Assessment of the Program for Enhanced Review Transparency and Communication for 351(k) BLAs in BsUFA II

Interim Report

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Executive Summary

Biosimilar biological products represent an important public health benefit through their potential to offer life-saving or life-altering benefits at reduced cost to patients. Since passage of the Biosimilar User Fee Act (BsUFA) in 2012, the Food and Drug Administration (FDA) has dedicated resources to facilitate the development of biosimilar biological products and the review of 351(k) Biologics License Applications (BLAs). With the reauthorization of BsUFA in 2017, FDA introduced the "Program for Enhanced Review Transparency and Communication for Original 351(k) BLAs" or "the Program" to improve the efficiency and effectiveness of application reviews, and to further ensure that patients have timely access to safe, effective, and high quality biosimilars.

FDA enlisted a contractor, Eastern Research Group, Inc. (ERG), to conduct an independent assessment of the Program. ERG prepared this Interim Report to provide initial data about Program implementation and outcomes during the first three years of BsUFA II: Fiscal Years (FYs) 2018-2020. The data encompass original 351(k) BLAs that were submitted and received a first-cycle action (Approval [AP], Complete Response [CR], or Withdrawal after Filing [WD]) during this time. Baseline data encompass original 351(k) BLAs submitted during BsUFA I (FYs 2013-2017) and acted on by September 30, 2020. 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 interim assessment of the Program. ERG will continue collecting data on Program applications and then produce a Final Report by June 30, 2022.

Table ES-1. Applications in the baseline and Program cohorts for this study through first three years of BsUFA II*

Applications		Baseline (FYs 2013-2017)	Program (FYs 2018-2020)
Filed and acted upon	Total	23	12
First-cycle actions	Approval (AP)	9	9
	Complete Response (CR)	14	3
	Withdrawal after Filing (WD)	0	0
Percent of filed applications approved in first cycle		39%	75%

** Original 351(k) BLAs received during FYs 2013-2017 and acted on by September 30, 2020 (baseline; 8 years of data) or received and acted on during FYs 2018-2020 (Program; 3 years of data).*

Answers to Evaluation Questions

Based on descriptive and qualitative analyses of the data collected, ERG answered a set of evaluation questions for this interim report. These questions and answers appear below.

1a. What is the relationship between Program attributes and 351(k) application first-cycle regulatory outcome?

Based on data from the first three years of the BsUFA II Program (FYs 2018-2020) and the baseline (FYs 2013-2017), ERG found that first-cycle approval rates in the Program (75%) were higher than in the baseline (39%). The numbers of applications are small, so we cannot assess the statistical significance of this difference. Nevertheless, based on the quantitative data, observations, and feedback from post-action interviews developed to date, it is reasonable to conclude that the BsUFA II Program has created conditions that enhance the ability of applicants and FDA reviewers to work toward application approval in the first review cycle.

It is important to note that applicants interviewed for this assessment viewed the BsUFA II Program as having value in terms of enhanced review transparency, communication, predictability, and efficiency regardless of its impact on first-cycle regulatory outcome.

1b. What is the relationship between Program attributes and 351(k) application first-cycle regulatory action time?

Based on data from the first three years of the BsUFA II Program (FYs 2018-2020) and the baseline (FYs 2013-2017), ERG's analyses revealed that first-cycle reviews for Program applications were longer than those for baseline applications—an unsurprising result given that there is a 2-month difference in the review clocks. Nevertheless, if the Program has created conditions that enhance the ability of applicants and FDA reviewers to work toward application approval in the first review cycle, over time 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); this possibility cannot be evaluated at this time.

2a. What is the relationship between review process attributes and 351(k) application first-cycle regulatory outcome?

Due to the small number of applications in BsUFA II to date, the data are insufficient to determine any relationships between review process attributes and first-cycle regulatory outcome.

2b. What is the relationship between review process attributes and 351(k) application first-cycle regulatory action time?

Due to the small number of applications in BsUFA II to date, the data are insufficient to determine any relationships between review process attributes and mean time to first-cycle regulatory action.

2c. What is the relationship between application attributes and 351(k) application first-cycle regulatory outcome?

In BsUFA II, the data suggest a possible relationship between an application's proposed indications and first-cycle approval: applications with solely oncologic indications were less likely to receive a first-cycle approval (50%) than applications with other indications (100%). The data are insufficient to determine whether this difference is statistically significant or meaningful; the difference could be an artifact of the high prevalence of oncologic indications for biosimilar biological products.

Baseline and BsUFA II Program applications with a major amendment were associated with a higher first-cycle approval rate (100%) than those without a major amendment (30%, baseline; 73%, BsUFA II). This aligns with the expectation that FDA will accept and review a major amendment when the Agency believes that this will lead to approval in the first cycle rather than requiring resubmission and a second cycle of review. Again, we caution that the numbers are too small to assess statistical significance or draw firm conclusions.

2d. What is the relationship between application attributes and 351(k) application first-cycle regulatory action time?

In both the baseline and BsUFA II Program, one application attribute was associated with a longer mean time from application to first-cycle action: a major amendment resulting in a 3-month goal extension. This is expected given that a 3-month extension by definition affects time to regulatory action.

Another measure of interest is overall mean time from original submission to approval, including approvals achieved in second or additional review cycles. In the first three years of the Program, no applications had been resubmitted and acted on in a second review cycle, so ERG was unable to compare overall mean time to approval in the BsUFA II Program with that in the baseline. If data are sufficient, ERG will do so for our final report.

3a. How do applicants and FDA review staff characterize enhanced communication under the Program?

Applicants characterized communications in the BsUFA II Program favorably: excellent, constructive, and in the spirit of collaboration. They characterized the Program's milestone communications (Mid-Cycle Communication [MCC] and Late-Cycle Meeting [LCM]) as valuable opportunities to communicate with FDA during the review process, gain a shared understanding of potential review issues, and resolve questions and issues whenever possible. They also complimented Regulatory Project Managers (RPMs) and other FDA review team members, describing them as responsive, constructive, and flexible. A few applicants suggested FDA could further improve communications by providing updates on review activities after the LCM, notifying the applicant if/when FDA considers Information Requests (IRs) and substantive issues to be resolved, and providing advance notice of the likelihood of an IR (and bundling IRs when possible).

FDA review staff characterized communications in the BsUFA II Program favorably: excellent, constructive, collaborative, efficient, and effective. Most review staff affirmed with varying degrees of

enthusiasm that MCCs and LCMs contributed to enhanced communication, transparency, and predictability. They commented that these meetings provided a useful opportunity to discuss substantive review issues, and that the meetings provided structure to the review process. Some reviewers felt that these meetings were unnecessary when substantive issues did not need to be discussed; they favored an ability to "opt out" in those circumstances.

3b. How do applicants and FDA review staff characterize application reviews under the Program?

Applicants characterized application reviews in the BsUFA II Program as transparent, predictable, and efficient. A few applicants suggested that FDA further enhance the review process by giving applicants more time to respond to IRs and labeling negotiations, especially when the applicant is part of a global team. They noted, however, that FDA staff were often flexible in adjusting IR timelines or allowing applicants to respond initially via email when asked.

Most FDA review staff characterized application reviews in the BsUFA II Program as transparent, predictable, and efficient. A few reviewers commented that the additional two months for review (gained by starting the review clock at application filing instead of receipt) did not increase the amount of time available for primary reviews because this time is consumed by communications with the Office of Therapeutic Biologics and Biosimilars (OTBB) and other late review activities. They also noted that inspections conducted close to the end of the review cycle were challenging if they uncovered manufacturing deficiencies. These reviewers proposed adjusting the review to allow more time for primary reviews and moving inspections earlier (to allow time for reinspection, if needed).

Interim Findings and Recommendations

ERG developed a set of interim findings and recommendations (Table ES-2) organized in two categories: overarching (related to the BsUFA II Program overall) and specific (related to particular aspects of the Program or review process). We note that these findings and recommendations are preliminary and might change as ERG collects and analyzes more data over the next year of the Program.

Table ES-2. Interim findings and recommendations

Type	No.	Interim Finding	Interim 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 (MCCs and LCMs) have enhanced the predictability of reviews by: • Serving as "anchor" points for review work and planning. • Providing a forum for multidisciplinary discussion of application status and paths forward to resolve approvability issues promptly, if possible.	No action needed.
	O3	By requiring application completeness, the Program has enhanced the ability of FDA to conduct first-cycle reviews more efficiently and effectively.	No action needed.
Specific	S1	In the BPD Type 4 meeting process, providing pre-submission advice and templates for application content and organization helps sponsors prepare applications that meet FDA expectations.	Establish this as good practice in the BPD Type 4 meeting process.
	S2	LCMs have generally been most valuable to applicants when they were able to discuss additional topics of interest (e.g., inspections, PMRs/PMCs, labeling) with FDA.	Consider soliciting discussion topics from the applicant and allocating time in the LCM agenda for applicant-identified discussion topics.
	S3	FDA communication regarding inspections has generally been clear, allowing for good inspection coordination and contributing to overall review transparency and predictability.	No action needed.
	S4	FDA target dates for IR responses were sometimes impractical for applicants with a global presence. In some cases, time zone differences prevented one or two-day response times.	Where feasible, propose IR response times of more than two days or issue IRs earlier to allow for extended response times.

BPD = Biological Biosimilar Product Development. PMR = Postmarket Requirement. PMC = Postmarket Commitment.

1. Introduction

1.1 The BsUFA II Program

Biosimilar biological products represent an important public health benefit through their potential to offer life-saving or life-altering benefits at reduced cost to patients. The Biosimilar User Fee Act (BsUFA) was created as part of the Affordable Care Act (ACA), signed into law in 2010. The ACA contains a subtitle called the Biologics Price Competition and Innovation Act of 2009 (BPCI Act) that amends the Public Health Service (PHS) Act and other statutes to create an abbreviated approval pathway for biosimilar and interchangeable biological products. Section 351(k) of the PHS Act, added by the BPCI Act, allows a sponsor to submit an application for licensure of a biosimilar or interchangeable biological product. The BPCI Act directed the Food and Drug Administration (FDA) to develop recommendations for a user fee program for 351(k) Biologics License Applications (BLAs) for Fiscal Years (FYs) 2013 through 2017. FDA consulted with the regulated industry and public stakeholders to develop recommendations for such a program, published the recommendations in the *Federal Register*, and held a public meeting to review the recommendations. The recommendations were provided to Congress on January 13, 2012 and BsUFA was enacted on July 9, 2012. FDA dedicates fees collected through BsUFA to facilitate the development of biosimilar biological products and the review of 351(k) applications.

For the first authorization of BsUFA (BsUFA I), FDA committed to certain performance goals and procedures for the review of biosimilar biological product submissions, including applications, supplements, notifications, responses, and meeting management. During the first few years of BsUFA I, FDA encountered challenges stemming from scientific, legal, and technical complexities and a greater-than-expected workload from sponsor meeting requests. In negotiating its commitments for the next authorization of BsUFA (BsUFA II), FDA sought to mitigate these and other challenges.

A significant BsUFA II commitment is establishing a program for enhanced review transparency and communication for original 351(k) BLAs ("the Program"). The goals of the BsUFA II Program are to increase the efficiency and effectiveness of the first review cycle, to enhance transparency and communication with applicants, and to decrease the number of review cycles necessary for approval so that patients have timely access to safe, effective, and high quality biosimilars. As part of the BsUFA II Program, the 10-month review clock for original 351(k) BLAs begins on the 60-day filing date, effectively increasing the time from application receipt to regulatory action by two months. This allows time for additional formal communications between FDA and the applicant and potential resolution of issues in time for first-cycle approval. The 351(k) BLA review process includes new milestone meetings, including the Mid-Cycle Communication (MCC) and Late-Cycle Meeting (LCM). Meetings and communications can also be customized in a jointly agreed-upon FDA-applicant Formal Communication Plan (FCP).

1.2 The BsUFA II Program Assessment

As part of the commitments under BsUFA II, FDA committed to an independent third-party assessment of the BsUFA II Program to determine the extent to which the intended goals are realized. FDA enlisted Eastern Research Group, Inc. (ERG) to conduct this independent assessment. Specifically, FDA asked ERG to:

- Using information from FDA's databases, construct and analyze a baseline data set of 351(k) applications received prior to implementation of the Program. This set of applications shall be used 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) for applications reviewed under the Program, collect and analyze data on all 351(k) applications reviewed under the Program.
- Determine the nature of relationships among attributes of the Program and the regulatory outcome and its timing in the first review cycle.
- Determine the nature of relationships among 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 *Program* attributes and 351(k) application first-cycle regulatory outcome?

1b. What is the relationship between *Program* attributes and 351(k) application first-cycle regulatory action time?

2a. What is the relationship between *review process* attributes and 351(k) application first-cycle regulatory outcome?

2b. What is the relationship between *review process* attributes and 351(k) application first-cycle regulatory action time?

2c. What is the relationship between *application* attributes and 351(k) application first-cycle regulatory outcome?

2d. What is the relationship between *application* attributes and 351(k) application first-cycle regulatory action time?

3a. How do applicants and FDA review staff characterize enhanced communication under the Program?

3b. How do applicants and FDA review staff characterize application reviews under the Program?

For the assessment of the Program, ERG is analyzing and reporting on results as follows:

- **Baseline analysis report** to FDA (completed on September 28, 2018)
  Counts of baseline (BsUFA I, FYs 2013-2017) activities and results from applications with at least a first-cycle action by September 28, 2018.
- **Interim report** for publication in *Federal Register* and public comment (this document)
  Initial results from Program applications with at least a first-cycle action by September 30, 2020, with comparisons to the baseline cohort.
- **Final report** for publication in *Federal Register* and public comment (to be published by June 30, 2022)
  Results from Program applications with at least a first-cycle action by September 30, 2021, with comparisons to the baseline cohort.

1.3 This Report

This Interim Report includes interim findings based on an analysis of BsUFA II Program applications that received a first-cycle action in FYs 2018-2020, as well as a comparison of Program data with data from a baseline cohort, defined as original 351(k) BLAs submitted during BsUFA I (FYs 2013-2017) that received at least a first-cycle action by September 30, 2020.

Please see Appendix A for a list of acronyms and a glossary of terms used in this report.

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 (BsUFA I, FYs 2013-2017) and one for the Program (BsUFA II, FYs 2018-2020, as of this Interim Report). For the baseline cohort, ERG did not collect data for Program-specific attributes (such as MCCs and LCMs) that did not exist in BsUFA I.

2.1 Metrics and Measures

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 original 351(k) BLAs in BsUFA II. The evaluation metrics address Program, review process, and application attributes, categorized as follows:

- Regulatory Outcomes
- Biosimilar Biological Product Development (BPD) Type 4 Meetings
- FCPs
- Application Completeness and Quality
- Unsolicited Amendments
- Day 74 Letters
- MCCs
- LCMs
- Advisory Committees (ACs)
- Post-Advisory Committee (Post-AC) Meetings
- Inspection Timing
- Clock Extensions
- Resubmissions
- Complete Response (CR) Issues
- Post-Action Interviews
- Discipline Review (DR) Letters
- FDA Information Requests (IRs)
- Application Amendments
- Therapeutic Areas

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

2.2 Protocols and Instruments

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

Table 2-1. Evaluation protocols and instruments

Protocol	Associated Instruments
Observation of FDA-Applicant Interactions	BPD Type 4 Pre-351(k) Meeting Observation Instrument FCP Information Instrument MCC Observation Instrument LCM Observation Instrument Post-AC Meeting Observation Instrument Other FCP Communications Observation Instrument
Data for and Evaluation of 351(k) Applications	Original 351(k) Application Data Instrument Original 351(k) Application Quality Evaluation Instrument Resubmission Data Instrument
Evaluation of FDA-Applicant Written Communications	FDA IRs Instrument Applicant Amendments Instrument Filing Letter Evaluation Instrument DR Letter Evaluation Instrument LCM Background Package Evaluation Instrument
Post-Action Interviews	FDA Interview Instrument Applicant Interview Instrument

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 (OMB) under the Paperwork Reduction Act. The OMB control number for the information collection is 0910-0746.

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 Assessment Tracking Tool that we developed to store raw data and compute metrics values based on the raw data. We developed a data collection protocol to specify the data fields and procedures used to calculate metrics values.

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 two 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.

- **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), 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 interim 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 Interim Report provides data on the Program for Enhanced Review Transparency and Communication for Original 351(k) BLAs in BsUFA II—specifically, Program implementation and outcomes during the first three years (FYs 2018-2020). The data encompass original 351(k) BLAs that FDA received and acted on during this time. Baseline data encompass original 351(k) BLAs received during BsUFA I (FYs 2013-2017) and acted on by September 30, 2020. 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, through first three years of BsUFA II*

Applications		Baseline (FYs 2013-2017)	Program (FYs 2018-2020)
Filed and acted upon	Total	23	12
First-cycle actions	Approval (AP)	9	9
	Complete Response (CR)	14	3
	Withdrawal after Filing (WD)	0	0
Percent of filed applications approved in first cycle		39%	75%

**Original 351(k) BLAs received during FYs 2013-2017 and acted on by September 30, 2020 (baseline; 8 years of data) or received and acted on during FYs 2018-2020 (Program; 3 years of data).*

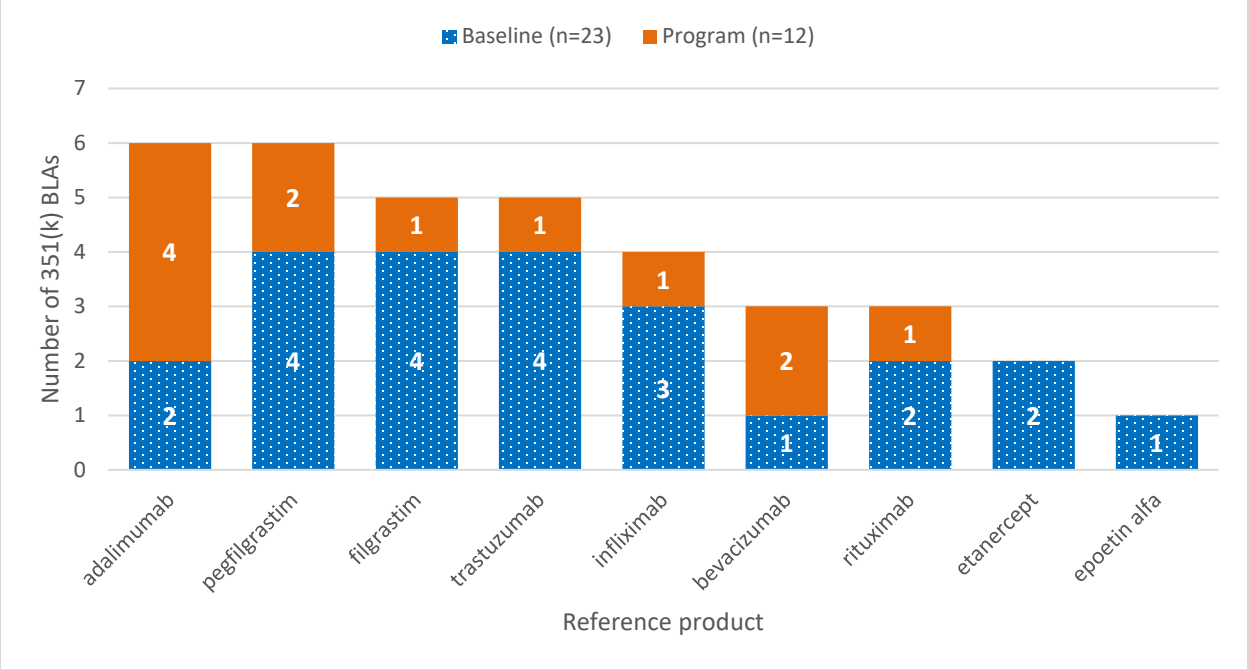
Table 3-2. Counts of baseline and BsUFA II Program applications by fiscal year of receipt*

Applications		FY 2013	FY 2014	FY 2015	FY 2016	FY 2017	Baseline	FY 2018	FY 2019	FY 2020	Program
Filed and acted upon	Total	0	2	5	3	13	**23**	6	6	0	**12**

**Original 351(k) BLAs received during FYs 2013-2017 and acted on by September 30, 2020 (baseline; 8 years of data) or received and acted on during FYs 2018-2020 (Program; 3 years of data). The data in this table are organized by fiscal year of application receipt (regardless of when FDA completed its review, which sometimes occurred in the next fiscal year).*

Figure 3-1 presents a list of the 9 biological products that are referenced by the 23 applications in the baseline cohort and 12 applications in the BsUFA II Program cohort.

Figure 3-1. Distribution of baseline (n=23) and BsUFA II Program 351(k) BLAs (n=12), by reference product



351(k) BLAs may belong to more than one therapeutic area, depending on the proposed indications of the biosimilar. Table 3-3 presents the distribution of therapeutic areas among BsUFA II Program and baseline 351(k) BLAs. Table 3-4 shows biological reference products with more than one therapeutic area that are represented by six Program and nine baseline 351(k) BLAs. While adalimumab can be categorized into Ophthalmology for its uveitis indication, note that market exclusivity has not expired as of the date of this assessment, and current biosimilars cannot yet be approved with a uveitis indication.

Table 3-3. Therapeutic areas of baseline (n=23) and BsUFA II Program (n=12) 351(k) BLAs with a first-cycle action

Therapeutic Area	Baseline	Program
Oncology	65%	58%
Rheumatology	39%	50%
Dermatology	30%	42%
Gastroenterology	22%	42%
Hematology	4%	0%

Table 3-4. Reference products with indications in multiple therapeutic areas for baseline (n=9) and BsUFA II Program (n=6) 351(k) BLAs with a first-cycle action

Reference Product (# of 351(k) BLAs)	Therapeutic Area				
	Dermatology	Gastroenterology	Oncology	Ophthalmology	Rheumatology
Adalimumab (Baseline: 2, Program: 4)	✓	✓		✓	✓
Etanercept (Baseline: 2, Program: 0)	✓				✓
Infliximab (Baseline: 3, Program: 1)	✓	✓			✓
Rituximab (Baseline: 2, Program: 1)			✓		✓

Regulatory Outcome Definitions

Regulatory outcome or action: Decision on a BLA. Decisions that close the BsUFA goal (end the review) include:

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

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

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

First-cycle approval rate: The percent of applications that received AP in the first review cycle.

Time to first-cycle action: Time from FDA receipt of an application to a first-cycle action. In this report, we focus only on time to first-cycle approval because other actions in the Program are too few for meaningful analysis.

Overall time to approval: Time from FDA receipt of an original application to its approval in any review cycle (regardless of the number of review cycles). In this report, we could not analyze overall time to approval because no Program applications have been resubmitted for a second review cycle; insufficient time has elapsed to enable other applicants to resubmit applications.

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, BsUFA II Program Overall
- Section 3.2, BPD Type 4 Pre-351(k) Application Meetings
- Section 3.3, Quality of BsUFA II 351(k) Applications
- Section 3.4, FCPs
- Section 3.5, Day 74 Letters
- Section 3.6, MCCs
- Section 3.7, LCMs
- Section 3.8, AC Meetings and Post-AC Meetings
- Section 3.9, Inspections and Inspection Completion
- Section 3.10, IR and Amendments
- Section 3.11, Good Review Management Principles and Practices

For these topics, we focus on relevant results from our qualitative and descriptive analyses. We provide additional information in Appendix B, Evaluation Metrics.

3.1 BsUFA II Program Overall

Key Findings

- In the BsUFA II Program, most applicants and FDA reviewers characterized:
  - Communications as excellent, constructive, and cooperative.
  - Application reviews as very transparent and predictable.
  - The additional two months of review time as valuable to the review process.
- FDA reviewers identified some good review practices: maintain regular communication and coordination with all involved FDA groups, and clearly communicate timelines.
- Applicants identified some good practices: provide information or templates for application content and organization, provide early notification of review/approvability issues, and hold ad hoc teleconferences to resolve specific questions/issues efficiently.
- Thus far, first-cycle approval rates are higher in the BsUFA II Program (75%) than in the baseline (39%).
- Thus far, the additional two months of review time available in the BsUFA II Program appears to benefit applications with substantive review issues that are resolvable in the first review cycle with that added time.

This section presents overarching results that encompass the BsUFA II Program as a whole:

- Communications between applicants and FDA reviewers
- Review transparency and predictability
- Review practices
- Regulatory outcomes and timing

Applicant-FDA Communications in the BsUFA II Program

After a 351(k) BLA reviewed in the BsUFA II Program receives a first-cycle regulatory action, ERG conducts separate interviews with the applicants (if they accept the interview invitation) and FDA review team to obtain feedback about various aspects of the review process. In the post-action interviews conducted thus far (n=21), applicants characterized communications with FDA reviewers as excellent and constructive, with a spirit of cooperation—both within and outside of the new milestone communications (MCCs and LCMs). Many applicants agreed that regular interactions with the Regulatory Project Manager (RPM) helped maintain lines of communication between milestone meetings. Similarly, most FDA review staff affirmed that milestone meetings were helpful in conveying issues to the applicant and providing internal structure to the review, though some felt that milestone meetings had the most utility in relatively complex reviews.

Review Transparency and Predictability

In post-action interviews, applicants characterized reviews in the BsUFA II Program as very transparent. They credited this transparency to the combination of (1) big-picture multidisciplinary status updates provided during the MCC and LCM, and (2) focused updates provided on an ongoing basis during email and

telephone interactions with the RPM. Some applicants suggested that an additional way to further increase transparency would be for RPMs to inform applicants when the Agency considers an IR to be resolved. A small minority of applicants noted instances where communications from the Agency were less frequent between the LCM and the BsUFA goal date for regulatory action.

Applicants also characterized reviews as very predictable. They credited this predictability to (1) the MCC and LCM, which "anchor" reviews with predictable milestones that provide updates on review status and plans for future steps and milestones, and (2) the FDA review team's commitment to moving the review forward efficiently.

In post-action interviews, most FDA review staff stated the belief that application reviews in the BsUFA II Program were transparent and predictable to applicants. Many stated that MCCs and LCMs provided them with opportunities to consider the inputs of all team members together, helping them to consider the application as a whole, prioritize issues, plan for review milestones, engage leadership, and review the application status with the applicant. Some reviewers felt that these meetings might be most beneficial for applications that require substantive discussion and issue resolution; they suggested that FDA have the option to opt out of MCCs or LCMs if such discussions are not needed.

Table 3-5 presents key points from applicant and FDA review team interviews.

Table 3-5. Post-action interview feedback on applicant-FDA review staff communications and review transparency and predictability in the BsUFA II Program, FY 2018-2020

Applicants (10 Interviews)	FDA Reviewers (11 Interviews)
• Overall, communications were excellent, constructive, and cooperative • Reviews were very transparent and predictable • RPMs were diligent and helpful in maintaining positive communications and keeping reviews moving forward • Contact with FDA outside of MCC and LCM contributed to transparency and sense of cooperation • Regular interactions with RPM and coordination between the RPM and FDA Regulatory Business Project Manager (RBPM) helped maintain communications • Ability to clarify IRs in meetings or in ad hoc teleconferences improved transparency • Receiving FDA rationale with IRs facilitated more effective responses • Flexibility to submit responses to IRs via email followed by a formal submission was helpful • It would be helpful for FDA to inform applicant when they consider IRs to be resolved • Application Orientation Meeting (AOM) was helpful to orient reviewers to the organization of the application • Communication decreased between the LCM and action date (rare opinion)	• Overall, communications were excellent, constructive, and cooperative • Reviews were very transparent and predictable • Milestone meetings were helpful in notifying the applicant of issues and providing internal structure to the review • Clearly communicating timelines, especially with large review teams, was helpful • Streamlined processes and collaboration between applicant, divisions, and external consults were necessary for a successful review • FDA staff would benefit from the ability to opt out of MCC or LCM when substantive discussions are not needed

Review Process

The BsUFA II Program instituted two key changes to the review process for 351(k) BLAs:

- Begin the BsUFA 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 (MCC and LCM) during the review to update the applicant on the status of their application.

Use of Two Additional Months

In post-action interviews, most FDA reviewers and applicants commented on the value of the additional two months of review time afforded by starting the review clock at filing. Reviewers emphasized that communication these two months were generally consumed by communication between the review team and the Office of Therapeutic Biologics and Biosimilars (OTBB), specifically involving language used in labeling and reviews. Reviewers agreed that OTBB's expertise with biosimilar labeling and reviews, especially across applications, is invaluable. Some recommended adding more time to complete primary reviews.

Other Good Practices in Review Process

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

- **Maintain regular communication and coordination with all involved groups—**Biosimilar applications can necessitate involvement of multiple review divisions, OTBB, the Center for Devices and Radiological Health (CDRH), and other groups at FDA. Clear communication, assigned roles, and coordination helped to ensure that the review ran smoothly, deadlines were met, and the Agency maintained clear communications with the applicant.

  Note: Some reviewers observed that biosimilar indications tend to fall in the same divisions, leading to those divisions consistently serving as the lead division, stressing these divisions' resources when extensive communication and coordination were needed. They suggested clarifying roles and streamlining communications between OTBB and review teams.

  Note: Some applicants encountered challenges when the RPM and the Chemistry, Manufacturing, and Controls (CMC) lead or other disciplines did not coordinate, resulting in a large number of IRs that could have been grouped.
- **Clearly communicate timelines—**Clear communication of timelines, both internally and externally, ensured that the Agency met all BsUFA deadlines in cases where reviews entailed involvement of multiple FDA centers, offices, and divisions.

During post-action interviews, applicants identified some good practices applicants and FDA staff employed during the review:

- **Provide information or templates for application content and organization—**During the BPD Type 4 meeting, FDA provided feedback on what information should be included in the application and

how this information should be organized. Applicants noted that it was helpful when FDA provided this information or templates for organizing applications. Some applicants recommended that this be standard practice.

- **Provide early notice of issues—**Applicants stated that they found it helpful when the Agency notified them of potential review and approvability issues early in the review process, preferably before the MCC. This allowed applicants time to respond or take corrective action.
- **Hold ad hoc teleconferences to address specific defined topics—**Outside of milestone meetings, FDA review teams occasionally held ad hoc teleconferences with applicants regarding IRs, inspections, or other topics. Applicants observed that these calls increased transparency and facilitated efficient resolution of questions and issues.

Regulatory Outcomes and Timing

In this interim report, we focus on first-cycle regulatory outcomes. Three years into the BsUFA II Program, not enough time has elapsed for most applicants receiving a CR to prepare and resubmit applications. Therefore, we do not provide data on resubmissions and second-cycle outcomes.

First-Cycle Approval Rates

Thus far, the first-cycle approval rate for Program applications has been higher than that of baseline applications (Table 3-6). The types of approvability issues cited in CR letters for non-approved applications are somewhat similar in the Program and baseline (Table 3-7). Of note, is the higher rate of Quality Microbiology issues in the Program; the number of CRs is too small to determine whether this is a meaningful difference.

Table 3-6. First-cycle approval rates in the baseline (n=23) and BsUFA II Program (n=12), by fiscal year of application receipt

First-Cycle Approval Rate									
FY 2013	FY 2014	FY 2015	FY 2016	FY 2017	Baseline	FY 2018	FY 2019	FY 2020	Program
--	50%	20%	67%	38%	**39%**	83%	67%	--	**75%**

Table 3-7. Approvability issues cited in baseline (n=14) and BsUFA II Program (n=3) CR letters

Issue Category Cited in CR Letter*	351(k) Applications Given a CR	
	Baseline (FYs 2013-2017) (n=14)	Program (FYs 2018-2020) (n=3)
Product Quality	93%	100%
Facilities	50%	33%
Immunogenicity	36%	0%
Quality Microbiology	29%	100%
Clinical	29%	0%

Clinical Pharmacology	14%	0%
Device	7%	33%
Nonclinical	0%	33%

*CR letters typically cite more than one type of approvability issue.

Goal Extensions

In BsUFA I, FDA could extend the BsUFA goal date for regulatory action on an application if the applicant submitted a major amendment during FDA's review; a major amendment is a submission of significant data that is expected to substantially increase the burden on the FDA review team. For 351(k) BLAs in BsUFA II, goal extensions are available to FDA if an amendment or series of amendments is considered a major amendment, or if an inspection is needed for manufacturing facilities inadequately identified in the application. Before extending the review clock, FDA considers whether this action might impact the regulatory outcome of the first cycle of review. Generally, FDA does not extend the goal date or review the amendment if it does not have the potential to bring the application to approval.

In the first three years of the BsUFA II Program, FDA issued one goal extension, compared to three in the baseline (Table 3-8). FDA issued these goal extensions in the last couple months of the review cycle: 1.0 to 0.5 months before the goal date (baseline), and 1.7 months before the goal date (Program). In all cases, the applications with goal extensions received a first-cycle FDA approval.

Table 3-8. Goal extensions in the first cycle among baseline (n=12) and BsUFA II Program (n=23) 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 (FYs 2013-2017)	13% *(3/23)*	100% *(3/3)*	9.0 to 9.5 months
Program (FYs 2018-2020)	8% *(1/12)*	100% *(1/1)*	10.3 months

**Original 351(k) BLAs received during FYs 2013-2017 and acted on by September 30, 2020 (baseline; 8 years of data) or received and acted on during FYs 2018-2020 (Program; 3 years of data).*

Time to First-Cycle Approval

In the BsUFA II Program, FDA aims to review 90% of original 351(k) applications within 10 months of the 60-day filing date—unless a goal extension is taken, in which case the BsUFA goal date is 3 months later. In the baseline, FDA aimed to review applications within 10 months of the original 351(k) application receipt date—unless a 3-month goal extension was taken.

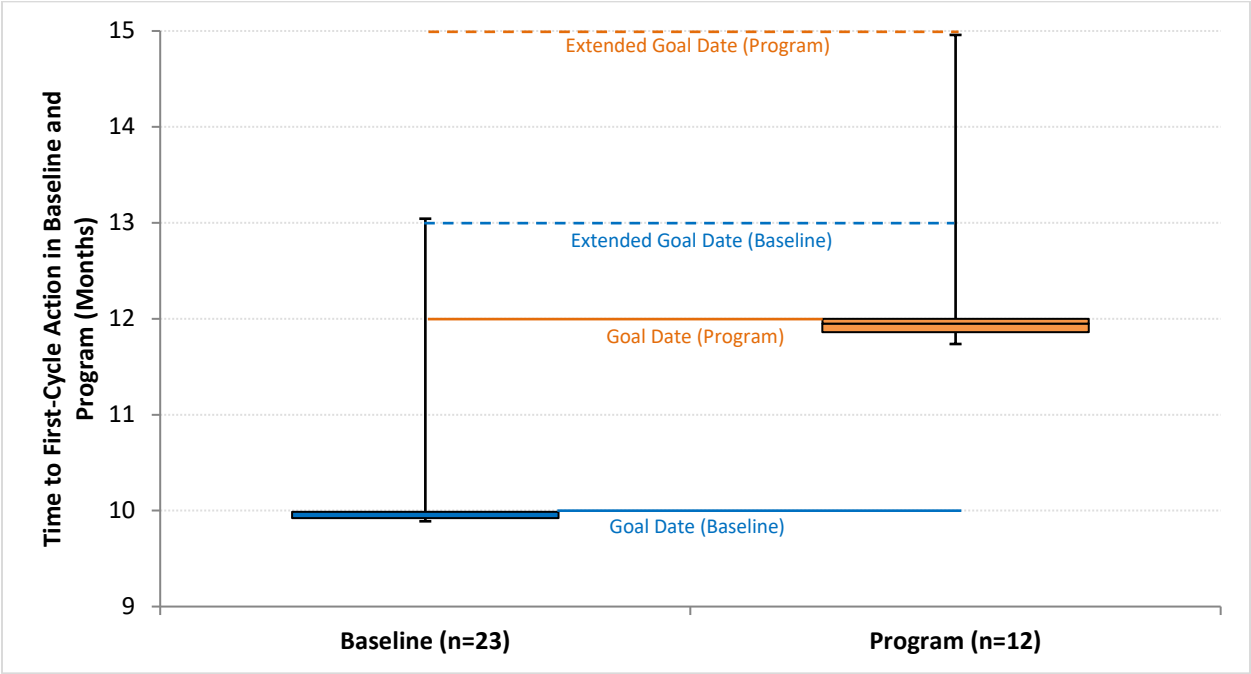
Based on BsUFA goal dates, we would expect that the median time to first-cycle action would be 60 days (2 months) longer in the Program than in the baseline. As expected, the median time to first-cycle approval was longer in the first three years of the Program than in the baseline (see Table 3-9).

Table 3-9. Median time to first-cycle action in the baseline (n=23) and BsUFA II Program (n=12), by type of action

Cohort	Median Time from Application Receipt to First-Cycle Action (Months)		
	Approval	Complete Response	Withdrawal
Baseline (FYs 2013-2017)	10.0 (n=9)	10.0 (n=14)	N/A
Program (FYs 2018-2020)	12.0 (n=9)	11.9 (n=3)	N/A

In the first three years of the BsUFA II Program, FDA reviewed 100% of applications by the goal date. Thus, the median first-cycle review time (from receipt to action) was nearly 12 months; because of a goal extension for one Program application and early action on some other Program applications, the range for first-cycle review time was 11.7-15.0 months. The range was similar in the baseline, with nearly all review times being at or near 10 months (regular reviews) or 13 months (reviews with extensions) (Figure 3-2).

Figure 3-2. First-cycle review times for baseline (n=23) and BsUFA II Program (n=12) applications



Based on the data thus far, the additional two months of review time with the BsUFA II Program appears to have benefitted applications with substantive review issues that had the potential to be resolved in the first review cycle, where FDA needed the full review clock. In contrast, no program is likely to benefit applications with serious deficiencies or applicants who do not respond promptly to FDA requests for more information.

RTF and WF Actions

During the first three years of the BsUFA II Program, no applications received an RTF decision; three applications were withdrawn by applicants before filing (reasons not disclosed). By September 30, 2020, one of the withdrawn applications had been resubmitted to the Program and received a first-cycle action of AP. In the baseline, one application received an RTF (due to facilities not being ready for inspection) and one was withdrawn before filing (reasons not disclosed). Both were later submitted and reviewed under the Program; they received a first-cycle action of AP.

3.2 Biosimilar Biological Product Development (BPD) Type 4 Pre-351(k) Application Meetings

Key Findings

- Most BsUFA II Program applicants requested a BPD Type 4 meeting from FDA.
- FDA held most Program BPD Type 4 meetings at least two months before application submission.
- Both Program applicants and FDA review teams consider the BPD Type 4 meeting process to be a valuable tool for outlining and understanding application expectations.
- In most cases where meetings were held, many of the sponsor's questions were resolved by FDA feedback in preliminary comments sent before the BPD Type 4 meeting.

This section presents information about BPD Type 4 meetings in the BsUFA II Program:

- Format and conduct
- Discussion topics and agreements
- Interview feedback

Format and Conduct

A BPD Type 4 pre-351(k) BLA meeting is a meeting between FDA staff and a sponsor to discuss the content and format of an anticipated 351(k) BLA submission. The BPD Type 4 meeting 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 BPD Type 4 meeting before 351(k) BLA submission is strongly recommended (but not required) in BsUFA II.

Commitment Letter Expectations

- Should occur 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.
- If applicable, include preliminary discussion on REMS or other risk management strategies.
- If applicable, discuss patient labeling.
- If applicable, develop a Formal Communication Plan.
- Summarize agreements and discussions.

Commitment Letter Recommendation

- Hold a BPD Type 4 meeting prior to application submission.

In the baseline period (BsUFA I), 17 of 23 applications had a BPD Type 4 meeting. Thus far in the Program (FYs 2018-2020), 11 of 12 applications have had a BPD Type 4 meeting, with 7 conducted on or after October 1, 2017 (during BsUFA II) and 4 conducted before October 1, 2017 (during BsUFA I); the sponsor for 1 Program application did not request a BPD Type 4 meeting. For this analysis of the BsUFA II Program, ERG excluded the 4 BPD Type 4 meetings that occurred before October 1, 2017 because they were not subject to BsUFA II Program expectations. Nevertheless, we note that FDA review teams incorporated Program elements into some of those four excluded meetings even though the Program elements were not yet expected.

This section focuses on the seven applications with a BsUFA II Program BPD Type 4 meeting. For 86% of Program applications with a Program BPD Type 4 meeting, the meeting was held at least 2 months before application submission, as expected in the BsUFA Commitment Letter. In the meetings, both Program

applicants and FDA raised discussion topics cited in the Commitment Letter; FDA staff were most often the ones to ensure that the topics had been addressed. In many 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 the meeting (e.g., preliminary comments or written responses) and did not need to address them again.

Regardless, both Program applicants and FDA staff considered the BPD Type 4 meeting to be a valuable opportunity to establish an understanding of FDA's expectations for a complete application. In post-action interviews, both parties noted that open communication about an application prior to submission (outside of the BPD Type 4 meeting 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.

Discussion Topics and Agreements

BsUFA II Program BPD Type 4 meetings primarily focused on specific questions posed by the sponsor to FDA in their meeting request. In most cases, many of the sponsor's questions were resolved by FDA feedback in the preliminary comments sent to sponsors before the meeting, leaving a few questions for further discussion or clarification at the BPD Type 4 meeting.

FDA's BsUFA II Commitment Letter expresses the expectation that sponsors and FDA staff will discuss and agree on the content of a complete application at the BPD Type 4 meeting. In BsUFA II BPD Type 4 meetings, sponsors and FDA staff explicitly discussed this topic in 43% of meetings and explicitly agreed on the content of a complete application in 0% of the meetings. However, sponsors and FDA staff typically discussed application-related topics where the sponsor had questions; they might have considered the totality of their communications (via meeting request and background package, preliminary comments, meeting discussion) to have implicitly addressed the content of a complete application. In interviews with sponsors, most agreed that they were able to achieve a good understanding of FDA's expectations of a complete application from the BPD Type 4 meeting process. Similarly, some FDA interviewees stated that they used the BPD Type 4 meeting process to proactively identify and suggest information for sponsors to include in a complete application rather than waiting for sponsors to ask specific questions about these items.

Another BsUFA II Commitment Letter expectation is that sponsors and FDA staff will discuss and agree on delayed submission of minor application components. This occurred in 29% of Program BPD Type 4 meetings. In those cases, the sponsor and FDA staff agreed that there would be no delayed application components, or FDA decided that the data was needed in the original submission and communicated that to the sponsor in the meeting minutes.

Other potential discussion topics identified in Commitment Letter expectations—to be discussed if applicable—were infrequent. Discussions regarding the approach to Risk Evaluation and Mitigation Strategies (REMS) development or patient labeling occurred in 29% of Program BPD Type 4 meetings. FCPs were not discussed in any Program BPD Type 4 meeting. In interviews, some FDA staff and sponsors

appeared to be unfamiliar with that process and most expressed satisfaction with the standard Program communications.

Interview Feedback

Table 3-10 provides additional feedback about Program BPD Type 4 meetings gleaned from post-action interviews with Program applicants and FDA staff.

Table 3-10. Post-action interview feedback on BsUFA II Program BPD Type 4 meetings, FYs 2018-2020

Applicants (10 Interviews)	FDA Reviewers (11 Interviews)
• BPD Type 4 meetings provided an opportunity to understand FDA's expectations and agree on late application elements • These meetings offered a time for applicants to ask questions about the organization of the application • These meetings were especially helpful when FDA provided information or templates demonstrating desired application organization	• BPD Type 4 meetings provided an opportunity for FDA to convey expectations for a complete application, to provide templates, and to agree on any late application elements • In some cases, when an applicant has previous BsUFA experience, the BPD Type 4 meeting is unnecessary

3.3 Quality of BsUFA II 351(k) Applications

Key Findings

- FDA staff and applicants have not identified specific items in BPD Type 4 meetings as required for a complete application.
- BsUFA II Program applications have been technically complete at the time of filing.
- After filing, FDA primary reviewers cited at least one type of quality/completeness deficiency for 5 of the 12 Program applications.
- In interviews, applicants stated that they had no difficulty understanding FDA's expectations for a complete application.

One of the expectations in the BsUFA II Program is that sponsors will provide 351(k) BLAs that are complete and of good quality on first submission. ERG examined the quality/completeness of BsUFA II applications in three ways:

- By assessing the extent to which the applications incorporated items agreed to during BPD Type 4 meetings.
- By examining RPM Filing Review documents to identify any quality/completeness issues documented at the time of filing.
- By asking FDA primary reviewers, at the midpoint of the review process, to identify any quality and completeness issues that they encountered.

Inclusion of Items from BPD Type 4 Meeting Agreements

Seven BsUFA II applications had a Program-style BPD Type 4 meeting. In three of these meetings, the sponsor and FDA staff explicitly discussed the content of a complete application, but they did not identify specific content items as required for application completeness. Rather, FDA staff expressed their expectation that the application would be complete on submission and sponsors confirmed their understanding. In one meeting, FDA staff confirmed with the sponsor that there would be no delayed application components submitted to the application. ERG had planned to track submission of items mentioned in BPD Type 4 meetings, but we have none to track because no specific items have been cited in meetings thus far.

Filing Review Assessments

The RPM Filing Review serves as a checklist for managing the application filing process. It contains sections for recording format/content quality and completeness issues. ERG examined RPM Filing Review documents for 11 of the 12 Program applications with a first-cycle action; none cited format/content quality or completeness issues. For the remaining application, no RPM Filing Review is available.

FDA Reviewer Assessments

To gain further insights into Program application quality and completeness, ERG consulted FDA primary review staff for their assessment of applications at the mid-cycle point of their reviews. At this point,

primary reviewers have usually identified data deficiencies that were not apparent during the initial filing review. FDA primary reviewers cited at least one type of quality/completeness deficiency for 5 of the 12 Program applications (Table 3-11); 2 of these 5 applications subsequently received a CR letter. In interviews, applicants stated that they had no difficulty understanding FDA's expectations for a complete application.

Table 3-11. BsUFA II Program application quality and completeness issues cited by FDA reviewers, by review discipline, FYs 2018-2020

Review Discipline	Quality and Completeness Issues (number of applications with issue)*
Product Quality	Missing qualifications of methods (1)
	Overly summarized data; lacking detail (1)
	Indigestible data dumps; lacking interpretation or analyses (1)
Clinical	Missing patient narratives and datasets (1)
	Coding issues and dictionary inconsistencies (1)
Clinical Pharmacology	Missing documents referenced by the application (1)

**More than one issue was cited for one application.*

3.4 Formal Communication Plans (FCPs)

Key Findings

- No FCPs have been developed under the BsUFA II Program.

An FCP is an agreement between the applicant and FDA reviewers to implement a different set of communications than is standard in the BsUFA II Program. For example, as part of an FCP FDA staff and applicants may mutually decide to omit some or all of the Program milestone meetings or add additional meetings to the review process. Discussion of and agreement on an FCP are expected to occur at the BPD Type 4 meeting and be captured in the meeting minutes. FDA staff and applicants have the option to revise the FCP later if they mutually agree.

Frequency of Use

FCPs have not been established for any of the twelve 351(k) BLA reviews in the BsUFA II Program. In interviews with applicants and FDA staff, some stated that they were not familiar with the FCP concept or were unsure of the process to create an FCP.

3.5 Day 74 Letters

Key Findings

- FDA issued Day 74 letters for all applications in the BsUFA II Program, largely conforming with Commitment Letter expectations.
- FDA use of filing letters in the Program was similar to that in the baseline:
  - One-third of baseline and Program applications had Day 74 letters that identified potential review issues.
  - Most potential review issues identified in Day 74 letters were related to Product Quality.

A Day 74 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 goal") to communicate potential review issues and FDA's planned review timeline. In FYs 2018-2020, FDA issued filing letters for all BsUFA II Program applications, following existing guidance. The letters included the topics expected in the Commitment Letter for BsUFA II.

Day 74 letters represent an opportunity for the FDA review team to convey any potential review issues identified during the filing period. For the 12 Program applications received and acted on in FYs 2018-2020, four Day 74 letters (33%) cited potential review issues, most often related to Product Quality (Table 3-12).

Commitment Letter Expectations

- Will use existing procedures on issuing Day 74 letters.
- Send within 74 calendar days of FDA receipt of original submission.
- Include notification of potential review issues.
- Include planned review timeline:
  - Planned date for internal mid-cycle review meeting.
  - Preliminary plans on whether to hold an AC meeting.
  - Target date for communicating FDA feedback on proposed labeling and FDA-requested postmarketing requirements and commitments.

Table 3-12. Potential review issues identified in Day 74 letters in baseline (n=8) and BsUFA II Program (n=4), by review topic

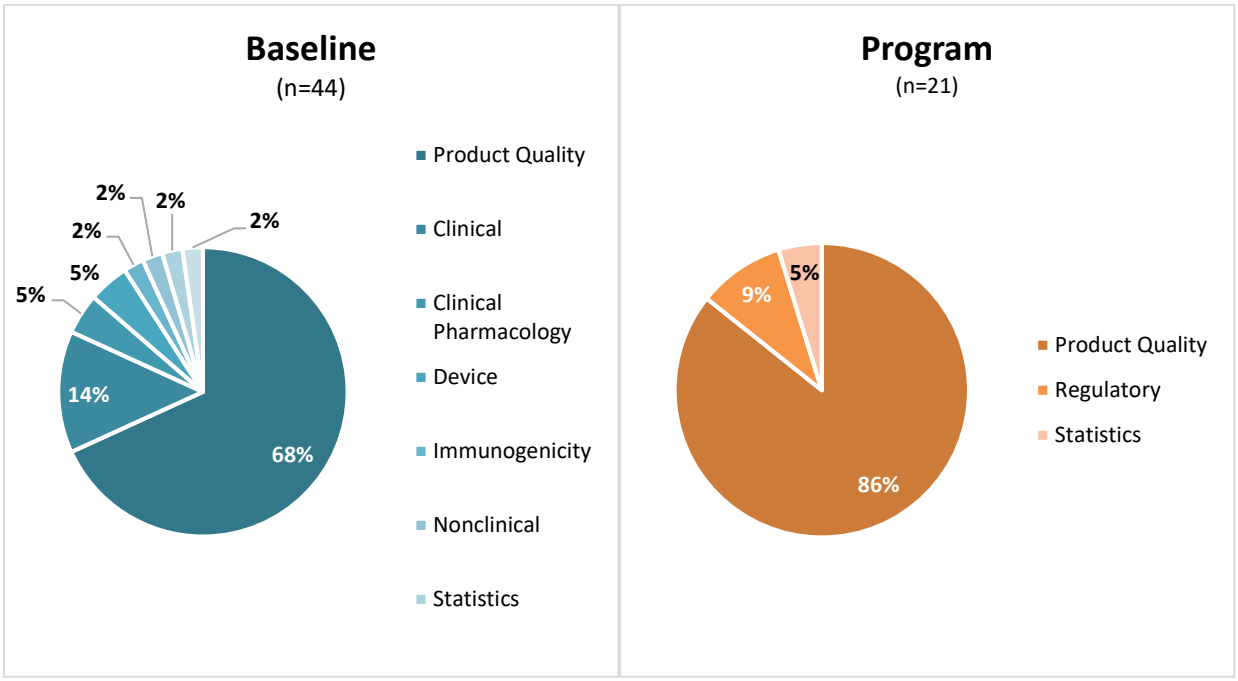
Potential Review Issue Topics*	351(k) Applications with Potential Review Issues	
	Baseline (FYs 2013-2017) (n=8)	Program (FYs 2018-2020) (n=4)
Product Quality	63%	75%
Clinical	38%	0%
Unspecified	13%	0%
Clinical Pharmacology	13%	0%
Device	13%	0%
Immunogenicity	13%	0%
Nonclinical	13%	0%
Statistics	13%	25%
Regulatory	0%	25%

*Day 74 letters may contain more than one potential review issue topic.

Day 74 letters that cite potential review issues often provide itemized lists of multiple issues organized by topic; Figure 3-3 presents a breakdown of those issues by topic. In the baseline and the BsUFA II Program, Product Quality issues accounted for the largest number of potential review issues in Day 74 letters. FDA also used some Day 74 letters as an opportunity to issue IRs to the applicant. Of the 27 IR items requested in Program Day 74 letters, most were related to Product Quality (81%).

ERG found no associations between the content of Day 74 letters and first-cycle review outcomes in either the baseline or the BsUFA II Program.

Figure 3-3. Distribution of potential review issue items for baseline (n=23) and BsUFA II Program (n=12) applications, by review topic



3.6 Mid-Cycle Communications (MCCs)

Key Findings

- FDA conducted MCCs for all eligible BsUFA II 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 valued the MCC as an opportunity to hold a holistic discussion about their application; some FDA reviewers considered the MCC to be redundant to their already open, real-time communication practices, especially if they had no substantive review issues to discuss.
- A lack of significant Product Quality issues at the MCC tended to be associated with application approval.

An MCC is a meeting between FDA review staff and the applicant, generally held as a teleconference within 2 weeks of FDA's internal mid-cycle meeting, to provide the applicant with an update on the status of their review. At the meeting, the applicant can expect to hear updates on any review issues identified to date, major concerns, and upcoming milestone dates.

This section presents information about MCCs in the BsUFA II Program:

- Format and conduct
- Discussion topics
- Interview feedback

Commitment Letter Expectations

- Ensure that RPM and appropriate review team members are present.
- Hold as a teleconference.
- Conduct within 2 weeks of internal mid-cycle meeting.
- Send agenda prior to MCC.
- Include significant issues identified to date.
- Include any IRs.
- Include major concerns with:
  - Analytical similarity data.
  - Data to support demonstration of no clinically meaningful differences, including immunogenicity issues.
  - Data to support interchangeability.
  - Product quality.
- If applicable, notify applicant about preliminary thinking on risk management.
- Notify applicant of proposed date for LCM.
- If applicable, provide update on plans for an AC.
- Provide projected milestone dates for remainder of review cycle.

Format and Conduct

In FYs 2018-2020, FDA review teams held MCCs for all 12 eligible BsUFA II Program applications. The MCCs generally conformed with the spirit of Commitment Letter expectations and recommendations (Table 3-13).[1] That is, FDA review teams:

- Conducted 58% of MCCs within 2 weeks, 83% within 3 weeks, and 100% within 4 weeks of FDA's internal mid-cycle meeting.
- Held 100% of MCCs as teleconferences.
- Provided updates on expected topics as relevant. They sometimes omitted topics that were addressed outside of the MCC.

[1] 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.

Table 3-13. MCC expectations of BsUFA II Program 351(k) BLAs with a first-cycle action (n=12)

MCC Expectation	Percent of MCCs Fulfilling Expectation
Held within 2 weeks after the Mid-Cycle Meeting	58%
Held as a teleconference	100%
Agenda sent to applicant prior to MCC	100%
Appropriate FDA team members present	92%
Significant issues identified by the review team	100%
Include information requests	50%
Information regarding major concerns with:	
1) Analytical similarity data	58%
2) Data to support demonstration of no clinically meaningful differences	75%
3) Data to support demonstration of interchangeability	58%
4) CMC issues	75%
Preliminary thinking on proposed REMS	100%*
Update on AC meeting plans	100%**
Proposed dates for the LCM	92%
Other projected milestone dates for the remainder of the review cycle	100%

*Although REMS were not applicable to any application, in 9 of 12 MCCs FDA confirmed that REMS was not needed.
**Although AC meetings were not applicable to any application, in 6 of 12 MCCs, FDA confirmed that no AC was planned.

Discussion Topics

At the time of the MCC, FDA's primary disciplines are reviewing the application and are expected to disclose any significant review issues they have identified to date. At the MCCs for the 12 BsUFA II Program applications, representatives of review disciplines spoke if they had issues to share with the applicant; those without issues usually did not comment unless asked by the applicant. FDA staff shared review issues at 8 of the 12 MCCs; FDA staff shared Clinical issues with applicants at 5 MCCs and Product Quality issues at 3 MCCs.

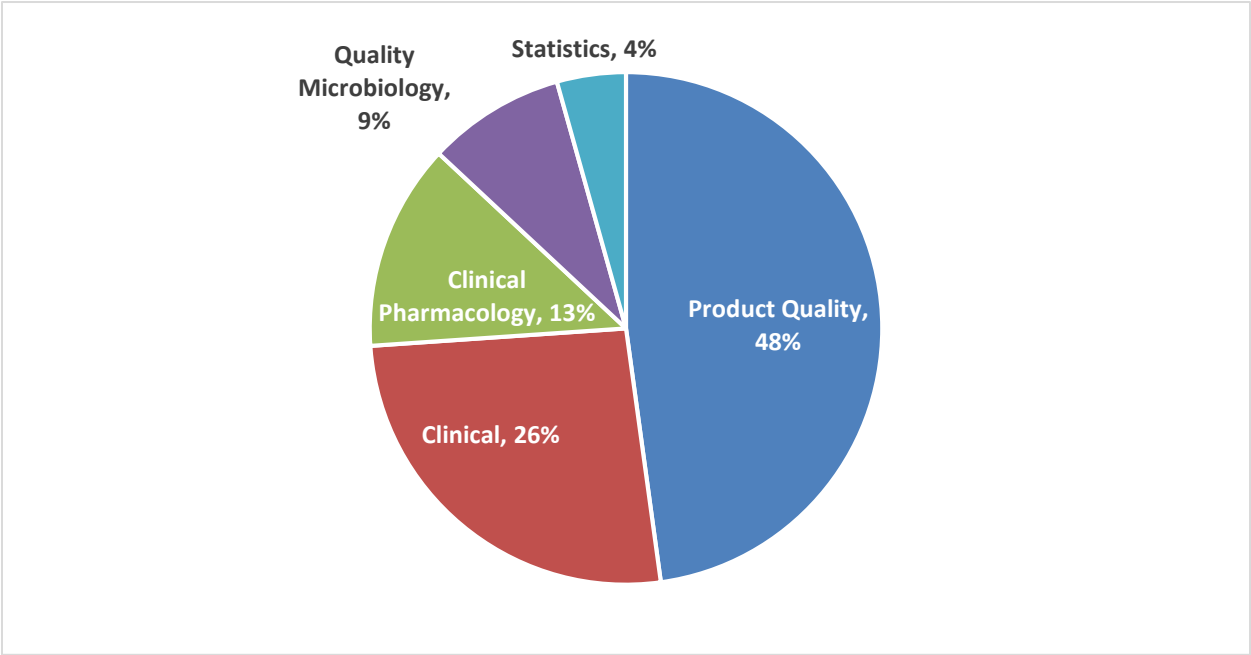
Applications that did not require discussion of Product Quality issues at the MCC were associated with higher first-cycle approval rates than those with Product Quality issues (see Table 3-14).

Table 3-14. First-cycle approval rates for BsUFA II Program applications (n=12), by MCC review issue

Discipline / MCC Issue	First-Cycle Approval Rate	
	Applications with Issue Discussed in MCC	Applications with Issue Not Discussed in MCC
Product Quality	33%	89%
Clinical	80%	71%
Clinical Pharmacology	100%	70%
Quality Microbiology	100%	70%
Statistics	100%	73%

More than one issue can be raised at a single MCC. Although Clinical issues were most commonly raised at MCCs, Product Quality issues were the most numerous. Figure 3-4 shows that nearly half of the 23 total issues identified in MCCs were related to Product Quality.

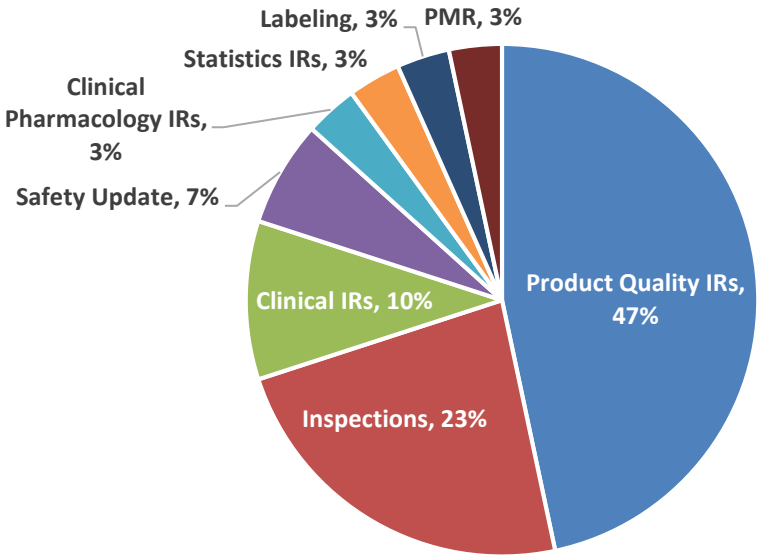
Figure 3-4. Distribution of review issues (n=23)* in MCCs for BsUFA II Program 351(k) BLAs (n=12)



*Multiple review issues can be cited per MCC.

In addition to sharing significant review issues, FDA staff and applicants often used the MCC to discuss other topics currently relevant to the review (Figure 3-5). Most of these discussions were related to IRs: whether FDA would be sending IRs or was already reviewing responses, or if applicants were requesting IR clarification or sharing when they expected to respond to an IR. In many MCCs (58%), applicants requested an update on the status of inspections for their application.

Figure 3-5. Distribution of other discussion topics (n=30) in MCCs for BsUFA II Program 351(k) BLAs (n=12)



Interview Feedback

Table 3-15 presents a summary of feedback about MCCs collected from post-action interviews with applicants and FDA reviewers. Both parties expressed the view that MCCs were 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, especially for applications with no substantive review issues to discuss. These reviewers stated that open, real-time communications are established practices, so the added burden of preparing for MCCs was not worthwhile—and diverted resources away from completing the primary reviews.

Table 3-15. Post-action interview feedback on BsUFA II MCCs, FYs 2018-2020

Applicants (10 interviews)	FDA Reviewers (11 interviews)
• MCC contributed to improved communication and improved review transparency and predictability • MCC helped applicant prepare for upcoming IRs • Would be helpful to be able to propose discussion topics during meeting to increase utility of meeting • Would be helpful for FDA to provide agenda earlier • Sometimes unclear whether significant/substantive issues were approvability issues	• MCC facilitated communication, early identification of issues, planning, and review progress • Divisions should have ability to opt out if division and sponsor agree or if division determines that meeting is unnecessary; status update can be accomplished through written communication if no significant issues have been identified (less common opinion) • Milestone meetings provided documentation that applicants were notified of potential issues

3.7 Late-Cycle Meetings (LCMs)

Key Findings

- FDA sent LCM background packages for all eligible BsUFA II Program applications, generally conforming with Commitment Letter expectations.
- FDA has issued no Discipline Review (DR) letters for 351(k) BLAs in the baseline or in the Program.
- FDA conducted LCMs for nearly all eligible Program applications, and FDA's management of these meetings mostly conformed with Commitment Letter expectations and recommendations.
- Applicants and FDA reviewers stated that the LCMs contributed to good communication during the review process; LCMs provided an opportunity to discuss significant issues and ways to move forward, and to discuss other end-of-review topics.
- In post-action interviews, some FDA reviewers favored the option to opt out of the LCM when there are no significant issues to discuss.
- A lack of significant Product Quality or Quality Microbiology issues identified at LCMs tended to be associated with application approval.

An LCM is a meeting (usually face-to-face, when possible) held near the end of the review cycle between members of the FDA review team and the applicant to discuss the status of the review, including topics like AC meeting preparation, outstanding IRs, and any remaining deficiencies in the application. This section presents information about LCMs held for the 351(k) BLAs reviewed in the Program to date:

- Background packages
- Format and conduct
- Discussion topics
- Interview feedback

Background Packages

Before the LCM, FDA sends a background package to the applicant to notify them of discussion topics to expect; this helps the applicant prepare to discuss any substantive issues identified. If an AC meeting was planned, the LCM background package could also include AC meeting discussion points.

Commitment Letter Expectations

- Sent to the applicant not less than 10 calendar days before the LCM.
- Include any discipline review letters to date.
- Include brief memorandum of substantive application issues.
- If applicable, include FDA background package for the AC meeting.
- If applicable, include potential questions and/or discussion points for the AC meeting.
- If applicable, include current assessment of the content of proposed REMS or other risk management actions.

In FYs 2018-2020, FDA review teams sent LCM background packages to applicants for all 12 eligible BsUFA II Program applications. Except for two background packages sent less than 10 days (9 and 7 days) before the scheduled LCM, FDA generally sent LCM background packages according to the BsUFA II Commitment Letter expectations (Table 3-16). In all cases, elements related to AC meetings or REMS were not applicable because no Program applications went to an AC meeting and no REMS were needed for the products associated with the applications.

Table 3-16. LCM background package expectations for BsUFA II Program (n=12) 351(k) BLAs with a first-cycle action

Expectation	Percent of LCMs Fulfilling Expectation
Sent to applicant not less than 10 calendar days before the LCM	83%
LCM background package contains:	
1) Any DR letters to date	100%
2) Memo of substantive application issues	100%
3) FDA's AC background package or a reference to FDA's AC background package (if AC planned)	N/A
4) Potential AC questions/discussion points (if AC planned)	N/A
5) Assessment of the content of proposed REMS or other risk management	N/A

Commitment Letter Expectations

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

FDA sends DR letters to convey thoughts about possible deficiencies identified by a discipline at the conclusion of their review. In the BsUFA II Program, FDA follows existing guidance on DR letters and strives to issue them in advance of the LCM, or alternatively as part of the background package for the LCM. To date, FDA has issued no DR letters for 351(k) BLAs reviewed under BsUFA I or BsUFA II. In the Program, DR letters might be deemed redundant or unnecessary given the opportunities for communicating review issues during the MCC and LCM.

Format and Conduct

In FYs 2018-2020, FDA review teams held LCMs for 92% of eligible BsUFA II Program applications, either as a face-to-face meeting (27%) or a teleconference (73%). In one case, the applicant canceled the LCM after receiving the background package. The LCMs conducted generally conformed with Program expectations, except that several LCMs were held later than expected (Table 3-17); 73% of LCMs occurred 60 to 89 days before the BsUFA goal date instead of at least 3 months before the goal date.

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.
- Analytical similarity data.
- Data to support demonstration of no clinically meaningful differences, including immunogenicity.
- Data to support interchangeability.
- Product quality issues.
- Inspection findings.
- If applicable, AC issues/topics.
- If applicable, assessment of REMS or other risk management actions.
- Information requests or additional data applicant wishes to submit.

Table 3-17. LCM expectations for BsUFA II Program (n=11) 351(k) BLAs with a first-cycle action

LCM Expectation	Percent of LCMs Fulfilling Expectation
If AC planned, held not less than 12 calendar days before the AC meeting	N/A
If AC not planned, held not less than 3 months before the BsUFA goal date	27%
Appropriate FDA team members present	91%
Potential discussion topics:	
1) Major deficiencies	100%*
2) Analytical similarity data	17%
3) Data to support demonstration of no clinically meaningful differences	9%
4) Data to support demonstration of interchangeability	0%
5) CMC issues	82%
6) Inspection findings	18%
7) Issues for AC meeting discussion (if AC planned)	N/A
8) Assessment of the content of proposed REMS or other risk management	100%
9) Information requests	82%
10) Additional data or analyses the applicant may wish to submit	55%
If the applicant wishes to submit additional data or analyses, discussion on whether the submission would constitute a major amendment	67%

**In 64% of LCMs, FDA discussed at least one major deficiency; in 36%, FDA confirmed that there were no major deficiencies.

Discussion Topics

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. Of the 11 LCMs that occurred in the Program, 7 (64%) included a discussion of review or approvability issues. In 6 of these 7 LCMs (86%), Product Quality or Quality Microbiology issues were discussed. In total, applicants and FDA reviewers discussed 33 review or approvability issues at LCMs, mostly related to Product Quality or Quality Microbiology (Figure 3-6).

In the BsUFA II Program thus far, first-cycle approval rates have been higher for applications that did not require discussion of Product Quality or Quality Microbiology issues at the LCM than for applications with those issues (Table 3-18).

Figure 3-6. Distribution of review issues (n=33) in LCMs for BsUFA II Program 351(k) BLAs (n=11)

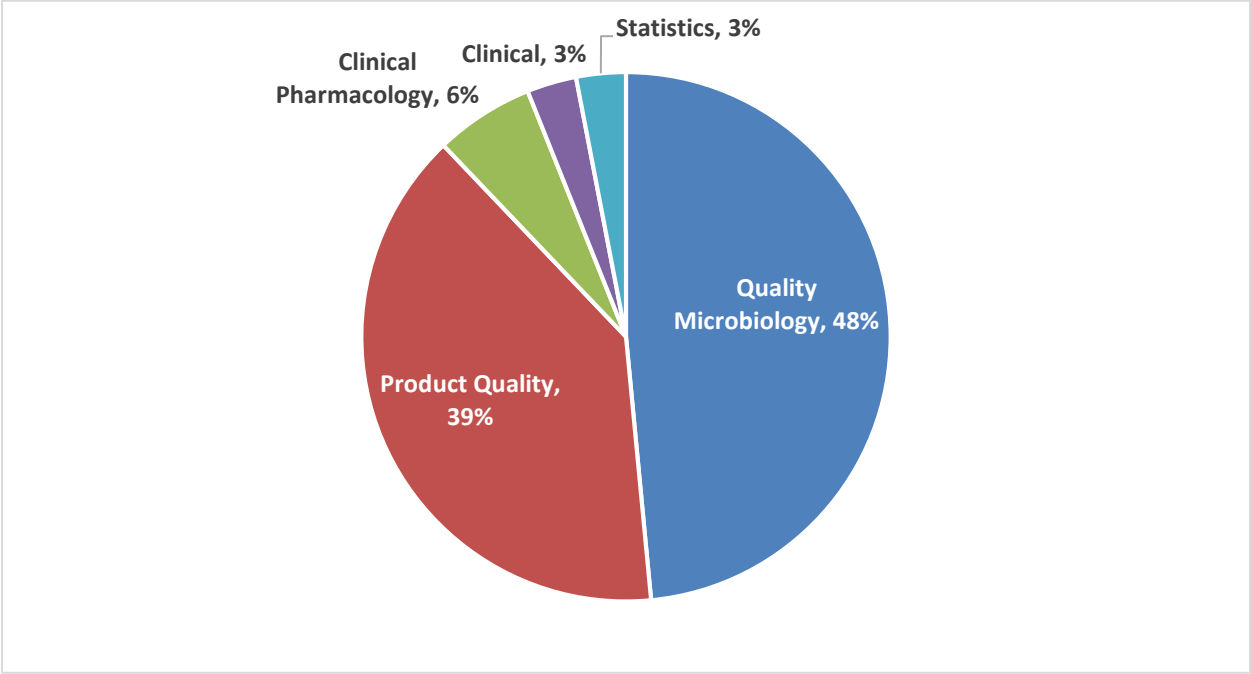
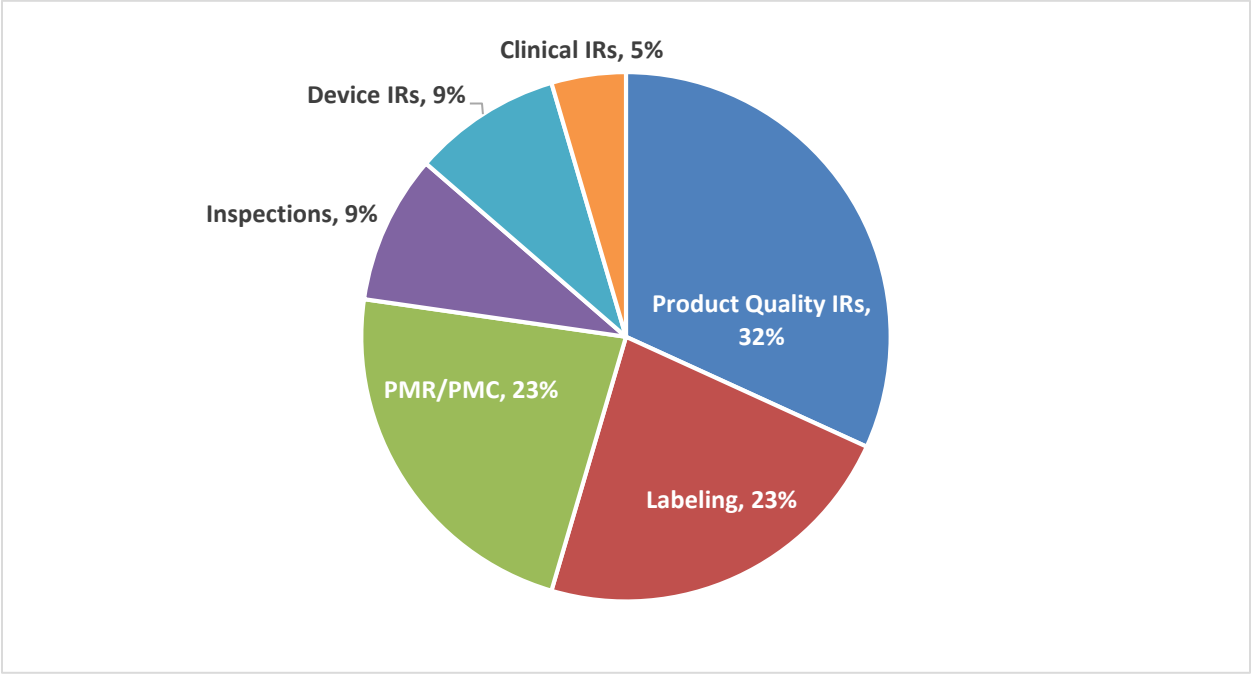


Table 3-18. First-cycle approval rates for BsUFA II Program applications (n=11), by LCM review issue

Discipline / LCM Issue	First-Cycle Approval Rate	
	Applications with Issue Discussed in LCM	Applications with Issue Not Discussed in LCM
Quality Microbiology	0%	80%
Product Quality	60%	83%
Clinical	100%	56%
Clinical Pharmacology	100%	70%
Statistics	100%	70%

At LCMs, FDA staff and applicants often discussed other topics besides review/approvability, such as IRs, Postmarketing Requirements/Postmarketing Commitments (PMRs/PMCs), labeling, and inspection wrap-up issues (Figure 3-7). For applications with few or no approvability issues, FDA and applicants used the LCM mainly to discuss end-of-review topics, such as PMRs/PMCs and labeling.

Figure 3-7. Distribution of other discussion topics (n=22) in LCMs for BsUFA II Program 351(k) BLAs (n=11)



To date, the presence of review issues at LCMs is not correlated with either a positive or negative regulatory outcome. However, all three applications that were not approved in the first review cycle had issues related to Product Quality or Quality Microbiology at the LCM.

Interview Feedback

In post-action interviews, some FDA reviewers favored the option to opt out of the LCM when there are no significant issues to discuss. Applicants valued the LCM, though, and did not suggest this option. Table 3-19 provides additional applicant and FDA review team feedback on LCMs.

Table 3-19. Post-action interview feedback on LCMs, FYs 2018-2020

Applicants (10 interviews)	FDA Reviewers (11 interviews)
• LCM contributed to good communication, transparency, and predictability • Would be helpful to be able to propose discussion topics prior to the meeting to increase utility of meeting • Would be helpful for FDA to provide agenda earlier, to give the applicant more time to prepare • Sometimes unclear whether significant/substantive issues are approvability issues	• LCM facilitated communication about substantive issues and ways to move the review process forward • Divisions should have ability to opt out if division and sponsor agree or if division determines that meeting is unnecessary (less common opinion); status update can be accomplished through written communication if no significant issues have been identified

3.8 Advisory Committee (AC) Meetings and Post-AC Meetings

Key Findings

- FDA held AC meetings for 22% of BsUFA I applications and 0% of BsUFA II applications.
- With no AC meetings in the BsUFA II Program to date, no post-AC meetings have taken place.

AC Meetings

FDA sometimes uses AC meetings to obtain professional opinions from outside the Agency about a product under review. In BsUFA I, FDA initially planned to hold an AC meeting for the first proposed biosimilar of a given reference product that was ready for public discussion.

FDA held an AC meeting for 22% of baseline 351(k) BLAs; FDA did not hold AC meetings for some applications that shared reference products and similar review timelines. In some cases, review issues precluded an AC meeting. To date, biosimilars in the BsUFA II Program with a first-cycle action share the same reference products as in BsUFA I, and FDA has held no AC meetings for BsUFA II applications.

Commitment Letter Recommendations

- (Intent to) Convene AC meetings no later than 2 months prior to the BsUFA goal date.
- LCM will occur not less than 12 calendar days before the date of the AC meeting.
- AC briefing package will accompany the LCM briefing document no less than 10 calendar days prior to the LCM.
- (Intent to) Provide final questions for the AC to the applicant and the AC 2 calendar days in advance of the AC meeting.

Post-AC Meetings

Post-AC meetings are held between FDA reviewers and applicants after an AC meeting. Because FDA has not held any AC meetings for the twelve 351(k) BLAs with a first-cycle action in the BsUFA II Program, no post-AC meetings have been held.

3.9 Inspections and Inspection Completion

Key Findings

- FDA completed 100% of inspections within 10 months of BsUFA II Program application receipt.
- A greater percentage of Program application inspections occurred earlier in the review cycle than in the baseline.
- Inspections for Program applications resulted in a Form 483 less often than inspections for baseline applications.
- In interviews, applicants stated that information and planning for inspections were direct and transparent.

Commitment Letter Expectation

- Complete all GCP/GLP/GMP inspections within 10 months of original receipt of the application.

In the BsUFA II Program, FDA strives to complete all inspections within 10 months of application receipt to allow time to resolve issues (if any) in the last two months of the review. For the purpose of this assessment, "all inspections" consists of Good Manufacturing Practice (GMP), Good Clinical Practice (GCP), and analytical similarity data inspections.[2] We define inspection completion as follows:

- ***GMP inspections:*** Complete on the date of the latest facility inspection conducted through the Office of Pharmaceutical Quality (OPQ).
- ***GCP inspections:*** Complete on the date of the latest clinical site inspection conducted by the Office of Scientific Investigations (OSI).
- ***Analytical similarity data inspections:*** Complete on the date of the latest analytical similarity site inspection conducted through OPQ.

In Spring 2020, the inspection process for BsUFA II Program applications began to be affected by travel restrictions coinciding with the COVID-19 pandemic. In some cases, FDA implemented alternatives to in-person inspections, such as remote document reviews, when risk assessments allowed. Due to uncertain timelines and dissimilar procedures used in those cases, ERG excluded alternative inspection task data (e.g., document review dates) from our interim assessment; if FDA continues to use alternative practices for a year or more, ERG will address these in our final assessment.

Numbers and Distributions of Inspections

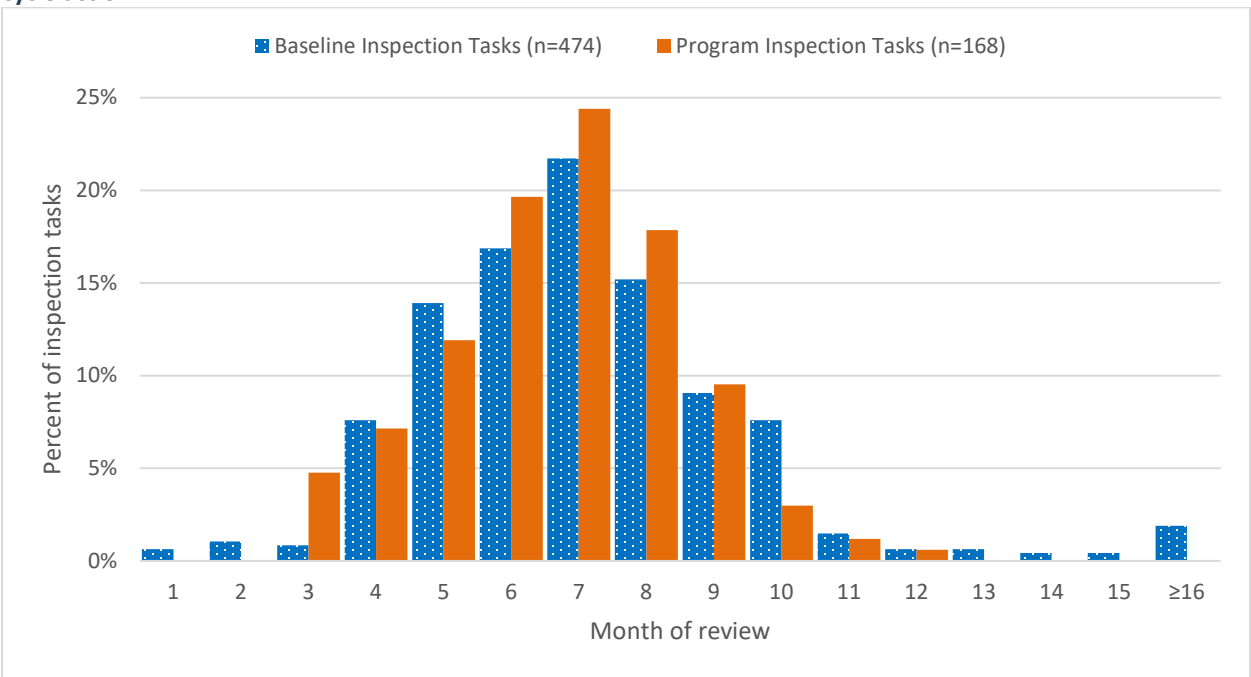
All 351(k) BLAs are associated with one or more sites that must be inspected as part of the application review, and each site undergoes one or more of the three types of inspections listed above. Thus, the number of inspections is greater than the number of 351(k) BLAs. ERG tracked the following inspection information:

[2] Good Laboratory Practice (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.

- ***Inspection completion date,*** *the date when FDA ends its GMP, GCP, or analytical similarity inspection at a site. Each inspection is associated with one completion date, so the number of inspection completion dates equals the number of site inspections.*
- ***Issue Form 483***, a document that an FDA inspector gives to an inspected site, usually on the last day of inspection, if deficiencies are found. The number of 483s is smaller than the number of inspections because FDA does not find deficiencies at all sites.
- ***Complete Establishment Inspection Report (EIR)***, a document that an FDA inspector creates after conclusion of a site inspection, usually within 30 days. The number of EIRs is usually close to the number site inspections.
- ***Make overall recommendation*** on the GMP, GCP, or analytical similarity acceptability of all the sites associated with a 351(k) BLA. In general, each 351(k) BLA is associated with three overall recommendations, one each for GMP, GCP, and analytical similarity.

Figure 3-8 illustrates the timing of these inspection tasks across baseline and BsUFA II Program applications with a first-cycle action. Most inspection tasks occurred between 4 and 10 months of application receipt and reached a peak at month 7 of the review in the baseline and Program. This is due to the numbers of inspections and EIRs that were completed within that time. In the baseline, inspections (168) and EIRs (167) were the most numerous inspection tasks, followed by 483s (71) and overall recommendations (68). Similarly, in the BsUFA II Program, inspections (58) and EIRs (54) have been the most numerous tasks to date, but overall recommendations (35) outnumbered 483s (21). As expected, the mean number of overall recommendations per application in the baseline and Program was three – one each for GMP, GCP, and analytical similarity inspections. The relatively low mean number of 483s per application in the Program (1.8) might represent a relatively higher level of site compliance compared to that observed in the baseline (3.1).

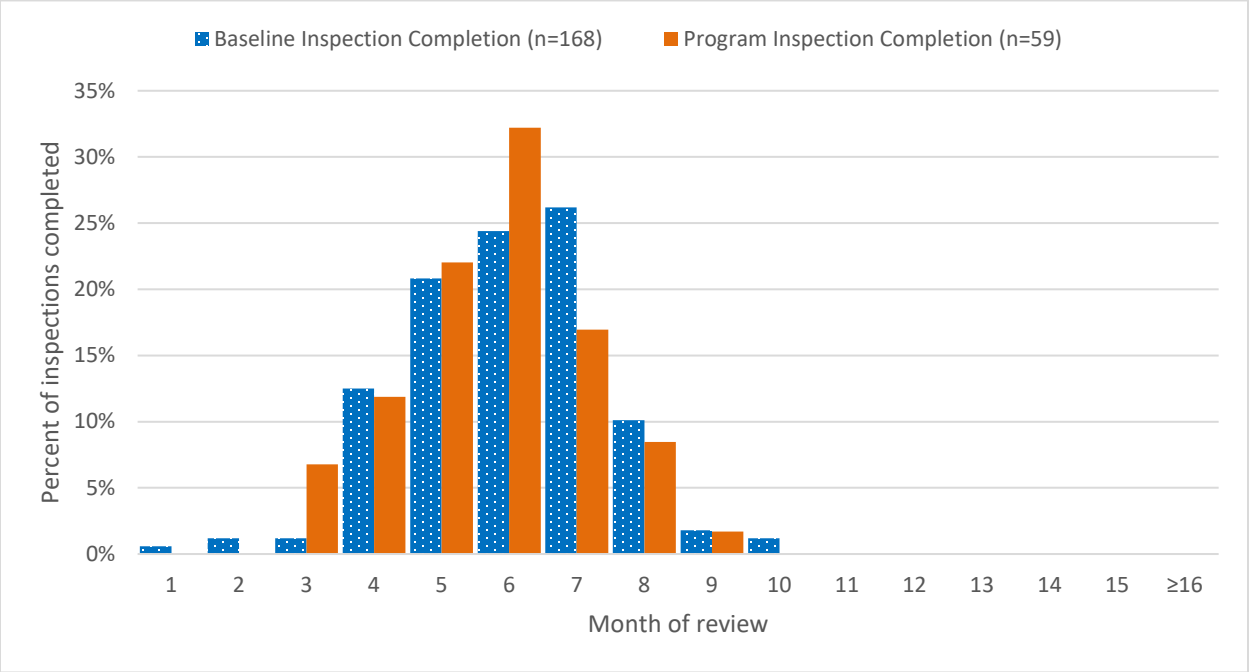
Figure 3-8. Timing of all inspection tasks for baseline (n=23) and BsUFA II Program (n=12) 351(k) BLAs with a first-cycle action



Inspection Completion Times

FDA completed on-site inspections within BsUFA II Program timetables for 100% of the applications received and acted on during the first three years of the Program (Figure 3-9). A greater percentage of Program application inspections occurred earlier in the review cycle than in the baseline. For Program applications with a CR, the number of inspections peaked at month 5, accounting for 38% of completed inspections, compared to the overall peak at month 6.

Figure 3-9. Timing of inspection completion for baseline (n=23) and BsUFA II Program (n=12) 351(k) BLAs with a first-cycle action



Interview Feedback

In post-action interviews, most applicants felt that information and planning for inspections were direct and transparent; a few applicants felt that more transparency and communication surrounding the timing and logistics of inspections could be beneficial. Reviewers noted that when applicants occasionally did not identify the sites for inspections in applications on original submission, these omissions were resolved before filing. The CMC team then requested this information via IRs. Review teams added that GMP and analytical similarity data inspections were occasionally combined if these inspections were being done at the same site, increasing efficiency. Table 3-20 provides a summary of applicant and FDA review team feedback on inspections.

Table 3-20. Post-action interview feedback on inspections, FYs 2018-2020

Applicants (10 interviews)	FDA Reviewers (11 interviews)
• Information on inspections was generally direct and transparent • Flexibility in scheduling inspections was helpful, especially if the applicant was working with a Contract Manufacturing Organization. • If FDA is combining the GMP and biosimilarity inspections, communicate this to the applicant • Challenges emerged when FDA conducted an inspection early, but sent queries late in the review (less common opinion)	• Inspections generally occurred within expected timelines • Inspections early in the review cycle provided time for applicant to address issues and reinspect in one review cycle • Some inspections were held late in the review cycle, jeopardizing approval if issues were identified (less common opinion)

3.10 Information Requests (IRs) and Amendments

Key Findings

- FDA issued fewer IRs per application in the BsUFA II Program than in the baseline, yet applicants submitted roughly the same number of amendments per application in the Program and baseline.
- Amendments in the Program and baseline were most often related to Product Quality.
- Most amendments were solicited by FDA or routine; unsolicited amendments were less frequent in the Program than in the baseline.

IRs and Amendments

Throughout the review of an application, FDA can issue an IR to the applicant if the review team determines that more information is necessary to move forward with the review. A given IR can include one or more requested items, which we call "IR items" in this report. In response to an IR, the applicant may submit an amendment to their application; an amendment can include one or more items, which we call "amendment items" in this report. IRs and amendments represent one indication of the level of information exchange taking place between FDA review teams and applicants.

Values for metrics related to IRs and amendments appear in Table 3-21 and Table 3-22. On average, FDA issued fewer IR items per application in the first three years of the BsUFA II Program than in the baseline, while the number of amendment items submitted by applicants per application increased. Note that the number of IRs (or IR items) does not align with the number of amendments (or amendment items) for several reasons. For example, not all IRs sent by FDA are documented as "information requests" in FDA's Document Archiving, Reporting, and Regulatory Tracking System (DARRTS), and applicants sometimes bundle or disaggregate responses to IRs. Moreover, FDA's databases do not link amendments with IRs, so these relationships cannot be ascertained readily.

Table 3-21. Number of IRs and requested items in baseline (n=23) and BsUFA II Program (n=12) 351(k) BLAs

	Baseline	Program
Mean number of IRs per application	19	12
Median number of IRs per application	17	10.5
Range of numbers of IRs per application	40 [5, 45]	15 [4, 19]
Mean number of requested items per application	62	23
Median number of requested items per application	34	20.5
Range of number of requested items per application	239 [9, 248]	50 [5, 55]

Table 3-22. Number of amendments and amendment items in baseline (n=23) and BsUFA II Program (n=12) 351(k) BLAs

	Baseline	Program
Mean number of amendments per application	37	34
Median number of amendments per application	35	38.5
Range of number of amendments per application	26 [30, 56]	28 [19, 47]
Mean number of amendment items per application	91	149
Median number of amendment items per application	68	128
Range of number of amendment items per application	308 [33, 341]	230 [37, 267]

The largest proportion of IR items in BsUFA II Program application reviews involved Clinical issues, followed by Product Quality issues; the reverse was true in the baseline (Figure 3-10). Despite the greater number of Clinical IRs in the Program, most amendment items for Program as well as baseline applications pertained to Product Quality (Figure 3-11). This might reflect a change in review management practices, where Product Quality IRs are less often recorded in DARRTS and more often recorded in a separate FDA database; for the final assessment, ERG will examine IRs in the other database to determine how they affect results. Application amendments are submitted to a single database, so there has been no change in how they are counted.

Figure 3-10. Percent of IR items for baseline (n=23) and BsUFA II Program (n=12) 351(k) BLAs with a first-cycle action, by review discipline

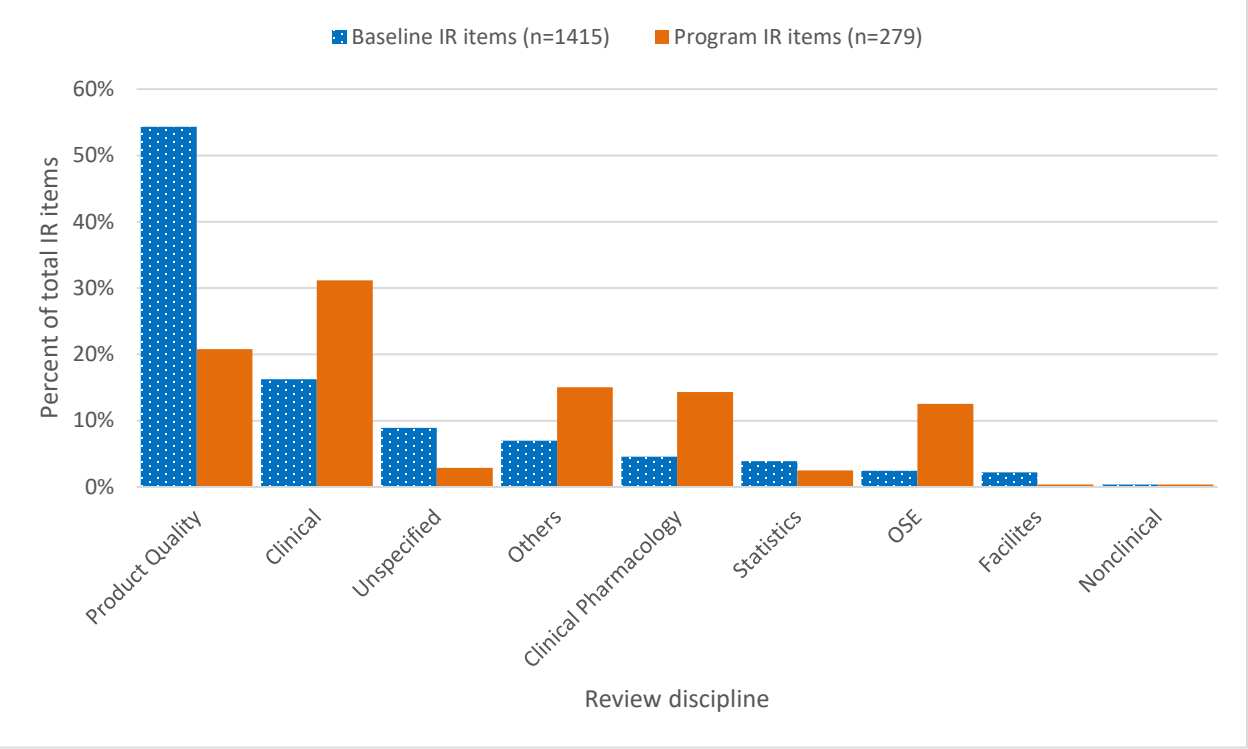
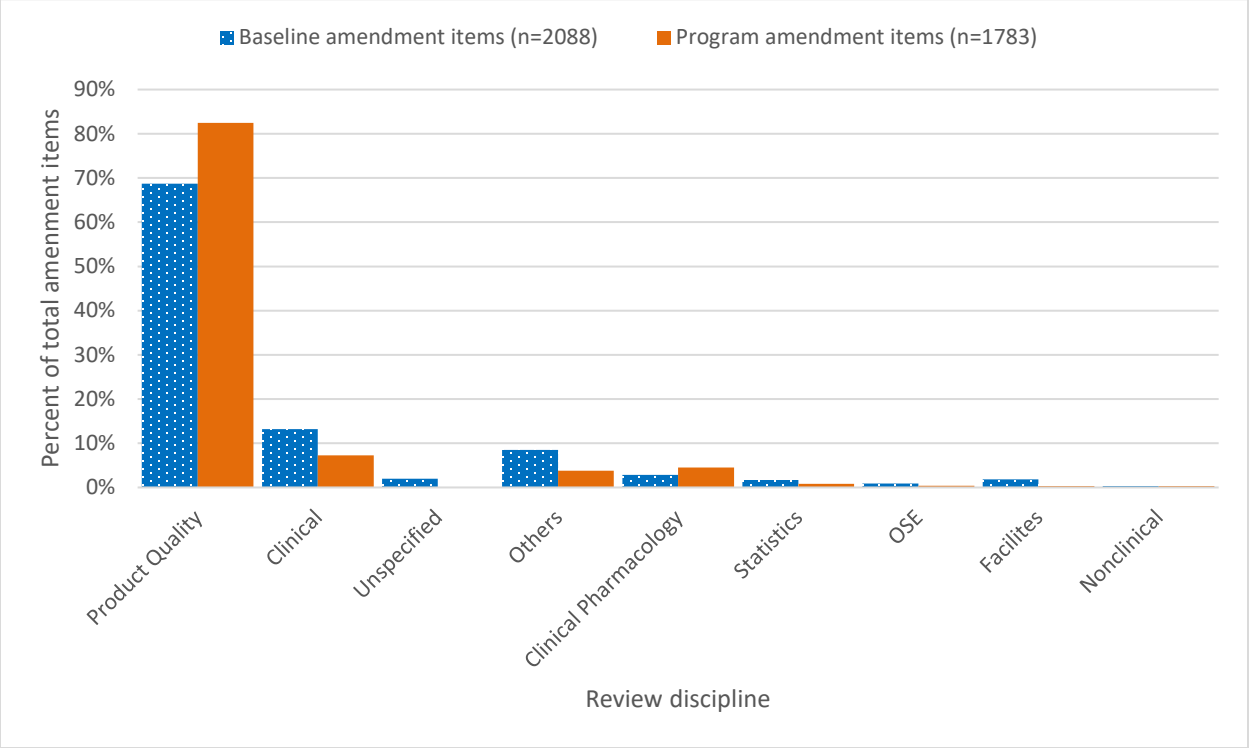


Figure 3-11. Percent of amendment items for baseline (n=23) and BsUFA II Program (n=12) 351(k) BLAs with a first-cycle action, by review discipline



ERG also examined the temporal distribution of IRs and amendments (Figure 3-12 and Figure 3-13). FDA issued the greatest proportions of IRs (and IR items) in the months around the filing date and the mid-cycle date. In the BsUFA II Program, the number of IRs also increased slightly near the LCM timeframe, in month 10.

For baseline and Program 351(k) BLAs, applicants submitted amendments throughout the review cycle, with a small peak after the filing date and a second, larger peak after the mid-cycle date (Figure 3-13). The greater difference in magnitude of amendment items in the second peak reflects the higher density of information in amendments after mid-cycle. IRs and amendments after month 12 (Program) or month 10 (baseline) were associated with reviews of applications with goal extensions.

Figure 3-12. Timing of IRs and IR items in the review cycle for baseline (n=23) and BsUFA II Program (n=12) 351(k) BLAs with a first-cycle action

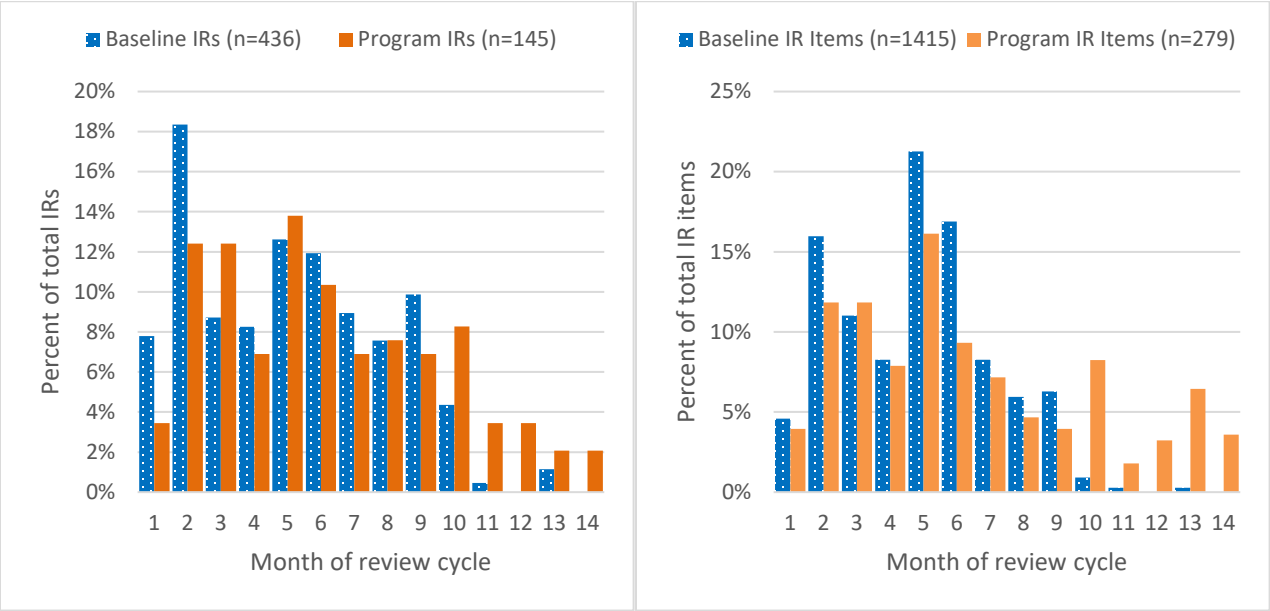
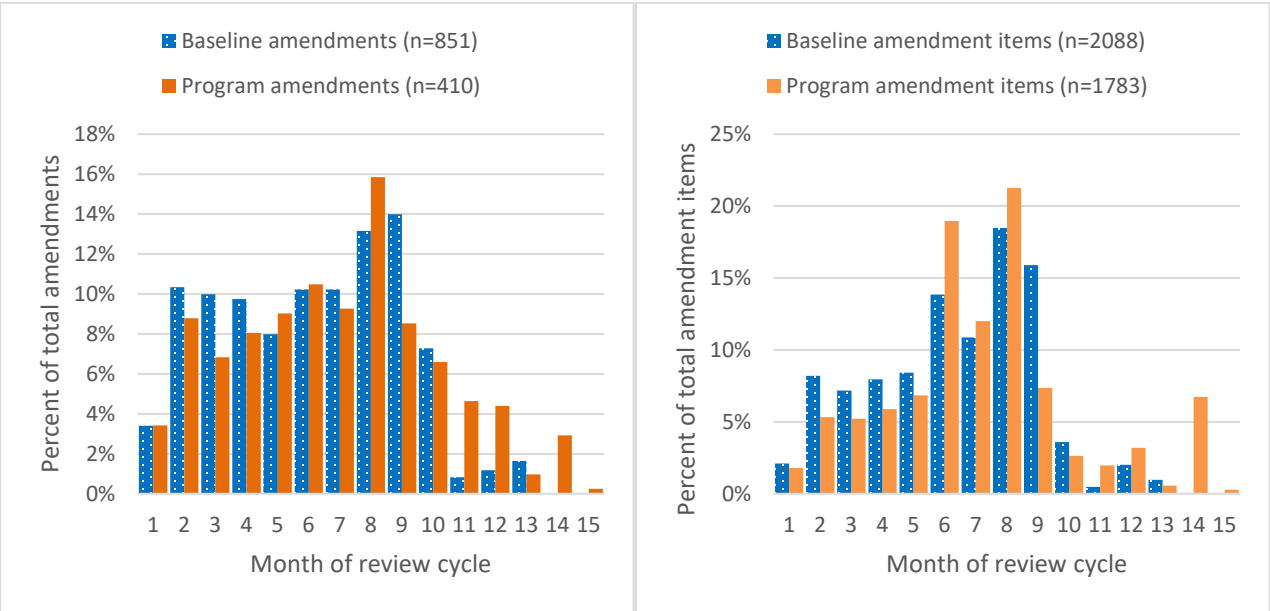


Figure 3-13. Timing of amendments and amendment items in the review cycle for baseline (n=23) and BsUFA II Program (n=12) 351(k) BLAs with a first-cycle action



Unsolicited Amendments

For the purpose of this assessment, ERG groups amendments into three categories:

- Solicited (requested in an IR from FDA)
- Routine (not solicited but expected by FDA, such as proprietary name review requests and safety updates)
- Unsolicited (not solicited and not expected by FDA; does not reference an FDA IR)

Most amendments submitted to FDA during the review of an application are solicited by FDA or routine and are a typical part of the information exchange process. Unsolicited amendments are not as frequent, but they can be disruptive to the review if they contain a large volume of data or affect FDA's regulatory decision on an application. Such amendments could constitute a major amendment and result in a BsUFA goal date extension. Since Program applications are expected to be complete upon submission, unsolicited amendments are expected to be rare.

The mean number of unsolicited amendment items per application was lower in the BsUFA II Program (0.8) than in the baseline (1.4). Figure 3-14 presents the distribution of unsolicited amendment items submitted by BsUFA II Program and baseline applicants by month of application review. Figure 3-15 shows the distribution of unsolicited amendments by topic/discipline, and Table 3-23 provides examples.

In 12 Program applications with a first-cycle action, 6 had at least one unsolicited amendment. Applications with at least one unsolicited amendment received a first-cycle AP 67%) slightly less often than applications without unsolicited amendments (83%). The numbers are too small to draw conclusions about the relationship between unsolicited amendments and regulatory outcomes.

Figure 3-14. Timing of unsolicited amendment items in baseline (n=23) and BsUFA II Program (n=12) 351(k) BLAs with a first-cycle action

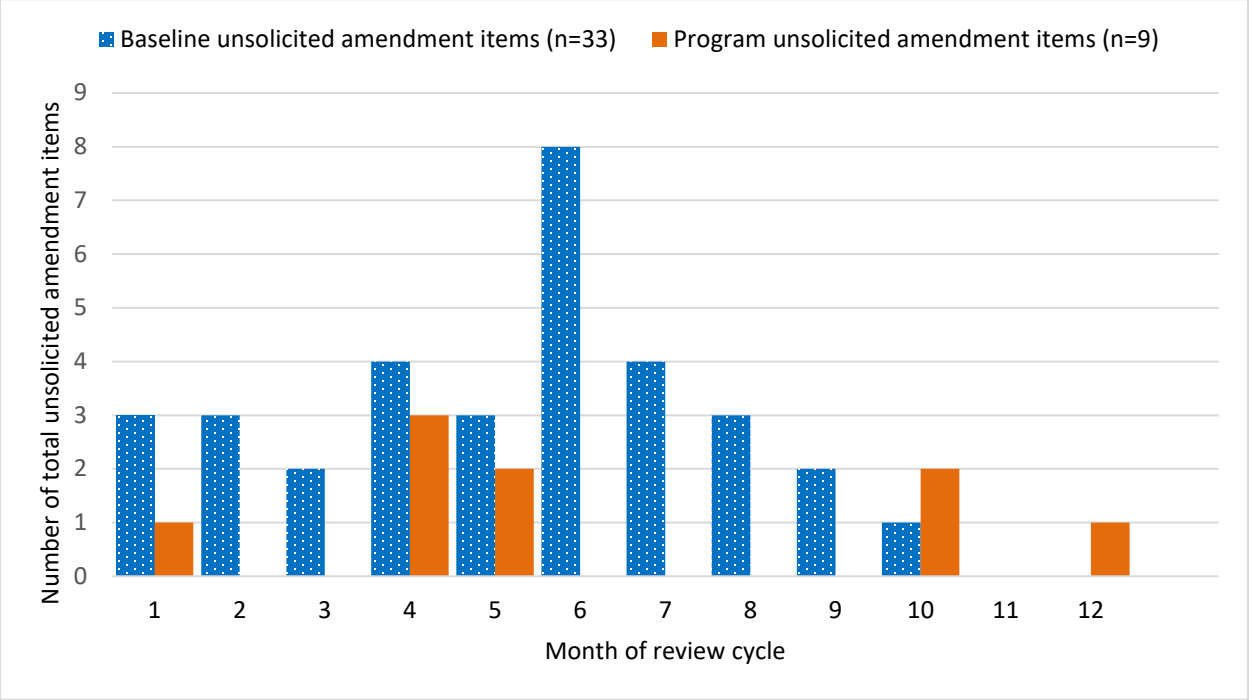


Figure 3-15. Distribution of unsolicited amendment item topics in baseline (n=23) and BsUFA II Program (n=12) 351(k) BLAs with a first-cycle action

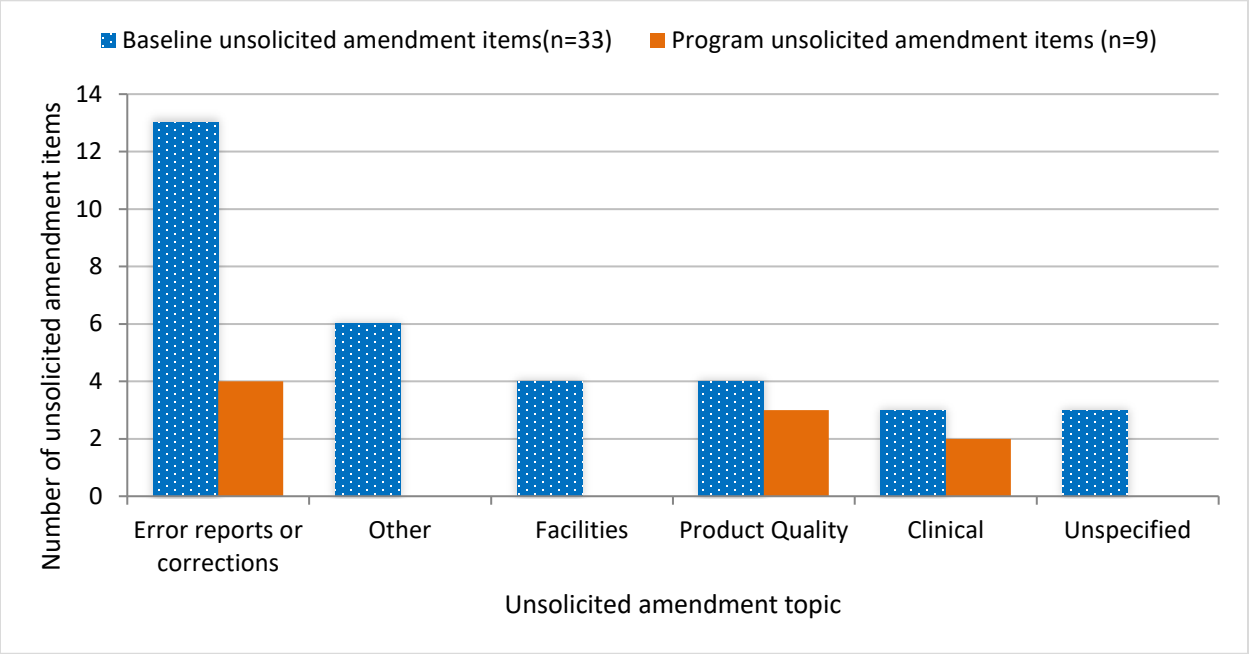


Table 3-23. Unsolicited amendment items for baseline (n=23) and BsUFA II Program (n=12) 351(k) BLAs with a first-cycle action

Category	Examples of Unsolicited Amendments
Error reports or corrections	Error report describing minor corrections to Module 3
	Corrected clinical study report (CSR) tables
	Corrected Module 5
	Errata for clinical studies
	Correction of transcription errors in Module 3
Product Quality	Notification of out-of-spec incident with manufacturing non-market product
	Shipping verification summary report
	Manufacturing schedule update
	Notification of damage to records
Clinical	Small updates to specific areas of a previously submitted CSR
	CSR addendum
	Revised summary of clinical safety
Facilities	Withdrawal of testing facility
	Clinical study information to facilitate Bioresearch Monitoring Program (BIMO) inspections
	Updated list of authorized representatives
Other	Change of address/contact
	Implications of a delayed FDA decision
Unspecified	Notification of adverse event regarding an EU-approved biosimilar
	Confidential response to Citizen's Petition
	Extrapolation document

3.11 Good Review Management Principles and Practices

Key Findings

- 100% of Program applications reached first-cycle action by the BsUFA goal date.
- 83% of Program Day 74 letters were issued by day 74 of the review.

FDA's Good Review Management Principles and Practices (GRMPs) are intended to promote the practice of good review management based on sound fundamental values and principles, and to support an effective and efficient application review process in the first cycle of review. In the context of the BsUFA II Program, GRMPs are the basic structure that the Program builds upon to enhance the efficiency and effectiveness of first-cycle reviews – by ensuring more complete original application submissions, adding opportunities for communication between the FDA and applicant, and adhering to consistent timelines associated with the Program.

For the purpose of this assessment, ERG cross-referenced our Program metrics with measurable GRMP timelines[3] to assess FDA and applicant adherence to existing GRMPs. Two of our metrics overlap with GRMP timelines.

In the BsUFA II Program thus far, FDA reviewed 92% of applications within 10 months of the 60-day filing date; the remaining 8% (one application) received a goal extension and was reviewed within 13 months of the 60-day filing date. By GRMP standards, this means that 100% of Program applications received a regulatory action by the BsUFA goal date (Table 3-24).

In the BsUFA II Program thus far, FDA signed and issued 83% of Day 74 letters by day 74; FDA signed and issues 17% of the Day 74 letters (2 of 12) on day 75, missing the goal by a single day.

Table 3-24. Metrics results for BsUFA II Program 351(k) BLAs (n=12) with similar GRMPs

Program Assessment Metric	Result	Applicable GRMP(s)	Result
Percent of 351(k) applications reviewed within 10 months of the 60-day filing date	92%	Action, by BsUFA goal date	100%
Percent of Day 74 letters issued within 74 days after application receipt	83%	Communicate filing review issues to applicant, by day 74	83%

[3] "Good Review Management Principles and Practices for New Drug Applications and Biologics License Applications," September 2018

4. Assessment Questions and Answers

4.1a What is the relationship between Program attributes and 351(k) application first-cycle regulatory outcome?

One of the goals of the Program is to improve the effectiveness and efficiency of the first review cycle of original 351(k) 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. Thus, first-cycle approval rate is one potential measure of review effectiveness and efficiency.[4] Another measure is number of review cycles to reach approval; because the Program has not been in place long enough for applications to undergo multiple review cycles, ERG was unable to use this measure in our interim assessment of the Program. If possible, we will use this measure in our final assessment, when we will have another year of Program data.

Based on data from the first three years of the BsUFA II Program (FYs 2018-2020) and the baseline (FYs 2013-2017), ERG found that first-cycle approval rates in the Program (75%) were higher than in the baseline (39%). The numbers of applications are small, so we cannot assess the statistical significance of this difference. Nevertheless, based on the quantitative data, observations, and feedback from post-action interviews developed to date, it is reasonable to conclude that the BsUFA II Program has created conditions that enhance the ability of applicants and FDA reviewers to work toward application approval in the first review cycle.

It is important to note that applicants interviewed for this assessment viewed the BsUFA II Program as having value in terms of enhanced review transparency, communication, predictability, and efficiency regardless of its impact on first-cycle regulatory outcome.

4.1b What is the relationship between Program attributes and 351(k) application first-cycle regulatory action time?

Another measure for improved effectiveness and efficiency of 351(k) BLA reviews could 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. [5] Because no BsUFA II Program applications have been resubmitted in FYs 2018-2020, data are insufficient to evaluate mean overall time to approval. Therefore, we focus only on mean time from application submission to first-cycle approval.

[4] 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.

[5] 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.

Based on data from the first three years of the BsUFA II Program (FYs 2018-2020) and the baseline (FYs 2013-2017), ERG's analyses revealed that first-cycle reviews for Program applications were longer than those for baseline applications—an unsurprising result given that there is a 2-month difference in the review clocks. Nevertheless, if the Program has created conditions that enhance the ability of applicants and FDA reviewers to work toward application approval in the first review cycle, over time 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); this possibility cannot be evaluated at this time.

We reiterate that applicants interviewed for this assessment viewed the BsUFA II 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.

4.2a What is the relationship between review process attributes and 351(k) application first-cycle regulatory outcome?

Due to the small number of applications in BsUFA II to date, the data are insufficient to determine any relationships between review process attributes and first-cycle approval.

The data thus far do suggest the possibility of a relationship between the timing of inspection completion and first-cycle outcome: on average, FDA completed most inspections around month 6 of review for BsUFA II Program applications with a first-cycle approval, compared to month 5 for applications that received a CR. This might reflect use of the latter months of the review to resolve inspection issues for applications that were approvable, which was not done for applications that were not approvable. In any case, the data are insufficient to draw firm conclusions. In the baseline, ERG found no differences in the timing of inspections between applications receiving first-cycle AP or CR.

4.2b What is the relationship between review process attributes and 351(k) application first-cycle regulatory action time?

Due to the small number of applications in BsUFA II to date, the data are insufficient to determine any relationships between review process attributes and mean time from application submission to first-cycle action.

4.2c What is the relationship between application attributes and 351(k) application first-cycle regulatory outcome?

In BsUFA II, the data suggest a possible relationship between an application's proposed indications and first-cycle approval: applications with solely oncologic indications were less likely to receive a first-cycle approval (50%) than applications with other indications (100%). The data are insufficient to determine whether this difference is statistically significant or meaningful; the difference could be an artifact of the high prevalence of oncologic indications for biosimilar biological products.

Baseline and BsUFA II Program applications with a major amendment were associated with a higher first-cycle approval rate (100%) than those without a major amendment (30%, baseline; 73%, BsUFA II). This aligns with the expectation that FDA will accept and review a major amendment when the Agency believes

that this will lead to approval in the first cycle rather than requiring resubmission and a second cycle of review. Again, we caution that the numbers are too small to assess statistical significance or draw firm conclusions.

4.2d What is the relationship between application attributes and 351(k) application first-cycle regulatory action time?

The overall review clock from application receipt to regulatory action is 2 months longer in the BsUFA II Program than it was in the baseline. As expected, the median time to first-cycle action was 2 months longer for applications in the Program than in the baseline.

In both the baseline and BsUFA II Program, one application attribute was associated with a longer mean time from application to first-cycle action: a major amendment resulting in a 3-month goal extension. This is expected given that a 3-month extension by definition affects time to regulatory action.

Another measure of interest is overall mean time from original submission to approval, including approvals achieved in second or additional review cycles. In the first three years of the Program, no applications had been resubmitted and acted on in a second review cycle, so ERG was unable to compare overall mean time to approval in the BsUFA II Program with that in the baseline. If data are sufficient, ERG will do so for our final report.

4.3a How do applicants and FDA review staff characterize enhanced communication under the Program?

Applicants

Applicants characterized communications in the BsUFA II Program favorably:

- ***Overall –*** Excellent, constructive, and in the spirit of collaboration. Many applicants stated that communications improved in the BsUFA II Program compared to BsUFA I. Many also commented that coordination between divisions and other FDA groups was effective.
- ***BPD Type 4 Meeting –*** Constructive and valuable opportunity to understand FDA's expectations for a complete application, ask questions about organization, and agree on late application elements. These meetings were especially helpful when FDA provided templates demonstrating desired application organization.
- ***Milestone communications (MCC and LCM) –*** Valuable opportunities to communicate with FDA during the review process, gain a shared understanding of potential review issues, and resolve questions and issues whenever possible. Some applicants suggested further enhancing the value of MCCs and LCMs by (1) allowing applicants to propose agenda items and (2) providing the agenda earlier to give the applicant more time to prepare. Some applicants noted that the AOM (an option in the BsUFA II Program) was a valuable opportunity to discuss the application's contents and organization with the review team.

- ***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, and were willing to establish and negotiate reasonable due dates for IRs***.***

A few applicants suggested FDA could further improve communications by:

- Providing updates on review activities after the LCM.
- Notifying the applicant if/when FDA considers IRs and substantive issues to be resolved.
- Providing advance notice of the likelihood of an IR – and bundling IRs when possible.

FDA Review Staff

Like applicants, FDA review staff characterized communications in the BsUFA II Program favorably:

- ***Overall –*** Excellent, constructive, collaborative, efficient, and effective.
- ***BPD Type 4 Meeting –*** Constructive and valuable opportunity to convey expectations, to provide templates, and to agree on any late application elements. Some reviewers felt that this meeting might not be as useful for applicants with previous experience submitting a 351(k) BLA.
- ***Milestone communications (MCC and LCM) –*** Most review staff affirmed with varying degrees of enthusiasm that MCCs and LCMs contributed to enhanced communication, transparency, and predictability. They commented that these meetings provided a useful opportunity to discuss substantive review issues, and that the meetings provided structure to the review process. Some reviewers felt that these meetings were unnecessary when substantive issues did not need to be discussed; they favored an ability to "opt out" in those circumstances.

4.3b How do applicants and FDA review staff characterize application reviews under the Program?

Applicants

Applicants characterized application reviews in the BsUFA II Program as transparent, predictable, and efficient:

- ***Transparent –*** In interviews, applicants characterized application reviews in the BsUFA II Program as very transparent. They credited this transparency to the combination of (1) big-picture multidisciplinary status updates provided during the MCC and LCM, and (2) focused updates provided on an ongoing basis during email and telephone interactions with the RPM.
- ***Predictable –*** In interviews, applicants characterized application reviews in the BsUFA II Program as very predictable. They credited this predictability to (1) the MCC and LCM, which "anchor" reviews with predictable milestones that provide updates on review status and plans for future steps and milestones, and (2) the FDA review team's commitment to moving the review forward efficiently.

Some applicants acknowledged that there will always be some degree of unpredictability in the review process; for example, although FDA strives to notify applicants about potential or actual review issues early in the review, in some cases a reviewer might not discover a deficiency until the applicant has responded to several IRs.

- ***Efficient –*** Applicants observed that FDA reviewers were effective in moving reviews forward efficiently.

A few applicants suggested that FDA further enhance the review process by giving applicants more time to respond to IRs and labeling changes, especially when the applicant is part of a global team. They noted, however, that FDA staff were often flexible in adjusting IR timelines or allowing applicants to respond initially via email when asked.

FDA Review Staff

Like applicants, most FDA review staff characterized application reviews in the BsUFA II Program as transparent, predictable, and efficient. As noted above, some reviewers suggested altering the review process to provide an opportunity to "opt out" of MCCs and LCMs when there are no substantive issues to discuss. A few reviewers commented that the additional two months for review (gained by starting the review clock at application filing instead of receipt) did not increase the amount of time available for primary reviews because this time is consumed by communications with OTBB and other late review activities. They also noted that inspections conducted close to the end of the review cycle were challenging if they uncovered manufacturing deficiencies. These reviewers proposed adjusting the review to allow more time for primary reviews and moving inspections earlier (to allow time for reinspection, if needed).

5. Preliminary Findings and Recommendations

This section provides preliminary findings and recommendations regarding BsUFA II Program implementation, categorized by type (overarching, specific). Please note that these preliminary findings and recommendations might change based on additional data collected during the next year of the Program.

Table 5-1. Interim findings and recommendations

Type	No.	Interim Finding	Interim 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 (MCCs and LCMs) have enhanced the predictability of reviews by: • Serving as "anchor" points for review work and planning. • Providing a forum for multidisciplinary discussion of application status and paths forward to resolve approvability issues promptly, if possible.	No action needed.
	O3	By requiring application completeness, the Program has enhanced the ability of FDA to conduct first-cycle reviews more efficiently and effectively.	No action needed.
Specific	S1	In the BPD Type 4 meeting process, providing pre-submission advice and templates for application content and organization helps sponsors prepare applications that meet FDA expectations.	Establish this as good practice in the BPD Type 4 meeting process.
	S2	LCMs have generally been most valuable to applicants when they were able to discuss additional topics of interest (e.g., inspections, PMRs/PMCs, labeling) with FDA.	Consider soliciting discussion topics from the applicant and allocating time in the LCM agenda for applicant-identified discussion topics.
	S3	FDA communication regarding inspections has generally been clear, allowing for good inspection coordination and contributing to overall review transparency and predictability.	No action needed.
	S4	FDA target dates for IR responses were sometimes impractical for applicants with a global presence. In some cases, time zone differences prevented one or two-day response times.	Where feasible, propose IR response times of more than two days or issue IRs earlier to allow for extended response times.

Appendix A. Acronyms and Glossary

Acronyms

Acronym	Term
AC	Advisory Committee
ACA	Affordable Care Act
AOM	Application Orientation Meeting
AP	Approval
BIMO	Bioresearch Monitoring Program
BLA	Biologics License Application
BPCI	Biologics Price Competition and Innovation Act
BPD	Biosimilar Biological Product Development
BsUFA	Biosimilar User Fee Act
CDRH	Center for Devices and Radiological Health
CMC	Chemistry, Manufacturing, and Controls
CR	Complete Response
CSR	Clinical Study Report
DARRTS	Document Archiving, Reporting, and Regulatory Tracking System
DR	Discipline Review
EIR	Establishment Inspection Report
ERG	Eastern Research Group, Inc.
FCP	Formal Communication Plan
FDA	Food and Drug Administration
FY	Fiscal Year
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
OMB	Office of Management and Budget
OPQ	Office of Pharmaceutical Quality
OSI	Office of Scientific Investigations
OTBB	Office of Therapeutic Biologics and Biosimilars
PHS	Public Health Service
PMC	Postmarket Commitment
PMR	Postmarket Requirement
Post-AC	Post-Advisory Committee
RBPM	Regulatory Business Project Manager
RPM	Regulatory Project Manager
RTF	Refuse to File
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 product's approval.

> **BsUFA II Commitment Letter**
>
> - (Intent to) Convene AC meetings no later than 2 months prior to the BsUFA goal date.
> - LCM will occur not less than 12 calendar days before the date of the AC meeting.
> - AC briefing package will accompany the LCM briefing document no less than 10 calendar days prior to the LCM.
> - (Intent to) Provide final questions for the AC to the applicant and the AC 2 calendar days in advance of the AC meeting.

Amendment (Major, Routine, Solicited, Unsolicited): Additional data or analysis submitted by an applicant after original submission of an application.

Major Amendment – Submission of significant data that is expected to substantially increase the burden on the FDA review team, allowing FDA to exercise a three-month extension of the BsUFA goal date at the discretion of the signatory authority.

Routine Amendment – Data or other submission not requested by FDA in an IR but nevertheless expected during the review process.

Solicited Amendment – Data or other submission requested by FDA in an IR.

Unsolicited Amendment – Non-routine data or analysis submission from the applicant that was not requested by FDA.

Applicant: Any entity that submits or plans to submit an application to FDA for premarket review.

Approval (AP): FDA regulatory action on an application (in this case, an original 351(k) BLA) that allows the applicant to commercially market the product; communicated in an approval letter.

Baseline Cohort: All original 351(k) BLAs received in FDA CDER and CBER under BsUFA I (FYs 2013-2017). Data from the baseline cohort serves as the baseline from which to measure impacts of the BsUFA II Program for Enhanced Review Transparency and Communication for Original 351(k) BLAs.

Biologics License Application (BLA): Is the application a manufacturer of a biosimilar or interchangeable product submits under section 351(k) of the PHS Act to FDA for consideration of approval

Biosimilar Biological Product Development (BPD) Type 4 meeting: Optional meeting requested by a sponsor who intends to submit a marketing application. Held between FDA and sponsors prior to application submission to discuss application content, format, and other preparatory topics.

BsUFA II Commitment Letter

- Should occur 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.
- If applicable, include preliminary discussion on REMS or other risk management strategies.
- If applicable, discuss patient labeling.
- If applicable, develop a Formal Communication Plan.
- Summarize agreements and discussions.
- Recommended to hold a BPD Type 4 meeting prior to application submission.

Biosimilar User Fee Act (BsUFA): The Biosimilar User Fee Act (BsUFA) was created as part of the Affordable Care Act (ACA), signed into law in 2010. The ACA contains a subtitle called the Biologics Price Competition and Innovation Act of 2009 (BPCI Act) that amends the Public Health Service (PHS) Act and other statutes to create an abbreviated approval pathway for biosimilar and interchangeable biological products. Section 351(k) of the PHS Act, added by the BPCI Act, allows a sponsor to submit an application for licensure of a biosimilar or interchangeable biological product. The BPCI Act directed the Food and Drug Administration (FDA) to develop recommendations for a user fee program for 351(k) applications for Fiscal Years (FYs) 2013 through 2017. In 2017, BsUFA was reauthorized for FYs 2018 through 2022.

BsUFA Goal Date: The prespecified date that FDA expects to issue a regulatory decision on an application. Under the Program, applications receive a 10-month review clock that officially begins on the filing date of the original submission.

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 351(k) BLAs received by CBER during BsUFA II will be reviewed under the Program.

Center for Drug Evaluation and Research (CDER): FDA organization that regulates over-the-counter and prescription drugs, including biological therapeutics and generic drugs, for human use and ensures that these products are safe, effective, and available to those who need them. Original 351(k) BLAs received by CDER during BsUFA II are reviewed under the Program.

Complete Response (CR): A CR action provides a consistent and neutral mechanism to convey to an applicant that FDA's initial review of an application is complete but FDA cannot approve the application in its present form. The CR action informs applicants of changes that must be made before an application can be reconsidered, but with no implication regarding the ultimate approvability of the application.

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: 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 planned review timeline, potential review issues, and preliminary plans on whether to hold an AC meeting.

For the purpose of the Program evaluation, the Day 74 letter is any formal correspondence that closes the Day 74 goal, along with other documents/letters included by reference (e.g., filing notification letter sent within 60 days of original application submission that does not communicate identified issues). *Synonym: filing letter/communication* (when referring to Day 74 letter and associated documents sent to applicant about application filing).

BsUFA II Commitment Letter

- Will use existing procedures on issuing Day 74 letters.
- Send within 74 calendar days of FDA receipt of original submission.
- Include notification of potential review issues.
- Include planned review timeline:
  - Planned date for internal mid-cycle review meeting.
  - Preliminary plans on whether to hold an AC meeting.
  - Target date for communicating FDA feedback on proposed labeling and FDA-requested postmarketing requirements and commitments.

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

CDER

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

CBER

- Clinical
- CMC
- Nonclinical
- Pharm/Tox
- Human Pharmacokinetics
- Bioavailability
- Facilities
- 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.

> **BsUFA II Commitment Letter**
>
> - Follow existing guidance on issuing DR letters.
> - Send before planned LCM or include in LCM background package.

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

Eastern Research Group, Inc. (ERG): Independent contractor enlisted to design and conduct the interim and final assessments of the Program for Enhanced Review Transparency and Communication for Original 351(k) BLAs in BsUFA II.

Establishment Inspection Report (EIR): Document created by an FDA inspector after conclusion of a site inspection. Completed within 30 days after inspection under normal circumstances.

Evaluation Metrics: Measurements used to evaluate the activities, performance, or impacts of a program. Evaluation metrics, when combined with context-based qualitative analysis, enable ERG to answer assessment questions about associations between Program, review process, and application attributes and review timeliness and outcomes.

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

Filing Notification Letter: Formal correspondence that the FDA review team sends to an applicant to communicate FDA's filing decision, review classification of application, and user fee goal date. Also see "Day 74 Letter".

First-Cycle Action: Regulatory decision (AP, CR, or WD) on an application that concludes FDA's first cycle of review and closes the BsUFA goal date; includes decisions on applications that previously received an RTF or WF, but not decisions on resubmissions after a CR.

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.

[FDA] Form 483: Document issued to an inspected site by an FDA inspector if deficiencies are found. Typically issued on the last day of inspection.

Formal Communication Plan (FCP): An optional alternate approach to the timing and nature of Program communications between FDA review teams and applicants. FCPs may include elements of the standard Program approach and other interactions sometimes used in the review process. Newly introduced by the BsUFA II Program.

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

Good Manufacturing Practice (GMP): A regulation containing minimum requirements for the methods, facilities, and controls used in manufacturing, processing, and packing of a 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 Day 74 and DR letters to the applicant, and as separate communications. For the purpose of the Program evaluation, ERG counts IRs issued during meetings, in Day 74 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 review discipline.

Inspection: For the BsUFA II Program assessment, relevant inspections include pre-license inspections supporting the review of an original 351(k) BLA. Inspections are expected to be complete for applications in the BsUFA II Program within 10 months of original receipt of the application. The remaining 2 months in the review cycle are intended to be used for addressing any inspection deficiencies.

BsUFA II Commitment Letter

- Complete all GCP/GLP/GMP inspections within 10 months of original receipt of the application.

Issue/Deficiency: 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.

Late-Cycle Meeting (LCM): Meeting (usually face-to-face) held near the end of the review cycle between members of the FDA review team and the applicant to discuss the status of the review.

BsUFA II Commitment Letter

- 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.
  - Analytical similarity data.
  - Data to support demonstration of no clinically meaningful differences, including immunogenicity.
  - Data to support interchangeability.
  - Product quality issues.
  - Inspection findings.
  - If applicable, AC issues/topics.
  - If applicable, assessment of REMS or other risk management actions.
  - Information requests or additional data applicant wishes to submit.

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

BsUFA II Commitment Letter

- Ensure that RPM and appropriate review team members are present.
- Hold as a teleconference.
- Conduct within 2 weeks of internal mid-cycle meeting.
- Send agenda prior to MCC.
- Include significant issues identified to date.
- Include any IRs.
- Include major concerns with:
  - Analytical similarity data.
  - Data to support demonstration of no clinically meaningful differences, including immunogenicity issues.
  - Data to support interchangeability.
  - Product quality.
- If applicable, notify applicant about preliminary thinking on risk management.
- Notify applicant of proposed date for LCM.
- If applicable, provide update on plans for an AC.
- Provide projected milestone dates for remainder of review cycle.

Mid-Cycle Meeting: Internal FDA meeting about an application held by month 5 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 AC meeting.
- Identify any issues that could preclude an AP action.
- Begin high-level discussion of labeling and need for post-marketing requirements and/or commitments.
- Determine if a 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".

Office of Surveillance and Epidemiology (OSE): Office at FDA within CDER responsible for maintaining a system of postmarketing 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.

Postmarketing Commitments (PMCs): Studies or clinical trials that an applicant has agreed to conduct, but are not required by a statute or regulation.

Postmarketing Requirements (PMRs): Studies and clinical trials that applicants are required to conduct under one or more statutes or regulations.

Primary Reviews: Reviews conducted by specified 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)

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 these primary review disciplines.*

Product Quality: The Product Quality review discipline includes topics identified by either applicants or FDA as:

- Analytical similarity
- Biopharmaceutics
- Chemistry
- CMC
- Immunogenicity
- Microbiology (quality)
- Product quality
- Quality

[The] Program: The Program is a new review model implemented by FDA under the second authorization of the Biosimilar User Fee Act to improve review transparency and communications between FDA review teams and applicants of original 351(k) BLAs received by FDA between October 1, 2017 and September 30, 2022. ERG is the independent contractor tasked with evaluating the Program. See also "Biosimilar User Fee Act (BsUFA)".

Refuse to File (RTF): A regulatory decision issued on an application that is not considered adequate to permit a substantive review. RTF decisions do not constitute a review cycle or a first cycle action. Applications that are filed over protest after receiving an 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 BsUFA goal (AP, CR, WD) and an action issued before complete review of the application (RTF, WF). ERG's assessment of the Program focuses primarily on the former, while also tracking the latter.

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.

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.

Review Cycle: Period from application receipt to regulatory action, during which an FDA review team reviews the application for filing and then regulatory action. In the Program, the review cycle consists of a 60-day filing review period followed by a 10-month review of the application.

Sponsor: The person or entity who takes responsibility for and initiates the marketing application. See "applicant."

Signatory Authority: A Division Director (or designee) who takes the action on the application.

Withdrawal: An action by the applicant to remove a submitted application from FDA consideration.

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 BsUFA review clock) begins when FDA files an application.

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 BsUFA review clock) begins when FDA files an application.

Appendix B. Evaluation Metrics

Regulatory Outcomes Metrics

Table B-1 presents values for regulatory outcomes metrics for applications in the baseline (FYs 2013-2017) and BsUFA II Program (FYs 2018-2020). 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
RO1	Percent of 351(k) applications reviewed within 10 months of the 60-day filing date		92%
RO2	Percent of 351(k) applications that received a first-cycle action of Withdrawal	0%	0%
RO2	Percent of 351(k) applications that received a first-cycle action of Complete Response	61%	25%
RO2	Percent of 351(k) applications that received a first-cycle action of Approval	39%	75%
RO3	Percent of 351(k) applications that received Approval in second review cycle or later	13%	N/A
RO4	Number of review cycles to Approval: mean	1.3	1
RO4	Number of review cycles to Approval: median	1	1
RO4	Number of review cycles to Approval: range	2 [1, 3]	0 [1, 1]
RO5	Time from receipt of 351(k) to first-cycle action: mean	10.4 mos.	12.2 mos.
RO5	Time from receipt of 351(k) to first-cycle action: median	10.0 mos.	12.0 mos.
RO5	Time from receipt of 351(k) to first-cycle action: range	3.1 mos. [9.9, 13.0]	3.3 mos. [11.7, 15.0]
RO6	Time from receipt of 351(k) to Approval: mean	14.8 mos.	12.3 mos.
RO6	Time from receipt of 351(k) to Approval: median	11.5 mos.	12.0 mos.
RO6	Time from receipt of 351(k) to Approval: range	31.0 mos. [9.9, 40.9]	3.3 mos. [11.7, 15.0]
RO7	Number of 351(k) applications withdrawn by sponsor before filing	1	3
RO8	Number of 351(k) applications with a Refuse-to-File decision	1	0
RO9	Percent of 351(k) applications that received a Refuse-to-File decision where a reason cited is: Inspections	100%	N/A

BPD Type 4 Meeting Metrics

Table B-2 presents values for BPD Type 4 meeting metrics. In the baseline cohort, most applications had BPD Type 4 meetings, but these meetings did not incorporate new recommendations instituted with the BsUFA II Program. Since Program BPD Type 4 meetings were not conducted during that time, we do not provide all values for the baseline cohort. ERG used these metrics to:

- Identify associations and correlations between BPD Type 4 meetings and regulatory outcomes.
- Identify good practices and lessons learned.

Table B-2. BPD Type 4 meeting metrics

		Baseline	Program
BPD1	Percent of BPD Type 4 meetings that were followed by 351(k) submission		86%
BPD2	Percent of 351(k) applications with a first-cycle action that had a BPD Type 4 meeting	74%	92%
BPD3	Of 351(k) applications with a first-cycle action with a Program BPD Type 4 meeting, percent with BPD Type 4 meeting that incorporated: Agreement on content of a complete application		0%
BPD3	Of 351(k) applications with a first-cycle action with a Program BPD Type 4 meeting, percent with BPD Type 4 meeting that incorporated: Discussion or agreement on delayed application components		29%
BPD3	Of 351(k) applications with a first-cycle action with a Program BPD Type 4 meeting, percent with BPD Type 4 meeting that incorporated: Discussion of approach to REMS or other risk management actions, if applicable		67%
BPD3	Of 351(k) applications with a first-cycle action with a Program BPD Type 4 meeting, percent with BPD Type 4 meeting that incorporated: Discussion of patient labeling		29%
BPD3	Of 351(k) applications with a first-cycle action with a Program BPD Type 4 meeting, percent with BPD Type 4 meeting that incorporated: Discussion of a Formal Communication Plan		0%
BPD3	Of 351(k) applications with a first-cycle action with a Program BPD Type 4 meeting, percent with BPD Type 4 meeting that incorporated: Summary of agreements and discussions		43%
BPD3	Of 351(k) applications with a first-cycle action with a Program BPD Type 4 meeting, percent with BPD Type 4 meeting that incorporated: Appropriate FDA staff		100%
BPD3	Of 351(k) applications with a first-cycle action with a Program BPD Type 4 meeting, percent with BPD Type 4 meeting that incorporated: Timing not less than 2 months prior to the planned submission date		86%
BPD4	For 351(k) applications with a first-cycle action, time from BPD Type 4 meeting to receipt of 351(k): mean	4.7 mos.	8.7 mos.
BPD4	For 351(k) applications with a first-cycle action, time from BPD Type 4 meeting to receipt of 351(k): median	4.4 mos.	3.9 mos.
BPD4	For 351(k) applications with a first-cycle action, time from BPD Type 4 meeting to receipt of 351(k): range	12.0 mos. [0.0, 12.0]	25.1 mos. (1.5, 26.6]

FCP Metrics

Table B-3 presents values for FCP metrics. Baseline applications did not have the option to create an FCP, so we do not provide values for the baseline cohort.

Table B-3. Formal communication plan metrics		Baseline	Program
FCP1	Percent of 351(k) applications with a first-cycle action that had an FCP		0%
FCP2	Percent of FCPs modified during 351(k) application review		N/A
FCP3	Number of times FCPs are modified during 351(k) application review: mean		N/A
FCP3	Number of times FCPs are modified during 351(k) application review: median		N/A
FCP3	Number of times FCPs are modified during 351(k) application review: range		N/A
FCP4	Of 351(k) applications with a first-cycle action and an FCP, percent of FCP elements implemented		N/A
FCP4	Of 351(k) applications with a first-cycle action and an FCP containing [insert FCP element], percent of [insert FCP element] implemented		N/A
FCP5	Of 351(k) applications with a first-cycle action and an FCP, percent with [insert FCP element]		N/A
FCP5a	Of 351(k) applications with a first-cycle action and an FCP, percent where FCP calls for omission of one or more Program milestone communications		N/A
FCP5b	Of 351(k) applications with a first-cycle action and an FCP, percent where FCP adds one or more FDA-applicant interactions		N/A

Application Completeness and Quality Metrics

Table B-4 presents values for application completeness and quality metrics for applications in the baseline (FYs 2013-2017) and BsUFA II Program (FYs 2018-2020). ERG used these metrics to:

- Identify associations and correlations between application completeness and quality and regulatory outcomes.
- Identify good practices and lessons learned.

Table B-4. Application completeness and quality metrics		Baseline	Program
ACQ1	Percent of 351(k) applications complete according to filing review	100%	100%
ACQ1	Percent of 351(k) applications complete according to FDA reviewers		58%
ACQ1	Percent of 351(k) applications complete according to BPD Type 4 meeting agreed-upon items		100%
ACQ1	Percent of 351(k) applications complete according to IRs	65%	92%
ACQ2	Number of quality or completeness deficiencies identified by filing reviews: mean	0	0
ACQ2	Number of quality or completeness deficiencies identified by filing reviews: median	0	0
ACQ2	Number of quality or completeness deficiencies identified by filing reviews: range	0	0
ACQ2	Number of quality or completeness deficiencies identified by FDA reviewers: mean		0.4
ACQ2	Number of quality or completeness deficiencies identified by FDA reviewers: median		0
ACQ2	Number of quality or completeness deficiencies identified by FDA reviewers: range		1 [0, 1]

Table B-4. Application completeness and quality metrics		Baseline	Program
ACQ2	Number of quality or completeness deficiencies identified by missing BPD Type 4 meeting agreed upon items: mean		0
ACQ2	Number of quality or completeness deficiencies identified by missing BPD Type 4 meeting agreed upon items: median		0
ACQ2	Number of quality or completeness deficiencies identified by missing BPD Type 4 meeting agreed upon items: range		0
ACQ2	Number of quality or completeness deficiencies identified by IRs: mean	0.9	0.1
ACQ2	Number of quality or completeness deficiencies identified by IRs: median	0	0
ACQ2	Number of quality or completeness deficiencies identified by IRs: range	6 [0, 6]	1 [0, 1]
ACQ3	Among 351(k) applications with quality or completeness deficiencies, percent with a deficiency identified by: IRs	100%	20%
ACQ3	Among 351(k) applications with quality or completeness deficiencies, percent with a deficiency identified by: FDA reviewers		100%
ACQ4	Number of IR items during filing period that pertain to missing items: mean	0.6	0
ACQ4	Number of IR items during filing period that pertain to missing items: median	0	0
ACQ4	Number of IR items during filing period that pertain to missing items: range	5 [0, 5]	0
ACQ5	Among 351(k) applications with IR items that pertain to missing items, percent with missing items that are: Pregnancy and Lactation Labeling Rule (PLLR)-related	50%	0%
ACQ5	Among 351(k) applications with IR items that pertain to missing items, percent with missing items that are: Product Quality-related	38%	0%
ACQ5	Among 351(k) applications with IR items that pertain to missing items, percent with missing items that are: Clinical Pharmacology-related	13%	0%
ACQ5	Among 351(k) applications with IR items that pertain to missing items, percent with missing items that are: Statistics-related	13%	0%
ACQ5	Among 351(k) applications with IR items that pertain to missing items, percent with missing items that are: Device-related	13%	0%
ACQ5	Among 351(k) applications with IR items that pertain to missing items, percent with missing items that are: Proprietary name-related	0%	100%

Unsolicited Amendments Metrics

Table B-5 presents values for unsolicited amendment metrics for applications in the baseline (FYs 2013-2017) and BsUFA II Program (FYs 2018-2020). ERG used these metrics to identify associations and correlations between unsolicited amendments and regulatory outcomes.

Table B-5. Unsolicited amendments metrics		Baseline	Program
UA1	Number of unsolicited amendment items per 351(k) application: mean	1.4	0.8
UA1	Number of unsolicited amendment items per 351(k) application: median	0	0.5
UA1	Number of unsolicited amendment items per 351(k) application: range	7 [0, 7]	3 [0, 3]
UA2	Percent of unsolicited amendment items received during month x of review	Figure 3-14	Figure 3-14
UA3	Percent of unsolicited amendment items that pertain to [insert unsolicited amendment topic]	Figure 3-15	Figure 3-15

Day 74 Letter Metrics

Table B-6 presents values for Day 74 letter metrics for applications in the baseline (FYs 2013-2017) and BsUFA II Program (FYs 2018-2020). ERG used these metrics to characterize review issues identified early in the review cycle.

Table B-6. Day 74 letter metrics

		Baseline	Program
FL1	Percent of Day 74 letters issued within 74 days after application receipt	96%	83%
FL2	Percent of Day 74 letter criteria met	99%	94%

MCC Metrics

Table B-7 presents values for MCC metrics for applications in the baseline (FYs 2013-2017) and BsUFA II Program (FYs 2018-2020). ERG used these metrics to:

- Identify associations and correlations between MCC attributes and regulatory reviews and outcomes.
- Identify good practices and lessons learned.

Table B-7. MCC metrics

		Baseline	Program
MCC1	Of 351(k) applications where an MCC is expected, percent of 351(k) applications with an MCC		100%
MCC2	Percent of MCC expectations implemented		Table 3-13
MCC3	Percent of MCC issues that are [insert MCC issue]		Figure 3-4
MCC4	Percent of other MCC discussion topics that are [insert MCC topic]		Figure 3-5

LCM Metrics

Table B-8 presents values for LCM metrics for applications in the baseline (FYs 2013-2017) and BsUFA II Program (FYs 2018-2020). ERG used these metrics to:

- Identify associations and correlations between LCM attributes and regulatory reviews and outcomes.
- Identify good practices and lessons learned.

Table B-8. LCM metrics

		Baseline	Program
LCM1	Of 351(k) applications where an LCM is expected, percent of 351(k) applications with an LCM		92%
LCM2	Percent of 351(k) applications with an LCM background package		100%
LCM3	Percent of LCM background expectations implemented		Table 3-16
LCM4	Percent of LCM meeting expectations implemented		Table 3-17
LCM5	Percent of LCM issues that are [insert LCM issue]		Figure 3-6

Table B-8. LCM metrics		Baseline	Program
LCM6	Percent of other LCM discussion topics that are [insert LCM topic]		Figure 3-7

AC Metrics

Table B-9 presents values for AC meeting metrics for applications in the baseline (FYs 2013-2017) and BsUFA II Program (FYs 2018-2020). ERG used these metrics to identify applications with an AC meeting and identify associations between AC meetings and regulatory reviews and outcomes.

Table B-9. AC metrics		Baseline	Program
AC1	Percent of 351(k) applications with an AC meeting	22%	0%

Post-AC Meeting Metrics

Table B-10 presents values for post-AC meeting metrics for applications in the baseline (FYs 2013-2017) and BsUFA II Program (FYs 2018-2020). ERG used these metrics to identify applications with a post-AC meeting and identify associations between post-AC meetings and regulatory reviews and outcomes.

Table B-10. Post-AC meeting metrics		Baseline	Program
PAC1	Percent of 351(k) applications with a post-AC meeting		0%

Inspection Timing Metrics

Table B-11 presents values for inspection timing metrics for applications in the baseline (FYs 2013-2017) and BsUFA II Program (FYs 2018-2020). ERG used these metrics to identify associations and correlations between the timing of inspections and regulatory reviews and outcomes.

Table B-11. Inspection timing metrics		Baseline	Program
IT1	Percent of 351(k) applications with on-time inspection completion		100%
IT2	Percent of inspection completions on day xx of review		Figure 3-9
IT3	Percent of 351(k) applications with late inspection completion, where inspection completion was delayed due to [insert reason]		N/A
IT4	Percent of inspection tasks conducted on day xx of review	Figure 3-8	Figure 3-8

Clock Extension Metrics

Table B-12 presents values for goal clock extension metrics for applications in the baseline (FYs 2013-2017) and BsUFA II Program (FYs 2018-2020). ERG used these metrics to identify applications with a goal clock extension and identify associations between goal clock extensions and regulatory reviews and outcomes.

Table B-12. Clock extension metrics

		Baseline	Program
CE1	Percent of 351(k) applications with a goal clock extension due to major amendment	13%	8%
CE2	Percent of 351(k) applications with a goal clock extension due to inadequately identified facilities		0%

Resubmission Metrics

Table B-13 presents values for resubmission metrics for applications in the baseline (FYs 2013-2017) and BsUFA II Program (FYs 2018-2020). ERG used these metrics to identify resubmitted applications and identify associations between resubmissions and regulatory reviews and outcomes.

Table B-13. Resubmission metrics

		Baseline	Program
RS1	Of 351(k) applications with a first-cycle Complete Response that are resubmitted, time from Complete Response to resubmission: mean	7.5	N/A
RS1	Of 351(k) applications with a first-cycle Complete Response that are resubmitted, time from Complete Response to resubmission: median	3.9	N/A
RS1	Of 351(k) applications with a first-cycle Complete Response that are resubmitted, time from Complete Response to resubmission: range	14.5 [1.9, 16.5]	N/A

CR Issues Metrics

Table B-14 presents values for CR issue metrics for applications in the baseline (FYs 2013-2017) and BsUFA II Program (FYs 2018-2020). ERG used these metrics to:

- Identify associations and correlations between issues cited in CR letters and regulatory reviews and outcomes.
- Identify good practices and lessons learned.

Table B-14. CR issues metrics

		Baseline	Program
CR1	Percent of 351(k) applications with a first-cycle action of Complete Response where a reason cited is [insert CR reason]	Table 3-7	Table 3-7
CR2	Percent of 351(k) applications with a first-cycle action of Complete Response where the first mention of a CR issue occurred in Day 74 letter		0%
CR2	Percent of 351(k) applications with a first-cycle action of Complete Response where the first mention of a CR issue occurred in FCP interaction		N/A
CR2	Percent of 351(k) applications with a first-cycle action of Complete Response where the first mention of a CR issue occurred in MCC interaction		67%

Table B-14. CR issues metrics		Baseline	Program
CR2	Percent of 351(k) applications with a first-cycle action of Complete Response where the first mention of a CR issue occurred in LCM		33%
CR2	Percent of 351(k) applications with a first-cycle action of Complete Response where the first mention of a CR issue occurred in DR letter		N/A
CR2	Percent of 351(k) applications with a first-cycle action of Complete Response where the first mention of a CR issue occurred in CR letter		0%

Post-Action Interview Metrics

Table B-15 presents metrics for FDA review team and applicant interviews for applications in the BsUFA II Program (FYs 2018-2020). ERG used these metrics to:

- Characterize FDA-applicant communications during the Program, including new milestone meetings.
- Collect feedback on how issues are resolved during the first review cycle.
- Identify good practices and lessons learned for future Program applications.
- Identify FDA and application suggestions for Program improvement.

Table B-15. Post-action interview metrics		Baseline	Program
PAI1	Types of FDA feedback on FDA-applicant communications		*(in report)*
PAI2	Types of FDA feedback on application		*(in report)*
PAI3	Types of FDA feedback on ability to resolve issues during first review cycle		*(in report)*
PAI4	Types of FDA suggestions for Program improvement		*(in report)*
PAI5	Types of applicant feedback on FDA-applicant communications		*(in report)*
PAI6	Types of applicant feedback on ability to resolve issues during first review cycle		*(in report)*
PAI7	Types of applicant feedback on ability to prepare for resubmission		*(in report)*
PAI8	Types of applicant suggestions for Program improvement		*(in report)*

DR Letter Metrics

Table B-16 presents values for DR letter metrics for applications in the baseline (FYs 2013-2017) and BsUFA II Program (FYs 2018-2020). ERG used these metrics to identify associations and correlations between DR letters issued and regulatory reviews and outcomes.

Table B-16. DR letter metrics		Baseline	Program
DR1	Percent of applications with DR letters	0%	0%
DR2	Number of DRs per 351(k) application: mean	0	0
DR2	Number of DRs per 351(k) application: median	N/A	N/A
DR2	Number of DRs per 351(k) application: range	0	0
DR3	Percent of DR letters where a discipline cited is [insert discipline]	N/A	N/A

FDA IR Metrics

Table B-17 presents values for FDA IR metrics for applications in the baseline (FYs 2013-2017) and BsUFA II Program (FYs 2018-2020). ERG used these metrics to identify associations and correlations between IRs sent by FDA and regulatory reviews and outcomes.

Table B-17. IR metrics		Baseline	Program
IR1	Number of IRs per 351(k) application: mean	19	12
IR1	Number of IRs per 351(k) application: median	17	10.5
IR1	Number of IRs per 351(k) application: range	40 [5, 45]	15 [4, 19]
IR2	Number of IR items per 351(k) application: mean	62	23
IR2	Number of IR items per 351(k) application: median	34	20.5
IR2	Number of IR items per 351(k) application: range	239 [9, 248]	50 [5, 55]
IR3	Percent of IR items that pertain to [insert discipline]	Figure 3-10	Figure 3-10
IR4	Percent of IRs issued on day xx of review	Figure 3-12	Figure 3-12
IR5	Percent of IR items issued on day xx of review	Figure 3-12	Figure 3-12

Application Amendment Metrics

Table B-18 presents values for application amendment metrics for applications in the baseline (FYs 2013-2017) and BsUFA II Program (FYs 2018-2020). ERG used these metrics to identify associations and correlations between application amendments and regulatory reviews and outcomes.

Table B-18. Application amendment metrics		Baseline	Program
AA1	Number of amendments per 351(k) application: mean	37	34
AA1	Number of amendments per 351(k) application: median	35	38.5
AA1	Number of amendments per 351(k) application: range	26 [30, 56]	28 [19, 47]
AA2	Number of amendment items per 351(k) application: mean	91	149
AA2	Number of amendment items per 351(k) application: median	68	128
AA2	Number of amendment items per 351(k) application: range	308 [33, 341]	230 [37, 267]
AA3	Percent of amendment items that pertain to [insert discipline]	Figure 3-11	Figure 3-11
AA4	Percent of amendments received on day xx of review	Figure 3-13	Figure 3-13
AA5	Percent of amendment items received on day xx of review	Figure 3-13	Figure 3-13

Therapeutic Area Metrics

Table B-19 presents values for therapeutic area metrics for applications in the baseline (FYs 2013-2017) and BsUFA II Program (FYs 2018-2020). ERG used these metrics to identify associations and correlations between therapeutic area types and regulatory reviews and outcomes.

Table B-19. Therapeutic area metrics

		Baseline	Program
TA1	Percent of 351(k) applications in the Oncology therapeutic area	65%	58%
TA1	Percent of 351(k) applications in the Gastroenterology therapeutic area	22%	42%
TA1	Percent of 351(k) applications in the Ophthalmology therapeutic area	0%	8%
TA1	Percent of 351(k) applications in the Dermatology therapeutic area	30%	50%
TA1	Percent of 351(k) applications in the Rheumatology therapeutic area	39%	50%
TA1	Percent of 351(k) applications in the Hematology therapeutic area	4%	0%