes that influence either approval rates or times to approval.

Consider the linear outcome equation:

$$Y = \beta_0 + \beta_1 PROG + \beta_2 ATT + e$$

where Y is the value for the outcome, PROG is equal to one if application is in the Program and zero if in the baseline, ATT is a set of variables that measure different program attributes such as review priority, Orphan Drug designation, and number of amendments, the β are regression coefficients to be estimated, and e is a random error term.

For binary outcomes, the linear model above was re-specified as a logistic regression model; for continuous outcomes, ERG uses simple linear regression. The estimated regression coefficient for β_1 measures the difference between Program and baseline applications for the outcome.[38] Inclusion of the ATT measures in the model controls for the impact that other attributes have on the outcome. In the logistic regression models, significance is tested using a Z test; in the linear regression models, significance is tested using a t-test.

A further extension of this model is to include interaction terms between attributes and being in the Program:

$$Y = \beta_0 + \beta_1 PROG + \beta_2 ATT + \beta_3 (PROG \times ATT) + e$$

The coefficient β_3 captures the association, in terms of the dependent variable, of being in the Program with the specific attribute. Using interaction terms, we can test whether applications in the Program with the attribute had better outcomes than applications in the baseline with the attribute (e.g., did Priority applications in the Program achieve higher first-cycle approval rates compared to Priority applications in the baseline). The test for whether in-Program applications with the attribute have different outcomes from baseline applications with the attribute involves a linear combination of the regression coefficients. For example, in the time to approval model, the test would be:

$$\beta_1 + \beta_3 = 0$$[39]

One limitation of this approach, especially in the expanded models that include interactions and controls, has to do with variability within the data. Specifically, regression models require some amount of variation to estimate regression coefficients. This might be problematic if most Program applications have the attribute being analyzed. Consider the simple model (i.e., just using Y, PROG, and ATT) for binary outcomes. These models involve three binary variables: the outcome, whether the application is in the Program, and whether the application has the attribute. This means there are 8 ($=2^3$) distinct combinations of the binary variables in the data (i.e., 0,0,0; 0,0,1; etc.). If some of these combinations are not represented in the data, the statistical estimations might not work. As the model is expanded to include an interaction (PROG×ATT) and controls, the issue still remains—the data must contain sufficient variation to allow for estimation of the different regression coefficients. Thus, it might be necessary to modify the analyses to accommodate limited variability in the data.

[38] For approval rates, the coefficient will measure the impact on the probability of approval. For time to approval, the coefficient directly measures the impact on time to approval in months.

[39] This is the reduced form of the test, which can be more completely written as $(\beta_1 + \beta_2 + \beta_3) - \beta_2 = 0$.

Summary of Attributes To Be Analyzed

Tables D-2 to D-4 present lists of attributes that ERG considered in the statistical tests, organized by Program assessment question.

As noted previously, in some cases statistical analysis may not be possible due to a lack of variation (e.g., filing letters submitted within Program timelines) or a small number of observations (e.g., Breakthrough designation). ERG assessed whether each attribute had sufficient data to perform a comparison in the within Program analysis. For the most part, the attributes reflect binary measures (yes/no). Thus, our tests involved comparing approval (or time to approval) between applications with and without the attribute. If either the "with" or "without" group had less than 20 applications we did not perform a comparison.

Table D-2. Attributes for Program Assessment Questions 1a and 1b

Attribute	Sub-Attribute
Non-Program pre-submission meeting conducted	N/A
Program pre-submission meeting conducted	Held at least 2 months before planned submission date
	Held at least 2 months before submission
	Content of a complete application discussed
	Content of a complete application agreed on
	Delayed application components discussed
	Delayed application components agreed on
	Agreed-upon at least one delayed application component
	Included preliminary discussion on REMS or other risk management actions
	Discussion and agreements summarized
	Held as a face-to-face meeting
Application complete at submission	Application included a list of all clinical sites
	Application included a list of all manufacturing sites
	Delayed application components received on time
Program filing letter sent	Sent within 74 days of FDA receipt of original application submission
	Contains internal MCM date
	States whether an AC Meeting was likely or not
Mid-cycle communication conducted	Held within 2 weeks after mid-cycle meeting
	Meeting agenda sent to applicant
	Held as a face-to-face meeting

Attribute	Sub-Attribute
	Discussion of major safety concerns and risk management
	Discussion of preliminary thinking on risk management
	Included proposal for late-cycle meeting date
	Update on plans for AC meeting
	Identified projected milestone dates
	Appropriate review team members present
	Significant issues identified to date
	Identified one or more significant issues
	Information requests issued (at MCC)
	Issued one or more information requests
Late-cycle meeting conducted	Briefing package sent in accordance with Program timelines
	Briefing package has Program content
	Scheduled in accordance with Program timelines
	Held as a face-to-face meeting
	Signatory authority and appropriate review team members present
	Identified major deficiencies or substantive review issues
	Identified one or more major deficiencies
	Information requests identified at meeting
	Issued one or more information requests
	Applicant identified additional data/analyses they wish to submit
	FDA discussed additional data/analyses and whether these would constitute a major amendment
Inspections completed within Program timelines	N/A
Application reviewed within applicable Program timeline	N/A

Table D-3. Attributes for Program Assessment Questions 2a and 2b

Attribute	Sub-Attribute
Number of information requests greater than average	N/A
Number of amendments greater than average	N/A
Discipline review letter(s) issued	N/A
Advisory Committee held	N/A
Time to primary review completion greater than average	N/A
Major amendment issued	N/A

Table D-4. Attributes for Program Assessment Questions 3a and 3b

Attribute	Sub-Attribute
Priority review	N/A
Early action	N/A
Breakthrough Therapy designation	N/A
Fast Track designation	N/A
Rolling Review	N/A
Orphan Drug designation	N/A
Accelerated Approval	N/A
MedDRA category*	Blood and lymphatic system disorders
	Cardiac disorders
	Congenital, familial, and genetic disorders
	Endocrine disorders
	Eye disorders
	Gastrointestinal disorders
	General disorders and administration site conditions
	Hepatobiliary disorders
	Immune system disorders
	Infections and infestations
	Injury, poisoning, and procedural complications
	Investigations
	Metabolism and nutrition disorders
	Musculoskeletal and connective tissue disorders
	Neoplasms benign, malignant and unspecified (including cysts and polyps)
	Nervous system disorders
	Pregnancy, puerperium and perinatal conditions
	Psychiatric disorders

Attribute	Sub-Attribute
	Renal and urinary disorders
	Reproductive system and breast disorders
	Respiratory, thoracic, and mediastinal disorders
	Skin and subcutaneous tissue disorders
	Surgical and medical procedures
	Vascular disorders
First in Class	N/A

*MedDRA = Medical Dictionary for Regulatory Activities. Note that this number of MedDRA categories will generate too few observations per area to produce statistically significant results. Therefore, ERG will provide descriptive statistics where warranted.

Appendix E. Statistical Results / Data Tables

Overview

ERG conducted an assessment of FDA's Program for Enhanced Review Transparency and Communication for NME NDAs and original BLAs in PDUFA V. Having collected extensive data on Program applications (October 1, 2012 to June 30, 2016) and a baseline cohort of applications (FYs 2008-2012), ERG performed statistical tests as described in Appendix D, Statistical Framework. This appendix provides the results, dividing into two categories:

1. *Within Program differences*—Comparisons of regulatory outcomes for Program applications with a first-cycle action that have certain attributes to those that do not have the attributes.

2. *Changes from baseline*—Comparisons of regulatory outcomes for Program applications with a first-cycle action to applications in the baseline cohort.

For each attribute, ERG determined whether the data were sufficient for a within-Program analysis. Most attributes were binary measures (yes/no). Thus, the statistical tests involved comparing first-cycle approval rate (or time to first-cycle approval) for applications with and without the attribute. If the "with" or "without" group included fewer than 20 applications we did not perform the statistical test.

Within Program Differences

Applications with First-Cycle Approvals and their Attributes

In Table E-1, each row displays the results of two-sided tests, reporting both the estimated Z value and the associated p-statistic for applications with or without certain Program attributes.

Table E-1. Comparison of first-cycle approval rate, by attribute

Attribute or Sub-Attribute		Proportion (or Mean Value) of Applications with First-Cycle Approval		Z-Statistic (First-Cycle Approval Rate)	p-Value
		With Attribute	Without Attribute		
Approval of submission within first review cycle (yes/no)					
Program Attributes					
Pre-submission meeting	Program PSM conducted	79.7% (n = 118)	79.2% (n = 53)	0.06	0.950
	Held at least 2 months before submission	83.3% (n = 96)	63.6% (n = 22)	2.07	0.038
	Content of a complete application discussed	81.2% (n = 69)	77.6% (n = 49)	0.48	0.631
	DAC Discussed	78.4% (n = 65)	81.1% (n = 53)	-0.36	0.720
	At least one DAC	67.7% (n = 31)	86.5% (n = 37)	-1.86	0.063
	Included preliminary discussion on REMS or other risk management actions	84.8% (n = 66)	73.1% (n = 52)	1.58	0.115
	Discussion and agreements summarized	87.7% (n = 65)	71.9% (n = 32)	1.93	0.054
	Held as face-to-face meeting	86.5% (n = 91)	62.9% (n = 27)	2.46	0.014

Mid-Cycle Communication	Held within 2 weeks after mid-cycle meeting	80.1% (n = 136)	79.4% (n = 34)	0.096	0.923
	Meeting agenda sent to applicant	81.2% (n = 69)	64.3% (n = 24)	1.77	0.077
	Discussion of major safety concerns and risk management	82.4% (n = 136)	70.6% (n = 34)	1.53	0.125
	Discussion of preliminary thinking on risk management	81.1% (n = 132)	76.3% (n = 38)	0.64	0.519
	Included proposal for late-cycle meeting date	81.9% (n = 149)	66.7% (n = 21)	1.63	0.103
	Identified projected milestone dates	85.6% (n = 132)	60.5% (n = 38)	3.41	< 0.001
	Identified one or more significant issues	73.4% (n = 124)	97.8% (n = 46)	-3.54	< 0.001
	Issued one or more information requests	82.5% (n = 40)	79.2% (n = 130)	0.45	0.651
Late-Cycle Meeting	Briefing package sent in accordance with Program timelines	81.7% (n = 109)	84.4% (n = 45)	-0.42	0.678
	Briefing package had all Program content	83.0% (n = 141)	63.3% (n = 30)	2.42	0.015
	Scheduled in accordance with Program timelines	86.6% (n = 112)	72.1% (n = 43)	2.13	0.033
	Held as a face-to-face meeting	76.9% (n = 78)	88.3% (n = 77)	-1.87	0.062
	Identified one or more major deficiencies	76.9% (n = 108)	95.7% (n = 47)	-2.85	0.004

	Issued one or more information requests	75.9% (n = 29)	84.1% (n = 126)	-1.06	0.290
	Applicant identified additional data/analyses they wish to submit	70.4% (n = 27)	85.2%% (n = 128)	-1.84	0.066
Attribute	Inspections completed within Program timelines	84.2% (n = 76)	80.9% (n =89)	0.56	0.577
Review Process Attributes					
Attribute	Number of information requests greater than average	84.5% (n = 71)	76.0% (n = 100)	1.36	0.174
	Number of amendments greater than average	80.2% (n = 81)	78.9% (n = 90)	0.22	0.826
	At least one potential review issue identified in the filing letter	76.5% (n = 80)	82.4% (n = 91)	1.00	0.319
	At least one IR issued with filing letter	79.2% (n = 77)	79.8% (n = 94)	0.09	0.927
	Advisory committee held	81.4% (n = 43)	78.9% (n = 128)	0.35	0.726
	Time to primary review completion greater than average	73.9% (n = 92)	86.1% (n =79)	-1.97	0.049
	Major amendment issued	89.7% (n = 39)	76.5% (n = 132)	1.80	0.072
Application Attributes					
Attribute	Priority review	90.1% (n = 81)	70.0% (n = 90)	3.26	0.001
	Early action	77.1% (n = 35)	80.1% (n = 136)	0.39	0.694

	Breakthrough Therapy designation	85.3% (n = 34)	78.1% (n = 137)	0.93	0.352
	Orphan Drug designation	85.9% (n = 64)	75.7% (n = 107)	1.61	0.108
	Fast Track	87.8% (n = 49)	76.2% (n = 122)	1.69	0.091
	Emerging	78.6% (n = 28)	79.7% (n = 143)	-0.14	0.890
	Rolling Review	89.2% (n = 37)	76.9% (n = 134)	1.64	0.100
	First in Class	88.9% (n = 45)	76.4% (n = 89)	1.73	0.084

Estimated Regression Model Results for First-Cycle Approval Times

In Table E-2, each row represents a separate regression model that involved regressing approval time (dependent variable) on the yes/no attributes or on continuous ones (e.g., number of amendments). Priority review status is included in each regression model to control for different review time frames for Priority applications. The regression approach appeared to work better than a simple t-test, despite not being dramatically different (most attributes, including Priority review, are all yes/no, with the regression coefficients being the change in the mean related to the variable). Interpretation of the estimated coefficients is as follows:

- Yes/no attributes: the estimated value reflects the difference in the number of months for applications with the attribute compared to those without the attribute. For example, a value of 1.2 indicates that applications with the attribute take 1.2 months longer than applications without the attribute.
- Continuous attributes: the estimated value reflects the change in review times (in months) for a one-unit increase in the attribute. For example, a value of 0.2 indicates that each unit of the attribute (e.g., the number of amendments) is associated with a 0.2 increase in the number of review months.

The coefficient values are in terms of months. For example, Priority application approval times are consistently 4-5 months shorter than Standard application approval times.

Table E-2. Comparison of time to first-cycle approval, by attribute

Attribute or Sub-Attribute (Yes/No unless otherwise noted)		Attribute's Regression Coefficient (t-Statistic)	Priority Review Regression Coefficient (t-Statistic)	Number of Observations Used in Regression Model	R2 (Adjusted R2)
Program Attributes					
Pre-Submission Meeting	Program pre-submission meeting conducted	-0.47 (-1.22)	-4.69*** (-13.28)	136	59.7% (59.1%)
	Held at least 2 months before submission	0.19 (0.32)	-4.97*** (-11.57)	94	60.1% (60.0%)
	Content of a complete application discussed	-0.31 (-0.74)	-4.94*** (-11.54)	94	61.1% (60.2%)
	DAC discussed	-0.43 (-1.03)	-4.94*** (-11.65)	94	61.3% (60.4%)
	At least one DAC	-0.87 (-1.51)	-5.31*** (-8.66)	53	60.3% (58.8%)

Attribute or Sub-Attribute (Yes/No unless otherwise noted)		Attribute's Regression Coefficient (t-Statistic)	Priority Review Regression Coefficient (t-Statistic)	Number of Observations Used in Regression Model	R2 (Adjusted R2)
	Included preliminary discussion on REMS or other risk management actions	-0.46 (-1.11)	-4.98*** (-11.87)	94	61,4% (60.5%%)
	Discussion and agreements summarized	-0.41 (-0.79)	-5.11*** (-10.54)	80	60.3% (59.3%)
	Held as face-to-face meeting	0.81 (1.54)	-4.95*** (-11.86)	94	61.8% (61.0%)
Mid-Cycle Communication	Held within 2 weeks after mid-cycle meeting	-0.0002 (< -0.0001)	-4.80*** (-13.90)	136	59.5% (58.6%)
	Meeting agenda sent to applicant	-0.009 (-0.01)	-4.73*** (-9.19)	74	54.4% (53.1%)
	Discussion of major safety concerns and risk management	0.03 (0.07)	-4.80*** (-13.91)	136	59.3% (58.6%)
	Discussion of preliminary thinking on risk management	-1.05** (-2.54)	-4.69** (-13.80)	136	61.1% (60.5%)
	Included proposal for late-cycle meeting date	-0.01 (-0.01)	-4.80*** (-13.70)	136	59.5% (58.6%)
	Identified projected milestone dates	-0.69 (-1.51)	-4.75*** (-13.83)	136	59.9% (59.3%)
	Identified one or more significant issues	0.23 (0.63)	-4.81*** (-13.94)	136	59.4% (58.8%)
	Issued one or more information requests	0.55 (1.39)	-4.76*** (-13.82)	136	59.8% (59.2%)

Late-Cycle Meeting	Briefing package sent in accordance with Program timelines	1.01 (2.63)	-4.51*** (-12.84)	127	60.4% (59.7%)
	Briefing package had all Program components	-0.05 (-0.10)	-4.80 (-13.91)	136	59.2% (58.6%)
	Scheduled in accordance with Program timelines	-1.31*** (-3.30)	-4.74*** (-13.92)	128	61.8% (61.2%)
	Held as a face-to-face meeting	0.66* (1.87)	-4.66*** (-13.27)	128	59.6% (59.0%)
	Identified one or more major deficiencies	1.31*** (3.68)	-4.53*** (-13.28)	128	62.5% (61.9%)
	Issued one or more information requests	0.72 (0.97)	-4.77*** (-13.27)	128	58.8% (58.1%)
	Applicant identified additional data/analyses they wish to submit	1.12** (2.26)	-4.61*** (-13.13)	128	60.1% (59.5%)
Attribute	Inspections conducted within Program timelines	-1.66*** (-5.31)	-4.82*** (-15.37)	136	66.4% (65.9%)
Review Process Attributes					
Attribute	Number of information requests greater than average	0.34 (0.98)	-4.85*** (-13.96)	136	59.6% (58.9%)
	Number of information requests (continuous)	0.02* (1.84)	-5.02*** (-13.92)	136	60.3% (59.7%)
	Number of amendments greater than average	0.89** (2.64)	-4.83*** (-14.35)	136	61.3% (60.7%)
	Number of amendments (continuous)	0.02** (2.39)	-4.85*** (-14.32)	136	60.9% (60.3%)
	Filing letter identified at least one issue	0.25 (0.74)	-4.79 (-13.92)	136	59.4% (58.8%)

	Filing letter had at least one IR	0.20 (0.58)	-4.79 (-13.88)	136	59.4% (58.7%)
	Discipline review letter(s) issued	0.24 (0.35)	-4.80*** (-13.88)	136	59.3% (58.7%)
	Advisory committee held	0.79** (2.03)	-4.83*** (-14.19)	136	60.5% (59.9%)
	Time to primary review completion greater than average	2.19*** (5.65)	-3.54*** (-9.24)	136	67.2% (66.7%)
	Time for primary review completion (continuous)	0.63*** (11.64)	-2.19*** (-6.60)	135	79.9% (79.6%)
	Major amendment issued	3.74*** (16.70)	-4.72*** (-24.02)	136	86.8% (86.7%)
Application Attributes					
Attribute	Application complete	-0.81 (-1.21)	-4.80 (-13.43)	132	59.6% (59.0%)
	Priority review	-	-4.80*** (-13.96)	136	59.3% (59.0%)
	Early action	-3.38*** (-9.48)	-3.85 (-13.52)	136	75.7% (75.3%)
	Breakthrough Therapy designation	-2.33*** (-5.34)	-3.88 (-10.83)	136	66.5% (66.0%)
	Orphan Drug designation	0.43 (1.11)	-4.99*** (-13.06)	136	59.6% (59.0%)
	Fast Track	-0.03 (-0.08)	-4.79*** (-12.44)	136	59.3% (58.6%)
	Accelerated Approval	-2.12*** (-4.46)	-4.82*** (-13.96)	136	59.4% (58.8%)
	Emerging	0.37 (0.79)	-4.82*** (-13.96)	136	59.4% (58.8%)
	Rolling Review	-0.85* (-1.95)	-4.49*** (-11.96)	136	60.4% (59.8%)

	First in Class	0.31 (-0.73)	-4.38 (-10.50)	108	54.2% (53.3%)

*Significant at the 10 percent level. **Significant at the 5 percent level. ***Significant at the 1 percent level.

Changes from Baseline

First-Cycle Approval Rates

ERG first tested whether Program applications had a statistically significantly higher approval rate compared to the baseline using a test for a difference between two proportions. This appears in Table E-3. The test was performed for all applications and then for Priority and Standard applications separately. For all applications, we found that Program applications had a statistically significantly higher first-cycle approval rate compared to baseline applications (79.5 percent compared to 54.8 percent). We also found a statistically significantly higher first-cycle approval rate among both Priority and Standard applications between Program and baseline.

Table E-3. Comparison of Program and baseline first-cycle approval rate, by review priority

Application	Proportion (or Mean Value) of Applications with First-Cycle Approval		Z-Statistic (First-Cycle Approval Rate)	p-Value
	Program	Baseline		
Approval of submission within first review cycle (yes/no)				
All	79.5% (n = 171)	54.8% (n = 219)	5.10	< 0.001
Priority	90.1% (n = 81)	71.8% (n = 78)	2.95	0.003
Standard	70.0% (n = 90)	45.4% (n = 141)	3.67	< 0.001

ERG also examined whether other factors influenced these approval rates using logistic regression analysis with first-cycle approval (yes/no) as the dependent variable. Table E-4 provides estimated odds ratios, [40] z-statistics, and model descriptors for three separate models:

A. A **base model** that included only Program and Priority status – this is a base model and is used primarily for comparison sake. Table E-3 found statistically significant differences between the Program and baseline for all applications and between the Program and baseline for Priority applications. Thus, we include the Program (as a whole) and Priority status as explanatory factors in this base model.

[40] Odds ratios reflect the proportional increase in likelihood of obtaining the outcome associated with attribute. For example, for a yes/no attribute, an odds ratio of 3.0 would indicate that applications with the attribute are three times as likely to be approved compared to those without the attribute.

B. An **expanded model** that included several attributes as covariates in addition to Program and Priority status. The purpose of this statistical model is to examine whether the significant difference that was found in Table E-3 above remains once we include other factors that could influence approval rates. The additional factors we include are attributes of applications that could occur under both the Program and Baseline. Thus, if including these attributes eliminates the statistical significance of the Program effect from the base model, then the differences between Program and baseline are attributable to the attributes and not to being in the Program itself.

C. A **further expanded model** that included several attributes as explanatory variables, Program and Priority status, and an interaction between Program and Priority status. ERG developed multiple versions of this model, interacting Program status with each of the attributes included in model (B) above. However, the only interaction that had statistically significant effects was the one that interacted Program and Priority statuses. The purpose of this type of model was to examine whether the interactions of attributes and the Program (i.e., the attributes as they occurred under the Program) were statistically significant.

The first model (A) repeated the result from above: there was a statistically significant difference between Program and baseline approval rates, as well as between Priority and Standard applications. A more comprehensive test, however, involved adding in additional explanatory attributes that may influence approval rates. We did this in models (B) and (C). In model (B), we found that even after adding in the attributes listed in Table E-4,[41] Program applications were approved at a statistically significant higher rate compared to the baseline. Finally, in model (C) we tested whether the interaction between Program status and Priority status was a significant factor in explaining differences between approval rates under the Program and under the baseline. We used the estimated logistic regression coefficients to test whether Priority applications in the Program were approved at a higher rate than Priority applications in the baseline (accounting for the interaction between the two) and found a positive significant impact. That is, Priority applications were approved at a statistically significantly higher rate in the Program compared to the baseline even after controlling for the attributes listed in Table E-4.[42] Model (C) also found that standard applications were also approved at statistically significant higher rates under the Program compared to the baseline.[43]

[41] The attributes were whether or not an Advisory Committee meeting was held, whether or not a major amendment was issued, if the application had orphan designation, and if the application had Fast Track designation, as well as whether or not the application was a Program application and whether or not the application was a Priority application.
[42] This is tested by testing whether the sum of logistic regression coefficients (not the odd ratios) for Program application, priority status, and the interaction between the two is greater than just the coefficient for Priority status alone.
[43] The test for whether standard applications were approved at higher rates under the Program compared to the baseline is simply the t-statistic for the Program application factor in the model which was statistically significant.

Table E-4. Three models for comparing Program and baseline first-cycle approval rates – odds ratios

Attribute	A Model that includes only Program status and priority status (z-statistic)	B Model with no interaction term (z-statistic)	C Model that includes interaction between Program and with priority status (z-statistic)
Program application	3.02*** (4.60)	3.07*** (2.26)	2.85*** (1.23)
Advisory committee meeting held	-	0.95 (-0.20)	0.96 (-0.19)
Major amendment issued	-	1.37 (1.17)	1.37 (1.18)
Orphan designation	-	1.20 (0.66)	1.20 (0.65)
Fast track designation	-	1.14 (0.43)	1.15 (0.44)
Priority status	3.32*** (4.84)	2.92*** (3.68)	2.68*** (2.89)
Program application and priority status	-	-	1.28 (0.47)
Number of applications	390	390	390
Likelihood ratio statistic	54.65***	54.65***	33.38***
Pseudo R^2	0.109	0.109	0.109
Test statistic (chi-square) for whether priority applications under the Program are approved faster	-	-	8.16**

* Significant at the 10 percent level; ** significant at the 5 percent level, *** significant at the 1 percent level.

Time to First-Cycle Approval

ERG estimated linear regression models to assess whether the Program is associated with changes in first-cycle approval times. Table E-5 presents two models: one without an interaction term between Program application and Priority status, and another model with the interaction term. The reason for including the interaction term follows the logic discussed with respect to approval times above. We also included a number of other attributes in the model to control for other influences on review times (whether an AC meeting was held, time to complete the primary review, whether a major amendment was issued, whether the application had an Orphan designation, and whether the application had a Fast Track designation). As we discussed above, including these attributes allowed us to determine whether differences in review times were statistically correlated with being in the Program or with the attributes that could occur either under the Program or under the baseline.

We found that time to first-cycle approval was significantly longer for Program applications than for baseline applications. This is seen in model D, where the regression coefficient for Program applications is positive and highly significant. Furthermore, the estimated impact controls for the factors listed above and included in the model. We also estimated a model that interacted Program applications with Priority status (model E). Once again, time to first-cycle approval was significantly longer for Program applications than for baseline applications. If we broke out Priority and Standard applications, we still found that time to first-cycle approval was longer for Priority applications in the Program than for Priority applications in the baseline. Based on the estimated regression coefficients, a Priority application in the Program takes 1.02 months longer than Priority applications under the baseline, a value that is statistically significant.[44] The same can be said for Standard applications, which is measured by the regression coefficient for Program applications alone.

[44] This is calculated as the sum of the regression coefficients for Program applications (1.62), priority status (-2.2), and the interaction term (-0.6) minus the coefficient for priority status (-2.2), or simply the sum of the Program application (1.62) and interaction term coefficients (-0.6).

Table E-5. Two models for comparing Program and baseline time to first-cycle approval, by attribute

Attribute	D Model with no interaction term (test statistic)	E Model that includes interaction between Program and with priority status (test statistic)
Regression constant	6.12*** (12.58)	5.99*** (12.22)
Program application	1.32*** (7.77)	1.62*** (6.87)
Advisory committee meeting held	0.70*** (3.94)	0.70*** (3.93)
Time to complete primary review	0.42*** (8.33)	0.42*** (8.35)
Major amendment issued	2.32*** (9.78)	2.30*** (9.76)
Orphan designation	-0.28 (-1.56)	-0.26 (-1.42)
Fast track designation	-0.28 (-1.45)	-0.30 (-1.51)
Priority status	-2.51*** (-9.17)	-2.20*** (-4.72)
Program application and priority status		-0.60* (-1.83)
Number of applications	255	255
R^2	83.2%	83.4%
Adjusted R^2	82.7%	83.0%
Impact on time to approval for priority applications reviewed under the Program compared to priority applications under the baseline [a]	-	18.54***

Note: the test statistic for the regression coefficients are t-statistics and the test statistics for the impacts of the combined effect of priority status and being under the Program are F statistics.
* Significant at the 10 percent level; ** significant at the 5 percent level, *** significant at the 1 percent level.
[a] Calculated by adding the relevant coefficients together and testing whether the combined sum is significantly different than zero. For model D, the coefficients for Program application and priority status are the relevant coefficients. For model E, the coefficients for Program application, priority status, and the interaction between the two are the relevant coefficients.