Product Quality Information Request Communications Assessment

Final Report

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Executive Summary

The Prescription Drug User Fee Act (PDUFA) provides the U.S. Food and Drug Administration (FDA) with stable, consistent funding that allows the Agency to focus on promoting innovative therapies and help bring critical products for patients to market. With the most recent reauthorization of PDUFA for fiscal years (FYs) 2023 through 2027, FDA committed to several activities that aimed to enhance communication between FDA and applicants during the application review process. An information request (IR) is one method of communication that FDA uses during application reviews to inform applicants when additional information or clarification is needed about their application. FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) perform product quality reviews and issue product quality IRs for their regulated products. CDER and CBER established procedures for reviewers to use Four-Part Harmony, a framework that describes four key elements that should be included IRs: (i) what was provided, (ii) what is the issue or deficiency, (iii) what is needed, and (iv) why it is needed. This framework was designed to help CDER and CBER facilitate clearer and more efficient communications between FDA and applicants and align with FDA's longstanding priority to enable timely access to safe and effective therapies to patients.

The FDA enlisted a contractor, Eastern Research Group, Inc. (ERG), to assess product quality communication practices through IRs between CDER, CBER, and applicants and the effectiveness of Four-Part Harmony. ERG collected data for this assessment from FDA databases, primary documentation, and interviews with FDA review teams and drug industry applicants. The data includes two samples of applications that reflect product quality IR communications before the implementation of PDUFA VII commitments (baseline sample) and after (current sample). The data ERG collected and analyzed for these two samples of applications included IR letters, IR items, amendments, and amendment items. IR letters often contained multiple requested items, typically in a numbered or bulleted format, which we call "IR items" in this report. Similarly, applicant-submitted amendments also contained multiple items, which we call "amendment items" in this report. An overview of the samples and the data is provided below.

- **Baseline Sample (n=40):** Application reviews conducted and completed between October 1, 2017 and September 30, 2022. These applications were associated with:
    - 427 IR letters and 2,744 IR items
    - 613 amendments and 3,022 amendment items
- **Current Sample (n=40):** Application reviews conducted and completed between October 1, 2023 and January 31, 2025. These applications were associated with:
    - 410 IR letters and 2,830 IR items
    - 588 amendments and 3,332 amendment items

Answers to Assessment Questions

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

1a. What are characteristics of *baseline* FDA review staff and sponsor communication practices via product quality IRs?

On average, Priority review applications, CBER applications, and Biologics License Applications (BLAs) had more IR letters, IR items, and amendments than other types of applications in the baseline sample.

1b. To what extent do *baseline* product quality IR communications incorporate Four-Part Harmony, recommended policies, practices, guidances, and standard operating procedures?

In the baseline sample, the 2,744 IR items incorporated Four-Part Harmony to the following extent:

- *What was provided* 77% of IR items
- *What is needed* 99% of IR items
- *What is the issue* 46% of IR items
- *Why is it needed (Impact)* 16% of IR items
- *Why is it needed (Reference)* 4% of IR items

2. How do *baseline* product quality IR communication practices vary by application characteristics such as application type, review priority, last action date, submission status, and review division?

Comparing application characteristics in the baseline sample showed that Priority review applications, CBER applications, and BLAs had more IR letters, IR items, and amendments than Standard review applications, CDER applications, and New Drug Applications (NDAs). However, the incorporation of Four-Part Harmony in baseline sample IR items generally did not differ by application characteristic.

Priority review applications in the baseline sample appeared to have a greater proportion of communications occurring in months three to five of the review timeline, compared to months five to eight for Standard review applications. This is primarily the result of the different review timelines, where communications and mid-cycle meetings occur earlier during Priority review timelines.

3a. What are characteristics of *current* FDA review staff and applicant communication practices via product quality IRs?

On average, Priority review applications, CBER applications, and BLAs had more IR letters, IR items, and amendments than other types of applications in the current sample.

3b. To what extent do *current* product quality IR communications incorporate Four-Part Harmony, recommended policies, practices, guidances, and standard operating procedures?

In the current sample, the 2,830 IR items incorporated Four-Part Harmony to the following extent:

- *What was provided* 82% of IR items
- *What is needed* 99% of IR items
- *What is the issue* 66% of IR items
- *Why is it needed (Impact)* 18% of IR items
- *Why is it needed (Reference)* 12% of IR items

4. How do *current* product quality IR communication practices vary by application characteristics such as application type, review priority, and review division?

Comparing application characteristics in the current sample showed that Priority review applications, CBER applications, and BLAs had more IR letters, IR items, and amendments than Standard review applications, CDER applications, and NDAs. However, the incorporation of Four-Part Harmony in current sample IR items generally did not differ by application characteristic.

Priority applications in the current sample appeared to have a greater proportion of IR items occurring in months three to five of the review timeline, compared to months three to six for Standard applications. For amendment items, peak volume occurred in month six for applications with Priority and Standard review timelines. Despite differences in review timelines, product quality IR communications were concentrated during similar periods of time in current sample applications.

5. How do *current* product quality IR communications compare to *baseline* product quality IR communications in incorporating Four-Part Harmony, recommended policies, practices, guidances, and standard operating procedures?

Four-Part Harmony elements were utilized more frequently in the current sample than in the baseline, as shown in the table below.

Table ES-1. Incorporation of Four-Part Harmony elements in baseline (n=2,744) and current (n=2,830) sample IR items

Four-Part Harmony Element	Baseline IR Items with Element (n=2,744)	Current IR Items with Element (n=2,830)
What was provided	77%	82%
What is needed	99%	99%
What is the issue	46%	66%
Why is it needed (Impact)	16%	18%
Why is it needed (Reference)	4%	12%

ERG did not observe an association between the increased utilization of Four-Part Harmony and the volume of IRs or amendments per application in the current sample.

6. How do FDA review staff and applicants characterize the effectiveness of *current* product quality IR communication practices and Four-Part Harmony?

FDA review staff and applicants characterized current product quality IR communications as a clear and effective means of conveying issues and receiving information. In nine out of ten applicant interviews, applicants agreed that product quality IRs contained sufficient context to avoid requesting clarification. FDA and applicants understand the value of reducing the need for follow-up IRs and requests for clarification and identified Priority reviews as an area where the efficiency of the IR process and clarity of IRs are particularly important.

FDA staff recognized that the purpose of Four-Part Harmony is to be clear and logical in their data requests to applicants, and applicants appreciated the rationale provided in IRs that use Four-Part Harmony. Applicants stated that understanding FDA's reasoning for requesting information enabled them to respond more comprehensively to an IR or to offer relevant data that FDA had not been aware of.

Contrary to ERG's assessment of FDA's use of Four-Part Harmony, applicants in interviews asserted that the IRs they received usually followed Four-Part Harmony and were complete. This suggests that FDA identifying "what was provided" or "what is the issue" in addition to "what is needed" might be sufficient for applicants to understand "why is it needed."

7. What practices enhance product quality IR communications, what challenges hinder communications, and what steps can FDA and applicants take to improve these processes moving forward?

FDA staff noted that reducing the need for follow-up IRs, issuing IRs as early as possible, and training new staff in Four-Part Harmony enhances the efficiency of IR communications. Applicants stated that receiving clear and organized IRs is important to achieve enhanced IR communications.

FDA staff often pointed to the difficulty in including the "why is it needed" element of Four-Part Harmony. FDA staff also described Four-Part Harmony as redundant when elements are repeated throughout an IR letter and suggested that condensing elements could reduce the burden. Applicants often noted the unpredictability of receiving IRs during the review, especially near the end of application review timelines, where timely responses are challenging.

Findings and Recommendations

ERG developed a set of findings and recommendations (Table ES-2) based on two overarching themes:

1. FDA and applicant product quality IR communications are essentially clear, efficient, and effective.
2. Four-Part Harmony, as described in CDER Manual of Policies and Procedures (MAPP) 5016.8 Rev. 1 and CBER Standard Operating Procedures and Policies (SOPP) 8401.1, is rarely utilized to its full extent.

Table ES-2. Findings and recommendations on product quality IR communications

No.	Finding	Recommendation(s)
S1	Applicants note that tracking and organizing IRs is particularly important when multiple IRs are received at the same time or in quick succession.	**To FDA:** Consider applying a numbering system (e.g., CMC #1, CMC #2, CMC #3, etc.) when issuing product quality IRs to prevent misidentification of IRs with the same date. *Note: Some FDA project managers currently use numbers to identify IRs.*
S2	FDA reviewers appreciate well-organized responses to IRs, which allow them to efficiently locate and review the relevant information.	**To applicants:** If not already, consider including summary documents containing itemized responses to IRs in addition to the necessary detailed data.
S3	Despite IRs frequently lacking an explicit *"why is it needed"* Four-Part Harmony element, applicants find that IRs are clear and complete. Applicants often understand why an IR is needed from FDA's explanation of "*what is the issue/deficiency.*"	**To FDA and applicants:** If effective IR communications are possible with fewer Four-Part Harmony elements, consider modifying Four-Part Harmony to establish two tiers of elements for inclusion: • Expected elements: "*what was provided*," "*what is the issue/deficiency*," and "*what is needed.*" • As-needed elements (e.g., for less common deficiencies): "*why is it needed [impact]*," and "*why is it needed [reference]*." This could improve the efficiency of drafting FDA IRs, while maintaining the clarity of IRs to applicants.
S4	*"Why is it needed"* is commonly omitted from IRs written with Four-Part Harmony. FDA reviewers described difficulty in immediately identifying the correct references to cite, or the absence of a reference to cite.	**To FDA:** Consider creating an office-wide product quality IR reference repository based on product quality topic areas or categories for IR drafters. Assess the scale of data and support needed and determine its feasibility. This could allow reviewers who are drafting IRs to easily access relevant references and increase the efficiency and consistency of IRs.
S5	Training to use Four-Part Harmony in IRs encourages new FDA staff to effectively organize and communicate their thoughts on quality issues in a clear and logical format. This is beneficial to applicants, and it is also helpful to other FDA team members reviewing a new reviewer's drafted IRs.	**To FDA:** Continue to conduct Four-Part Harmony training with new reviewers. Continue to offer Four-Part Harmony training to all FDA reviewers. Discuss and share examples of what to include for the *"why is it needed"* element.

1. Introduction

User Fee Commitment

The Prescription Drug User Fee Act (PDUFA) provides the Food and Drug Administration (FDA) with a source of stable, consistent funding that has made it possible for the Agency to focus on promoting innovative therapies and help bring to market critical products for patients. When PDUFA was originally authorized in 1992, it had a five-year term. The program has been subsequently reauthorized every five years. To prepare for reauthorization of PDUFA for the next five-year period (2023 to 2027), FDA conducted negotiations with the regulated industry and held regular consultations with public stakeholders including patient advocates, consumer advocates, and healthcare professionals between September 2020 and February 2021.

Following these discussions, related public meetings, and Agency requests for public comment, FDA published the "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027" document, also known as the PDUFA VII "goals letter," to supplement the statute.[1] The goals letter includes the performance goals, procedures, and commitments that apply to aspects of the human drug review program that are important for facilitating timely access to safe, effective, and innovative new medicines for patients. Several of these commitments aim to continue to enhance communication between FDA and applicants during application review.

Enhancing Communication Between FDA and Applicants During Application Review

Efficient and effective reviews of marketing applications are an important part of the Food and Drug Administration's (FDA's) mission to protect the public's health by assuring the safety, efficacy, and security of drugs, biologics, and other medical products. To enable such reviews, FDA committed to activities and practices focusing on enhanced communication between FDA and applicants during drug development and application review. FDA often communicates to applicants through information requests (IRs), which are issued to applicants during application reviews. FDA uses IRs to request additional information or clarification from applicants, and to allow completion of their review. When assessing drug or biological product quality, FDA uses IRs to request further information needed for FDA's assessment of identity, strength, quality, purity, or potency. Clear and concise communications can save valuable time and effort by reducing the need for multiple back-and-forth interactions between FDA and applicants

The Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) may issue a product quality, or Chemistry, Manufacturing, and Controls (CMC) IR as a result of CMC assessments conducted in support of an application for a drug or biological product. CDER and CBER have established procedures for assessors to use Four-Part Harmony, a framework that describes four key elements that should be included in product quality IRs, specifically: (i) what was

[1] *PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027.* https://www.fda.gov/media/151712/download

provided, (ii) what is the issue or deficiency, (iii) what is needed, and (iv) why it is needed.[2, 3] Additionally, the fourth element should include the *impact* on the review or regulatory decision and a *reference* to a relevant guidance, rule, statute, or other FDA-recognized standard, as appropriate. The goal of Four-Part Harmony is to reduce the need for follow-up clarification questions from applicants and follow-on requests from FDA due to inadequate responses. Through FDA's implementation of Four-Part Harmony in product quality IRs, applicants should understand what information FDA needs to continue their review.

Assessment of Communication Through Product Quality IRs During Application Review

During PDUFA negotiations and discussions with industry, industry representatives provided feedback that the context and rationale for quality IRs was not always clear, which could cause industry to provide unnecessary information to FDA in response. FDA and industry agreed that a more consistent use of Four-Part Harmony in CDER and CBER IR letters might be beneficial to address the concern. To address this, the PDUFA VII goals letter included commitments for FDA to update and conduct training on existing policies and procedures related to Four-Part Harmony. As a result, CBER Standard Operating Procedures and Policies (SOPP) 8401.1 *Issuance of and Review of Responses to Information Request Communications to Pending Applications* was revised in October 2022, and CDER Manual of Policies and Procedures (MAPP) 5016.8, *Using Four-Part Harmony in Quality-Related Assessment Communications* was revised in September 2023.

In addition to updating the documents and conducting training, FDA committed to contracting with an independent third party to assess current practices of CDER, CBER, and applicants in communicating through product quality IRs during application review and the effectiveness of Four-Part Harmony.[4] Accordingly, FDA enlisted Eastern Research Group, Inc. (ERG) to conduct such an assessment. Specifically, FDA asked ERG to:

1. Characterize and analyze trends across the baseline state of communication between FDA review teams and applicants via product quality IRs, before the implementation of PDUFA VII commitments (i.e., updating MAPPs and SOPPs and conducting training).
2. Characterize and analyze trends across the current state of communication between FDA review teams and applicants via product quality IRs, after implementation of PDUFA VII commitments, as compared to the baseline, expectations of FDA and applicants, and the practices stated in relevant FDA MAPPs and SOPPs.
3. Identify what is working well and what is not working well with the current status of product quality IR communication after implementation of PDUFA VII commitment; this includes identifying best practices and areas for improvement.

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[2] *CDER MAPP 5016.8 Rev. 1, Using Four-Part Harmony in Quality-Related Assessment Communications (September 2023).* https://www.fda.gov/media/171613/download

[3] *SOPP 8401.1: Issuance of and Review of Responses to Information Request Communications to Pending Applications (October 2022).* https://www.fda.gov/media/85301/download

[4] Section I.N.1.c, *PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027.* https://www.fda.gov/media/151712/download

4. Make recommendations for both FDA review staff and applicants on how to improve communications via product quality IRs.

ERG operationalized these objectives into measurable assessment questions, listed below. For this assessment, the baseline sample was designed to include product quality IRs and amendments associated with applications reviewed by FDA prior to updating MAPPs, SOPPs, and conducting Four-Part Harmony training, while the current sample included applications reviewed by FDA after such activities. ERG compared product quality IRs and amendments in the baseline and current samples to inform characterizations of communication in each sample.

Assessment Questions

1a. What are characteristics of ***baseline*** FDA review staff and applicant communication practices via product quality IRs?

1b. To what extent do ***baseline*** product quality IR communications incorporate Four-Part Harmony, recommended policies, practices, guidances, and standard operating procedures?

2. How do ***baseline*** product quality IR communication practices vary by application characteristics such as application type, review priority, last action date, submission status, and review division?

3a. What are characteristics of ***current*** FDA review staff and applicant communication practices via product quality IRs?

3b. To what extent do ***current*** product quality IR communications incorporate Four-Part Harmony, recommended policies, practices, guidances, and standard operating procedures?

4. How do ***current*** product quality IR communication practices vary by application characteristics such as application type, review priority, and review division?

5. How do ***current*** product quality IR communications compare to ***baseline*** product quality IR communications in incorporating Four-Part Harmony, recommended policies, practices, guidances, and standard operating procedures?

6. How do FDA review staff and applicants characterize the effectiveness of ***current*** product quality IR communication practices and Four-Part Harmony?

7. What practices enhance product quality IR communications, what challenges hinder communications, and what steps can FDA and applicants take to improve these processes moving forward?

8. What steps should FDA take to improve product quality information requests?

9. What steps should applicants take to improve responses to product quality information requests?

This report describes ERG's assessment of product quality IR communications under PDUFA VII. The remainder of this report includes:

- Section 2: Methods
- Section 3: Results
- Section 4: Answers to Assessment Questions
- Section 5: Findings and Recommendations
- Appendix A. Acronyms and Glossary

2. Methodology

ERG used a systematic process to identify, collect, and analyze comprehensive data for this assessment of product quality IR communications. This process involved five key steps:

1. **Develop evaluation metrics** — ERG established a set of objective, measurable evaluation metrics that are directly related to the product quality IR communications assessment questions. ERG organized these metrics into the following categories: Original application data, FDA IRs, and applicant amendments.
2. **Develop data collection protocols and instruments** — ERG prepared data collection protocols and instruments (Table 2-1) to serve as a guide for ERG to obtain descriptive information. This includes collecting data about original applications, FDA-issued IRs, applicant submissions, and conducting interviews with applicants and FDA staff to elicit information and opinions about product quality IR communication practices. For the interviews with applicants, FDA prepared and submitted an Information Collection Request (ICR) to the Office of Management and Budget (OMB) to request permission to conduct this information collection. OMB approved the ICR, assigning an OMB Control Number of 0910-0746.[5]

Table 2-1. Product quality IR communications assessment data collection protocols and instruments

Data Collection Protocol	Associated Data Collection Instruments	Purpose
Application Reviews	Application Information Information Requests Amendments	Collect descriptive data to characterize samples and analyze/compare across traits of interest. Collect quantitative data from product quality IRs and amendments to characterize IR communication practices and compliance with Four-Part Harmony.
Interviews	Interview Script: FDA Interview Script: Applicant	Collect qualitative data about product quality IR communication experiences, good practices, challenges, suggestions for improvement, and other comments.

3. **Create samples** — For this assessment, ERG developed two samples (Table 2-2) of applications. ERG first developed a retrospective baseline sample to capture IRs and amendments associated with CBER and CDER original New Drug Applications (NDAs) and Biologics License Applications (BLAs) one year prior to FDA's implementation of PDUFA VII commitments regarding Four-Part Harmony on October 1, 2023. The current sample was built prospectively during the 15-month data collection period from October 1, 2023 to January 31, 2025. For the prospective current sample, ERG added applications to the sample each month according to the following process: (1)

[5] https://www.regulations.gov/document/FDA-2013-N-0093-0015

identify original applications that received an "approval" or "complete response" action from FDA that month; (2) identify whether those original applications were submitted on or after October 1, 2023; (3) add the application to the sample; (4) assess conformance of the current sample with target distributions for traits of interest based on the baseline sample; and (5) if some traits are underrepresented, replace applications with others that have underrepresented traits.

Table 2-2. Product quality IR communications assessment application samples

Sample	Description	Sample Size (n)
Baseline	Original NDAs and BLAs with first-cycle review before implementing PDUFA VII commitments (before October 1, 2022)	40 (10 CBER BLAs, 30 CDER NDAs and BLAs)
Current	Original NDAs and BLAs with first-cycle review after implementing PDUFA VII commitments (after October 1, 2023)	40 (7 CBER BLAs, 33 CDER NDAs and BLAs)

BLA = Biologics License Application, NDA = New Drug Application

To the extent feasible, ERG designed the samples to represent traits of interest to stakeholders:

- *Centers:* CDER or CBER
- *Application type:* NDA or BLA
- *Review priority:* Priority (six or eight months) or Standard (10 or 12 months)
- *Regulatory action:* Approval or Complete Response

Using FDA data on CBER and CDER original NDAs and BLAs from Fiscal Year (FY) 2018 to 2022, ERG generated target allocations for the traits of interest in the baseline and current samples. In building the current sample each month during the assessment period, ERG found that reaching the target allocations was infeasible due to an insufficient number of NDAs and BLAs reaching "approval" or "complete response" actions with the desired the traits of interest.

4. **Collect data** — For each of the samples, ERG collected quantitative data in accordance with the procedures specified in the data evaluation protocols and instruments. ERG manually evaluated IRs for the explicit inclusion of Four-Part Harmony elements as part of the quantitative data collection process. ERG entered quantitative data into an Excel database designed to store the raw data and compute metrics values. For the current sample, ERG collected qualitative data from FDA and applicant interviews. Qualitative data were stored separately in interview logs. To protect proprietary and non-public information, ERG performed all data collection and analysis on secure computers with secure FDA email. All ERG personnel have public trust clearances and signed Non-Disclosure Agreements. To protect the privacy of interview and survey respondents, ERG maintained identifying information only for the purpose of scheduling interviews and kept this information in a secure environment inaccessible to anyone outside ERG's internal project team. ERG anonymized and aggregated interview results for analysis and reporting purposes.
5. **Analyze data** — The data collected served as a foundation for analysis to generate meaningful information to answer the assessment questions. ERG performed two types of data analysis: (1) quantitative analysis to compute and analyze evaluation metrics, and to examine differences

based on traits of interest; and (2) qualitative analysis to gain insights into current product quality IR communication practices from FDA review teams and applicants. Due to the small sample sizes, the data were insufficient to determine statistical significance. ERG is not reporting on statistical significance.

6. **Develop 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

Throughout the review of an application, FDA can issue an IR letter to the applicant if the review team determines that more information is necessary to move forward with the review. An IR letter often contains multiple requested items, typically in a numbered or bulleted format, which we call "IR items" in this report. In response to an FDA IR letter, applicants may submit an amendment to their application; similar to an IR letter, an amendment can contain multiple items, which we call "amendment items" in this report. Applicants often include FDA IR items copied from IR letters in their amendments to aid in organizing their amendment items, although applicants may also sometimes bundle or disaggregate responses to IR letters.

For the PDUFA VII product quality IR communications assessment, ERG collected and analyzed IR letters, IR items, amendments, and amendment items associated with two samples of original NDAs and BLAs reviewed by CDER and CBER:

- **Baseline Sample (n=40):** 14 BLA and 26 NDA reviews conducted and completed between October 1, 2017 and September 30, 2022. These applications were associated with:
    - 427 IR letters and 2,744 IR items
    - 613 amendments and 3,022 amendment items
- **Current Sample (n=40):** 18 BLA and 22 NDA reviews conducted and completed between October 1, 2023 and January 31, 2025. These applications were associated with:
    - 410 IR letters and 2,830 IR items
    - 588 amendments and 3,332 amendment items

In selecting applications for the current sample, ERG chose applications with traits similar to those in the baseline sample when possible. A breakdown of applications in the baseline and current samples by application trait is shown in Table 3-1. The resultant current sample was generally similar to the baseline sample.

Table 3-1. Number of applications in baseline (n=40) and current (n=40) samples, by application trait

Application Trait		Number of Baseline Applications with Trait (n=40)	Number of Current Applications with Trait (n=40)
Application Type:	NDA	26	22
	BLA	14	18
Review Priority:	Standard	21	21
	Priority	19	19
Regulatory Action:	Approval	29	28
	Complete Response	11	12
Review Center:	CDER	30	33
	CBER	10	7

ERG presents the results as follows:

Section 3.1, Number of FDA Information Requests (IRs) and Applicant Amendments

Section 3.2, Timing of IR Items and Amendment Items

Section 3.3, Four-Part Harmony in FDA IRs

Section 3.4, FDA and Applicant Interview Feedback

3.1 Number of FDA Information Requests (IRs) and Applicant Amendments

For each application in the baseline and current samples, ERG collected and analyzed the number of product quality and CMC IR letters and IR items, and applicant-submitted quality amendments and amendment items to identify characteristics of IR communications between the two samples. In this section, ERG presents the overall results of this analysis, as well as results by application trait.

Overall Number of IRs and Amendments per Application in the Baseline and Current Samples

Results for numbers of IR letters and IR items associated with applications in the baseline and current samples appear in Table 3-2. Overall, FDA issued similar numbers of IR letters and IR items per application in both samples.

Table 3-2. Number of IR letters and IR items per application in baseline (n=40) and current (n=40) samples, overall

	Baseline (n=40)	**Current** (n=40)
Mean number of IR letters per application	11	10
Median number of IR letters per application	7	8
Range of numbers of IR letters per application	39 [1, 40]	29 [1, 30]
Mean number of IR items per application	69	71
Median number of IR items per application	42.5	36
Range of number of IR items per application	231 [5, 236]	232 [4, 236]

The numbers of amendments and amendment items associated with applications in the baseline and current samples are shown in Table 3-3. Applicants submitted similar numbers of amendments per application in both samples, while the average and median number of amendment items slightly increased in the current sample.

Table 3-3. Number of amendments and amendment items per application in baseline (n=40) and current (n=40) samples, overall

	Baseline (n=40)	**Current** (n=40)
Mean number of amendments per application	15	15
Median number of amendments per application	10	11.5
Range of number of amendments per application	52 [1, 53]	49 [4, 53]
Mean number of amendment items per application	76	83
Median number of amendment items per application	48	66
Range of number of amendment items per application	319 [9, 328]	180 [11, 191]

Application Type: Number of IRs and Amendments per Application in the Baseline and Current Samples

Table 3-4 compares the numbers of IR letters and IR items associated with BLAs and NDAs in the baseline and current samples. **In both samples, BLAs on average have two to three times the amount of IR letters and more than four times the number of IR items of NDAs**.

BLAs and NDAs differ in the type of product submitted for FDA review and approval. Biologic molecules, which are the subject of BLAs, are generally larger and more complex than drug products submitted under an NDA. The nature of biologics presents product quality and CMC challenges that FDA and applicants often communicate on to ensure that biologics are manufactured within acceptable tolerances. FDA and applicants expect slight variations in biological molecules resulting from the manufacturing process, and FDA's review of the manufacturing process and the applicant's strategies to control variations are often an important topic of discussion during BLA reviews.

Table 3-4. Number of IR letters and IR items per application in baseline (n=40) and current (n=40) samples, by application type

	Baseline - BLAs (n=14)	**Current - BLAs** (n=18)
Mean number of IR letters per application	19	14
Median number of IR letters per application	16.5	13.5
Range of numbers of IR letters per application	33 [7, 40]	29 [1, 30]
Mean number of IR items per application	140	116
Median number of IR items per application	122.5	128.5
Range of number of IR items per application	177 [59, 236]	232 [4, 236]
	Baseline - NDAs (n=26)	**Current - NDAs** (n=22)
Mean number of IR letters per application	6	7
Median number of IR letters per application	6	7
Range of numbers of IR letters per application	11 [1, 12]	9 [1, 10]
Mean number of IR items per application	30	34
Median number of IR items per application	24.5	26
Range of number of IR items per application	87 [5, 92]	103 [11, 114]

Table 3-5 compares the numbers of amendments and amendment items associated with BLAs and NDAs in the baseline and current samples. This follows the pattern observed in Table 3-4 for FDA IRs and IR items. **BLAs in the baseline and current samples averaged two to three times the number of amendments and more than three times the number of amendment items in NDAs.**

Table 3-5. Number of amendments and amendment items per application in baseline (n=40) and current (n=40) samples, by application type

	Baseline - BLAs (n=14)	**Current - BLAs** (n=18)
Mean number of amendments per application	28	23
Median number of amendments per application	30	22
Range of number of amendments per application	44 [9, 53]	48 [5, 53]
Mean number of amendment items per application	153	132
Median number of amendment items per application	158	152
Range of number of amendment items per application	281 [47, 328]	180 [11, 191]
	Baseline - NDAs (n=26)	**Current - NDAs** (n=22)
Mean number of amendments per application	8	10
Median number of amendments per application	8.5	8.5
Range of number of amendments per application	15 [1, 16]	15 [4, 19]
Mean number of amendment items per application	34	45
Median number of amendment items per application	27.5	30
Range of number of amendment items per application	100 [9, 109]	174 [11, 185]

Review Priority: Number of IRs and Amendments per Application in the Baseline and Current Samples

FDA assigns different review timelines to applications at the time of filing, or 60 days after FDA receives the application. Broadly, FDA assigns a "Standard" or "Priority" review timeline, with Standard reviews targeting 10 to 12 months from the date of receipt to FDA regulatory action and Priority reviews targeting six to eight months. FDA's decision to designate Priority review on an application is based on whether the drug can reasonably be expected to significantly improve the safety or effectiveness of the treatment, diagnosis, or prevention of a serious condition.

Table 3-6 compares the numbers of IR letters and IR items per application by FDA review priority. In both samples, Priority review applications tended to have more IR letters and IR items than Standard review applications. **In the current sample, Priority review applications had greater numbers of IR items per application (mean 105 items, median 120 items) than Priority review applications in the baseline (mean 89 items, median 78 items)**.

Table 3-6. Number of IR letters and IR items per application in baseline (n=40) and current (n=40) samples, by review priority

	Baseline - Priority (n=19)	**Current - Priority** (n=19)
Mean number of IR letters per application	13	13
Median number of IR letters per application	12	11
Range of numbers of IR letters per application	39 [1, 40]	27 [3, 30]
Mean number of IR items per application	89	105
Median number of IR items per application	78	120
Range of number of IR items per application	231 [5, 236]	220 [16, 236]
	Baseline - Standard (n=21)	**Current - Standard** (n=21)
Mean number of IR letters per application	9	8
Median number of IR letters per application	7	7
Range of numbers of IR letters per application	27 [3, 30]	22 [1, 23]
Mean number of IR items per application	50	40
Median number of IR items per application	29	26
Range of number of IR items per application	221 [5, 226]	126 [4, 130]

Table 3-7 compares the numbers of amendments and amendment items per application by FDA review priority. Priority review applications in the baseline and current samples had more amendments and amendment items than Standard review applications. **Comparing the current sample to the baseline sample, Priority review applications had a greater median number of amendment items per application (143 items) than Priority review applications in the baseline (median 57 items).** This somewhat reflects the level of communication in IR letters and IR items shown in Table 3-6.

Table 3-7. Number of amendments and amendment items per application in baseline (n=40) and current (n=40) samples, by review priority

	Baseline - Priority (n=19)	**Current - Priority** (n=19)
Mean number of amendments per application	18	19
Median number of amendments per application	11	17
Range of number of amendments per application	52 [1, 53]	47 [6, 53]
Mean number of amendment items per application	63	61
Median number of amendment items per application	57	134
Range of number of amendment items per application	177 [9, 186]	175 [16, 191]
	Baseline - Standard (n=21)	**Current - Standard** (n=21)
Mean number of amendments per application	13	11
Median number of amendments per application	10	9
Range of number of amendments per application	48 [5, 53]	29 [4, 33]
Mean number of amendment items per application	62	55
Median number of amendment items per application	29	35
Range of number of amendment items per application	318 [10, 328]	121 [11, 132]

Regulatory Action: Number of IRs and Amendments per Application in the Baseline and Current Samples

Applications in the baseline or current samples must have received an "Approval" or "Complete Response" regulatory action from FDA by the end of a Priority or Standard review timeline. In the baseline sample, applications that received an Approval had slightly more IR letters (mean 11) and IR items (mean 72) than Complete Response applications (mean 9 IR letters, mean 59 IR items), on average (Table 3-8). This pattern does not appear to be present in the current sample, and **applications in the current sample with a Complete Response have higher mean and median numbers of IR items per application (mean 83, median 63.5) than applications with an Approval (mean 65, median 30).**

Table 3-8. Number of IR letters and IR items per application in baseline (n=40) and current (n=40) samples, by regulatory action

	Baseline - Approval (n=29)	**Current - Approval** (n=28)
Mean number of IR letters per application	11	10
Median number of IR letters per application	8	7.5
Range of numbers of IR letters per application	39 [1, 40]	29 [1, 30]
Mean number of IR items per application	72	65
Median number of IR items per application	33	30
Range of number of IR items per application	231 [5, 236]	202 [4, 206]
	Baseline - Complete Response (n=11)	**Current - Complete Response** (n=12)
Mean number of IR letters per application	9	11
Median number of IR letters per application	7	9.5
Range of numbers of IR letters per application	25 [5, 30]	17 [5, 22]
Mean number of IR items per application	59	83
Median number of IR items per application	51	63.5
Range of number of IR items per application	213 [7, 220]	225 [11, 236]

Table 3-9 provides a comparison of the number of amendments and amendment items per application based on an Approval or Complete Response regulatory action. Applications that received an Approval action in the baseline sample had similar numbers of amendments (mean 16) and amendment items (mean 76) to applications that received a Complete Response (mean 14 amendments, mean 75 amendment items). Unlike the pattern observed for IR letters and IR items in Table 3-8, **applications in the current sample that received a Complete Response had lower mean and median numbers of amendment items (mean 81, median 66) than applications that received an Approval (mean 85, median 84).**

Table 3-9. Number of amendments and amendment items per application in baseline (n=40) and current (n=40) samples, by regulatory action

	Baseline - Approval (n=29)	**Current - Approval** (n=28)
Mean number of amendments per application	16	14
Median number of amendments per application	11	11.5
Range of number of amendments per application	52 [1, 53]	49 [4, 53]
Mean number of amendment items per application	76	85
Median number of amendment items per application	38	84
Range of number of amendment items per application	201 [9, 210]	180 [11, 191]
	Baseline - Complete Response (n=11)	**Current - Complete Response** (n=12)
Mean number of amendments per application	14	15
Median number of amendments per application	9	11
Range of number of amendments per application	49 [4, 53]	28 [6, 34]
Mean number of amendment items per application	75	81
Median number of amendment items per application	49	66
Range of number of amendment items per application	317 [11, 328]	154 [11, 165]

Review Center: Number of IRs and Amendments per Application in the Baseline and Current Samples

The scope of this assessment under PDUFA VII includes original BLAs and NDAs reviewed by CBER and CDER. As the FDA Center primarily involved in reviewing biologics, CBER is represented in our baseline and current samples by BLAs. CDER applications in our samples are primarily NDAs, with a smaller number of BLAs. Table 3-10 shows a difference in the volume of product quality IR communications between CBER and CDER, in that **CBER issued more than two or three times the number of IR letters and IR items per application on average in the baseline and current samples**. This result is likely related to the complexity of biologics and reflects a similar trend as that in Table 3-4 for NDAs and BLAs.

Table 3-10. Number of IR letters and IR items per application in baseline (n=40) and current (n=40) samples, by FDA Center

	Baseline - CDER (n=30)	**Current - CDER** (n=33)
Mean number of IR letters per application	7	8
Median number of IR letters per application	7	7
Range of numbers of IR letters per application	16 [1, 17]	18 [1, 19]
Mean number of IR items per application	49	54
Median number of IR items per application	30	27
Range of number of IR items per application	221 [5, 226]	186 [4, 190]
	Baseline - CBER (n=10)	**Current - CBER** (n=7)
Mean number of IR letters per application	22	22
Median number of IR letters per application	21.5	22
Range of numbers of IR letters per application	28 [12, 40]	19 [11, 30]
Mean number of IR items per application	129	150
Median number of IR items per application	108.5	133
Range of number of IR items per application	177 [59, 236]	162 [74, 236]

Table 3-11 reflects the results in Table 3-10, which shows a higher volume of product quality IR communications during CBER application reviews. **CBER applications received two to three times the numbers of amendments and amendment items per application on average in the baseline and current samples.**

Table 3-11. Number of amendments and amendment items per application in baseline (n=40) and current (n=40) samples, by FDA Center

	Baseline - CDER (n=30)	**Current - CDER** (n=33)
Mean number of amendments per application	10	11
Median number of amendments per application	9	9
Range of number of amendments per application	36 [1, 37]	30 [4, 34]
Mean number of amendment items per application	50	70
Median number of amendment items per application	31	36
Range of number of amendment items per application	201 [9, 210]	180 [11, 191]
	Baseline - CBER (n=10)	**Current - CBER** (n=7)
Mean number of amendments per application	32	32
Median number of amendments per application	31.5	31
Range of number of amendments per application	40 [13, 53]	33 [20, 53]
Mean number of amendment items per application	153	148
Median number of amendment items per application	152	159
Range of number of amendment items per application	281 [47, 328]	82 [104, 186]

3.2 Four-Part Harmony in FDA IRs

ERG evaluated FDA IRs to examine the effect of implementing Four-Part Harmony in product quality and CMC IRs. ERG manually reviewed each product quality IR associated with an application in the baseline and current samples, and assessed whether each IR item included explicit text applicable to an element of Four-Part Harmony.

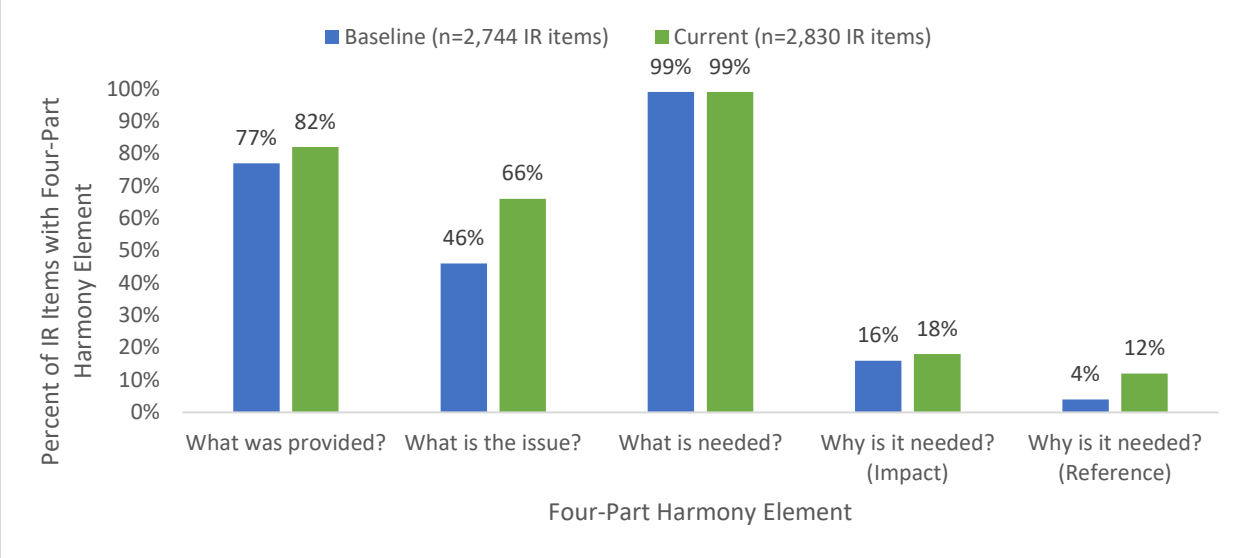
Use of Four-Part Harmony in FDA IRs

Figure 3-1 provides an overall view of how often Four-Part Harmony elements were explicitly included in IR items in the baseline and current samples. **In both the baseline and current samples, "*what was provided*" (77% baseline, 82% current) and "*what is needed*" (99% baseline, 99% current) were most often included in IR items. In the current sample, IR items included Four-Part Harmony elements more often than IR items in the baseline sample.** This is evident in the current sample for the following elements:

- *What is the issue* 20% increase over baseline
- *Why is it needed (Reference)* 8% increase over baseline
- *What was provided* 5% increase over baseline
- *Why is it needed (Impact)* 2% increase over baseline

For one Four-Part Harmony element, "*what is needed",* there was no change in how often it was included in baseline and current sample IR items (99%).

Figure 3-1. Frequency of Four-Part Harmony Elements in baseline sample (n=40) and current sample (n=40) IR items, overall



Figures 3-2a and 3-2b present a granular view of the use of Four-Part Harmony elements in baseline and current sample IR items by application trait. **Within each sample, the use of Four-Part Harmony in IR items varied little for most application traits**. The most notable difference is that the inclusion of the "*why is it needed*" element decreased from the baseline to the current sample in NDAs (19% to 18%), Standard applications (21% to 19%), and Complete Response applications (20% to 14%).

Figure 3-2a. Frequency of Four-Part Harmony Elements in baseline sample (n=40) IR items, by application trait

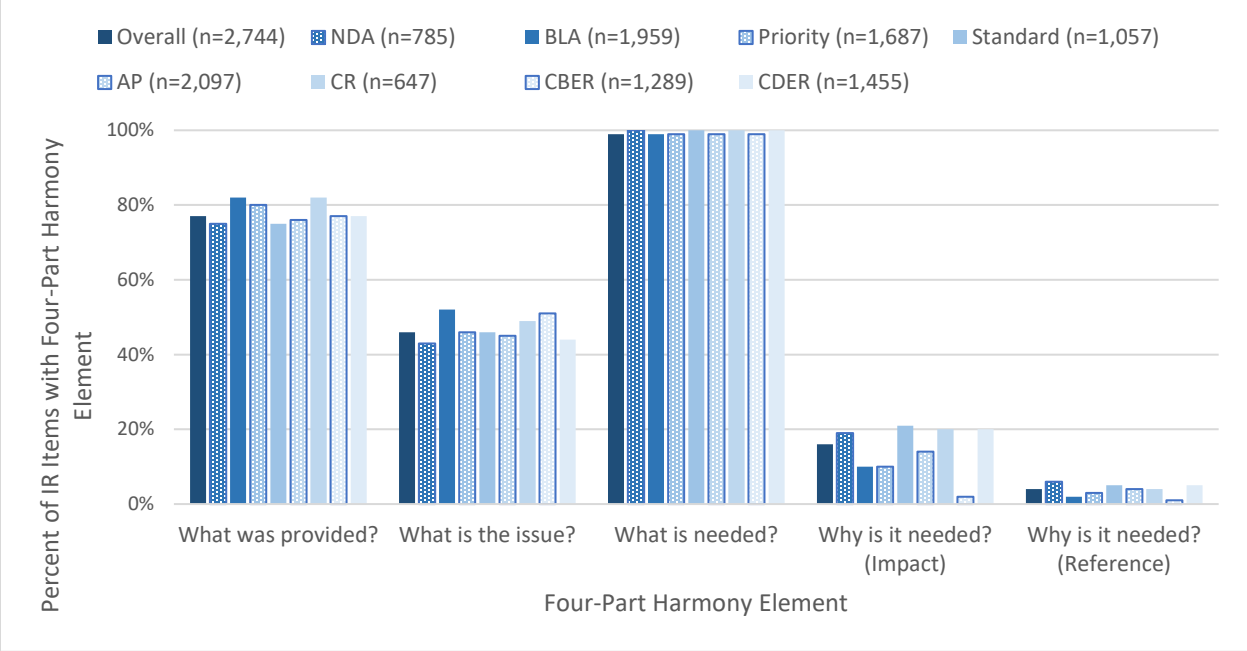
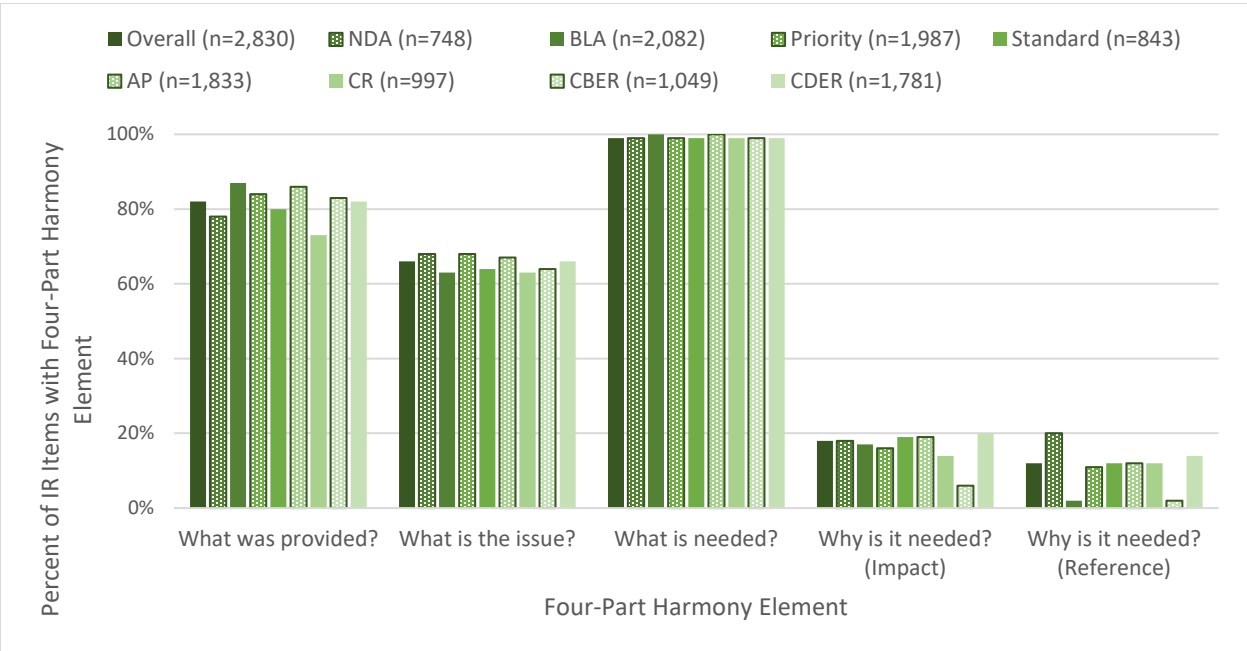


Figure 3-2b. Frequency of Four-Part Harmony Elements in current sample (n=40) IR items, by application trait



Effect of Four-Part Harmony on Volume of Product Quality IR Communications

ERG examined whether the frequency that Four-Part Harmony elements were included in IR items affected the volume of IR letters and IR items, or numbers of amendments and amendment items in the baseline and current samples. In both the baseline and current samples, ERG did not find clear evidence that inclusion of Four-Part Harmony elements affected the amount of IR letters, IR items, amendments, or amendment items when compared to the average. ERG also analyzed the data for effects of specific Four-Part Harmony elements on IR communication volume and did not observe any definite results. Further analysis of the data with respect to application traits did not result in any discernable differences that could be isolated from the effect of using smaller numbers of applications in each subset of application traits.

3.3 Timing of IR Items and Amendment Items

In this section, ERG presents results on the timing of IR items and amendment items relative to Standard and Priority review timelines in the baseline and current samples. Data in these charts are cumulative for IR items or amendment items in Standard or Priority review applications to amplify patterns in the timing.

Figures 3-3a and 3-3b show the timing of IR items and amendment items for Standard review applications in the baseline and current samples. **Compared to the baseline sample, IR items in the current sample peaked two months earlier in the Standard review timeline.**

In contrast, Figures 3-4a and 3-4b show that **IR items and amendment items for Priority review applications in the current sample peaked in months five and six, compared to month four for applications in the baseline.** Like the baseline sample, however, IR items and amendment items did not commonly occur in the later months of current sample Priority reviews.

Figure 3-3a. Volume of IR and amendment items per Standard review month in baseline sample (n=21)

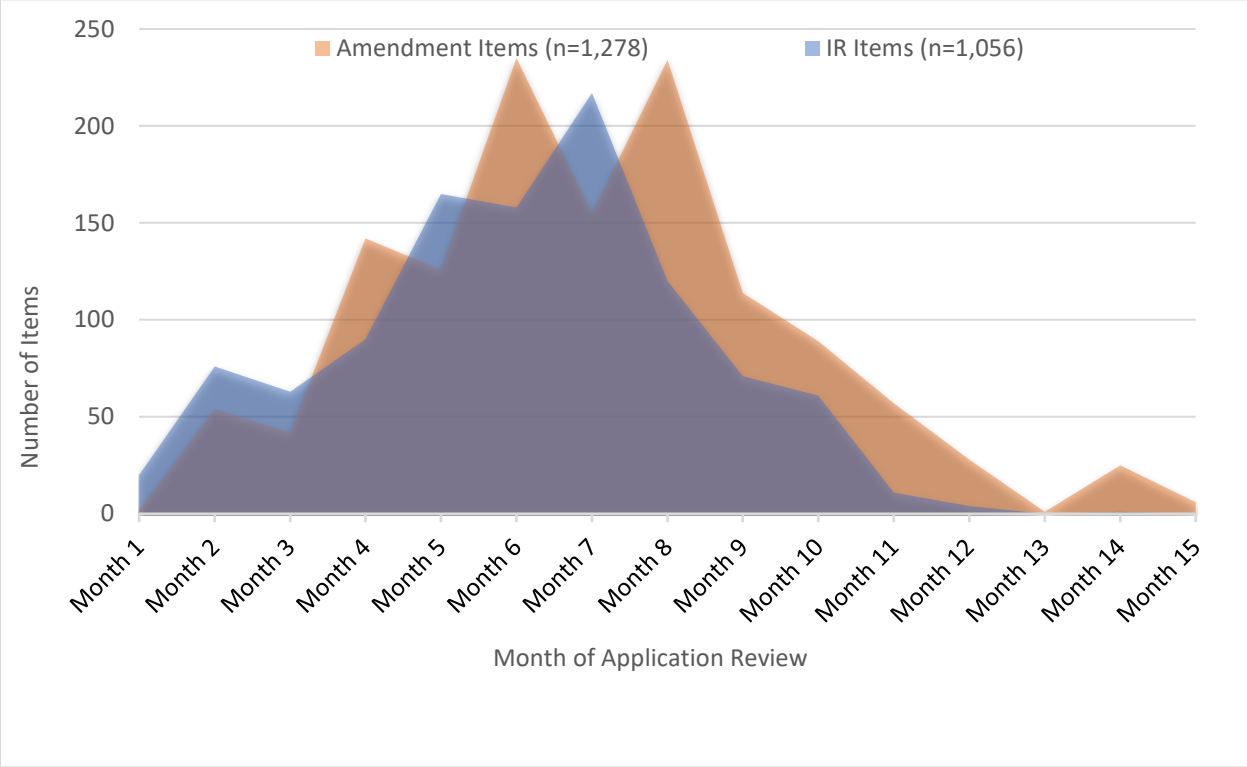


Figure 3-3b. Volume of IR and amendment items per Standard review month in current sample (n=21)

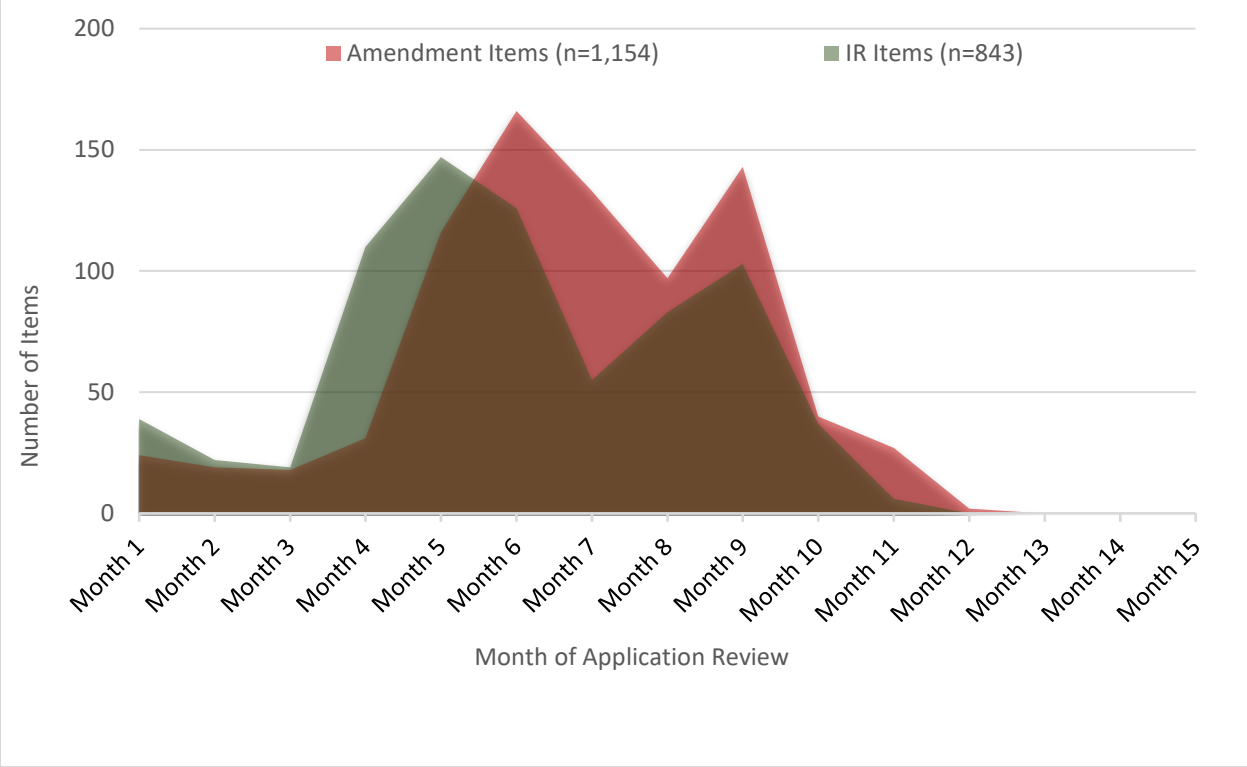


Figure 3-4a. Volume of IR and amendment items per Priority review month in baseline sample (n=19)

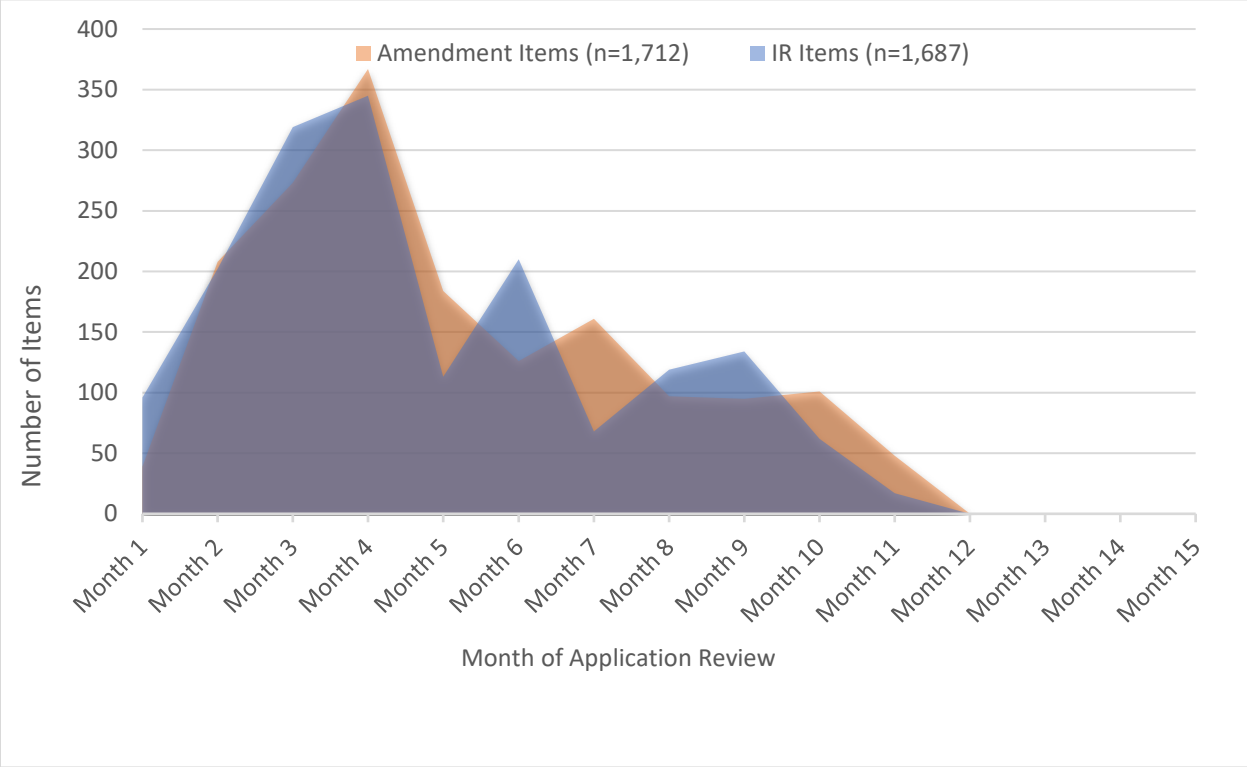
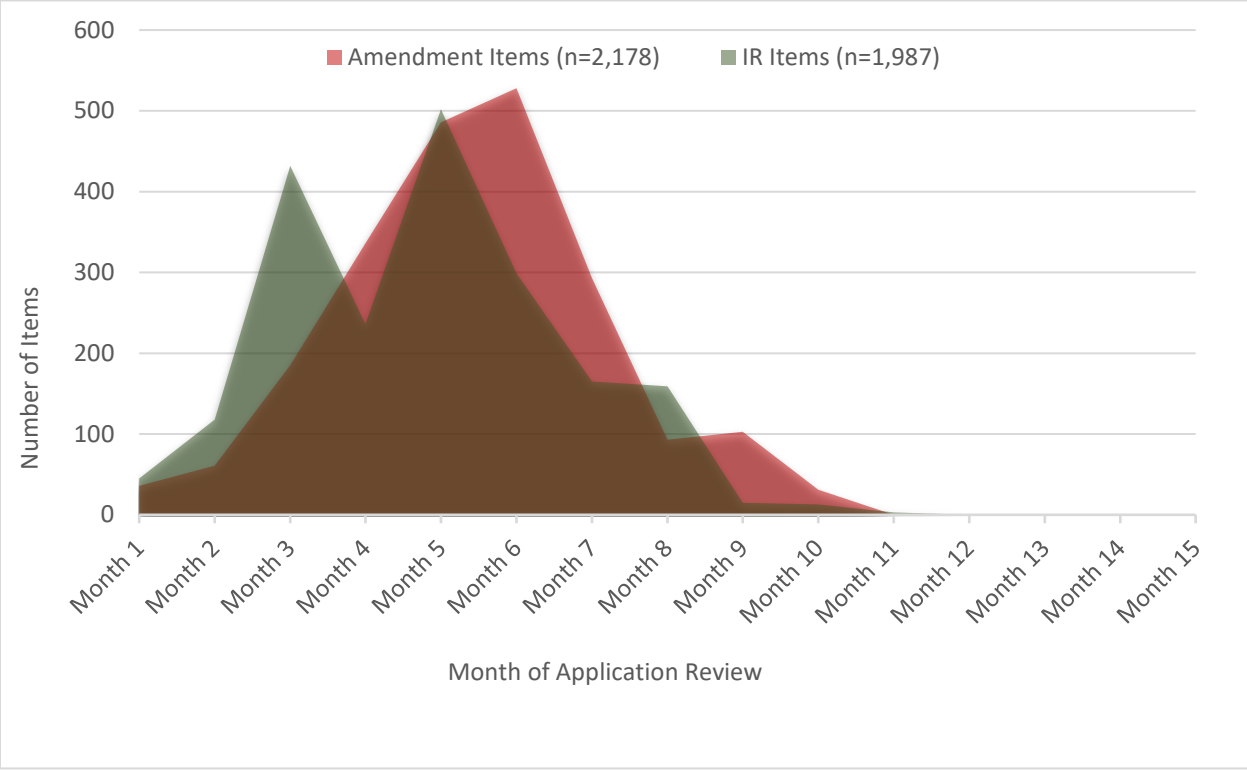


Figure 3-4b. Volume of IR and amendment items per Priority review month in current sample (n=19)



3.4 FDA and Applicant Interview Feedback

For the 40 applications in the current sample, ERG extended interview offers and solicited feedback about the product quality IR communication process from FDA product quality and CMC review teams, and applicant quality and CMC staff representatives through group interviews that were conducted after applications received a first-cycle Approval or Complete Response action. As a result, ERG conducted:

- 38 FDA group interviews, with 186 participants
- 10 applicant group interviews, with 26 participants

In some cases, ERG did not conduct interviews due to limitations on the time available for data collection and reporting. For many interview requests, however, ERG did not receive a response, or the interview request was declined.

Feedback from FDA review teams and applicants on their experience with the product quality or CMC IR process was largely positive, with many describing their communications with each other to have benefitted from the use of Four-Part Harmony. They recognized and emphasized the need for clarity and context in IRs to enable applicants to provide adequate responses, and additional or alternate information, if available. Other common themes that emerged relating to good practices, challenges, and suggestions for improving the product quality IR process are summarized in Table 3-12.

Table 3-12. Common themes from FDA and applicant interviews on product quality IR communications

Topic	**Feedback from FDA Review Teams** (38 interviews)	**Feedback from Applicants** (10 interviews)
Overall	IR communications with applicants were effective, clear, and timely. The concept of Four-Part Harmony has been in use at FDA for many years and has only recently become a formal policy. Sending multiple IRs for related issues is sometimes unavoidable when the submitted data leads to more questions. Efficiency of the product quality IR process is affected by how efficient and organized the Regulatory Business Process Manager (RBPM) is at facilitating team interactions and communicating IRs.	IRs were usually clear and did not need a follow-up email for clarification. IRs that did not follow Four-Part Harmony were rare. FDA's use of Four-Part Harmony allows applicants to understand context and rationale behind why FDA is requesting data, and to respond with more comprehensive data or related information.

Topic	Feedback from FDA Review Teams (38 interviews)	Feedback from Applicants (10 interviews)
Good practices	**Reduce the need for follow-up IRs**: Four-Part Harmony increases the clarity of issues communicated in IRs to applicants and enables applicants to provide effective initial responses. **Issue IRs as early as possible**: To obtain the necessary data to continue reviews and meet review timelines, IRs should be sent to applicants as soon as they are developed and cleared. **Submit well-organized responses**: In addition to detailed data, summary documents containing itemized responses to IRs facilitate FDA's review of amendments. **Include IR response due dates:** Establishing a due date for IR responses from the applicant helps reviewers manage their time and tasks. **Training new staff in Four-Part Harmony:** Training establishes a standard of IR writing that is accessible to a wide range of people on FDA and applicant teams with different educational backgrounds. **Group IRs by category:** When possible, group IRs by category or topic to reduce the overall number of IRs and to make it easier for applicants to organize their response.	**Issue clear and organized IRs**: References to specific sections and context for what is being requested allows applicants to provide more comprehensive responses to IRs. **Supplement formal amendments with informal responses:** Prior to submitting the formal amendment and updating the electronic common technical document (eCTD), applicants send responses to IRs by email to provide the requested information as soon as possible, and to increase the efficiency of the IR process. **Allow flexibility with IR due dates**: When requested and if possible, FDA is generally open to granting applicants extensions to IR response due dates to develop the necessary data to respond. **Send IR letters as an attachment:** Receiving IR letters as an attachment rather than text in an email allows applicants to better account for FDA IRs and organize their own records. **Include IR response due dates:** Clear timelines and due dates in IRs helps applicants manage tasks and resources within their organization. **Group IRs by discipline:** IRs grouped by discipline allow applicants to effectively allocate team members and prepare responses efficiently.
Challenges or pain points	**Including "why is it needed (reference)" component of Four-Part Harmony:** Reviewers find it difficult to identify specific references relevant to their IRs, which could result in pushback from applicants and lead to multiple IRs. **Four-Part Harmony can be time-consuming:** IR letters become convoluted and redundant when Four-Part Harmony elements in IR items are repeated unnecessarily**.**	**Unpredictability of IR timing**: IR letters issued by FDA can be unpredictable, making it difficult for applicants to have team members prepared to respond immediately. **End of review IR timelines:** FDA-requested due dates on IRs near the end of reviews become shorter and less realistic. Publishing responses and submitting through the electronic gateway within FDA's timeline can be challenging.

Topic	**Feedback from FDA Review Teams** (38 interviews)	**Feedback from Applicants** (10 interviews)
Suggestions	**Develop an office-wide product quality IR repository or database:** A shared database of past IRs could increase consistency in the format and language of IRs. This database could also help FDA reviewers find and use previously cited references for Four-Part Harmony. **Consolidate Four-Part Harmony elements:** When possible, convey multiple Four-Part Harmony elements in fewer sentences to reduce the length of IRs while maintaining the necessary elements.	**Expand Four-Part Harmony beyond product quality IRs:** The Four-Part Harmony approach improves the clarity of IRs and would be useful for IRs from other FDA offices or review disciplines. **Advance notice of upcoming IRs:** Notification that an IR might be coming at least a couple days ahead of time would allow applicants to prime the necessary staff and resources to respond efficiently. This is particularly useful for IRs with short turnaround times. **Assign numbers to IR letters:** FDA should expand the practice of assigning numbers to IRs to aid tracking and to simplify references to previously issued IRs.

4. Answers to Assessment Questions

1a. What are characteristics of baseline FDA review staff and applicant communication practices via product quality IRs?

On average, Priority review applications, CBER applications, and BLAs had more IR letters, IR items, and amendments than other types of applications in the baseline sample. Baseline sample applications had an average of 11 product quality IR letters, 69 IR items, and 15 amendments per application. Priority review applications (mean: 13, 89, and 18, respectively), CBER applications (mean: 22, 129, and 32, respectively), and BLAs (mean: 19, 140, and 28, respectively) had more communications between FDA review staff and applicants than the overall baseline sample average. The higher-than-average numbers of IRs and amendments for Priority review applications is an indication of intense communication activities as FDA and applicants quickly worked to address issues within shorter review timelines than Standard reviews. BLAs and CBER applications had the highest numbers of IRs, IR items, amendments, and amendment items among baseline applications, which is likely due to the complexity of large molecule biologics compared to small molecule drugs. The frequency and volume of IR communications between FDA and applicants of biologics in the baseline appear to reflect this.

1b. To what extent do *baseline* product quality IR communications incorporate Four-Part Harmony, recommended policies, practices, guidances, and standard operating procedures?

In the baseline sample, the 2,744 IR items incorporated Four-Part Harmony to the following extent:

- *What was provided* 77% of IR items
- *What is needed* 99% of IR items
- *What is the issue* 46% of IR items
- *Why is it needed (Impact)* 16% of IR items
- *Why is it needed (Reference)* 4% of IR items

Individual items within FDA IRs almost always (99%) included an explicit request for information, and a majority (77%) of IR items described what had been provided by the applicant. About half the time, FDA did not explicitly communicate the exact issue to the applicant (46%), and seldomly explained why the data was needed (16%).

2. How do *baseline* product quality IR communication practices vary by application characteristics such as application type, review priority, last action date, submission status, and review division?

Comparing application characteristics in the baseline sample showed that Priority review applications, CBER applications, and BLAs had more IR letters, IR items, and amendments than Standard review applications, CDER applications, and NDAs. However, the incorporation of Four-Part Harmony in baseline sample IR items generally did not differ by application characteristic (Figure 3-2a).

Priority review applications appeared to have a greater proportion of communications occurring in months three to five of the review timeline (Figure 3-4a) compared to months five to eight for Standard

review applications (Figure 3-3a). This is primarily the result of the different review timelines, where communications and mid-cycle meetings occurred earlier during Priority review timelines.

3a. What are characteristics of *current* FDA review staff and applicant communication practices via product quality IRs?

Current FDA staff and applicant communication practices closely resemble baseline sample communication practices. On average, Priority review applications, CBER applications, and BLAs had more IR letters, IR items, and amendments than other types of applications in the current sample. Current sample applications had an average of 10 product quality IR letters, 71 IR items, and 15 amendments per application. Priority review applications (mean: 13, 105, and 19, respectively), CBER applications (mean: 22, 150, and 32, respectively), and BLAs (mean 14, 116, and 23, respectively) had more communications between FDA review staff and applicants than the overall current sample average.

3b. To what extent do *current* product quality IR communications incorporate Four-Part Harmony, recommended policies, practices, guidances, and standard operating procedures?

In the current sample, the 2,830 IR items incorporated Four-Part Harmony to the following extent:

- *What was provided* 82% of IR items
- *What is needed* 99% of IR items
- *What is the issue* 66% of IR items
- *Why is it needed (Impact)* 18% of IR items
- *Why is it needed (Reference)* 12% of IR items

Individual items within FDA IRs almost always (99%) included an explicit request for information, most (82%) IR items described what had been provided by the applicant, and many (66%) contained an explanation of the issue or deficiency. FDA seldomly explained the impact of requested data on the review (18%) or justified the request with a reference (12%).

4. How do *current* product quality IR communication practices vary by application characteristics such as application type, review priority, and review division?

Comparing application characteristics in the current sample showed that Priority review applications, CBER applications, and BLAs had more IR letters, IR items, and amendments than Standard review applications, CDER applications, and NDAs. However, the incorporation of Four-Part Harmony in current sample IR items generally did not differ by application characteristic (Figure 3-2b).

Priority applications in the current sample appeared to have a greater proportion of IR items occurring in months three to five of the review timeline (Figure 3-4b), compared to months three to six for Standard applications (Figure 3-3b). For amendment items, peak volume occurred in month six for applications with Priority and Standard review timelines. Despite differences in review timelines, product quality IR communications were concentrated during similar periods of time in current sample applications.

5. How do *current* product quality IR communications compare to *baseline* product quality IR communications in incorporating Four-Part Harmony, recommended policies, practices, guidances, and standard operating procedures?

Four-Part Harmony elements were utilized more frequently in the current sample than in the baseline, as shown in the table below.

Table 4-1. Incorporation of Four-Part Harmony elements in baseline (n=2,744) and current (n=2,830) sample IR items

Four-Part Harmony Element	Baseline IR Items with Element (n=2,744)	Current IR Items with Element (n=2,830)
What was provided	77%	82%
What is needed	99%	99%
What is the issue	46%	66%
Why is it needed (Impact)	16%	18%
Why is it needed (Reference)	4%	12%

ERG did not observe an association between the increased utilization of Four-Part Harmony and the volume of IRs or amendments per application in the current sample.

6. How do FDA review staff and applicants characterize the effectiveness of *current* product quality IR communication practices and Four-Part Harmony?

FDA review staff and applicants characterized current product quality IR communications as a clear and effective means of conveying issues and receiving information. In nine out of ten applicant interviews, applicants agreed that product quality IRs contained sufficient context to avoid requesting clarification. FDA and applicants understand the value of reducing the need for follow-up IRs and requests for clarification and identified Priority reviews as an area where the efficiency of the IR process and clarity of IRs are particularly important.

FDA staff recognized that the purpose of Four-Part Harmony is to be clear and logical in their data requests to applicants, and applicants appreciated the rationale provided in IRs that use Four-Part Harmony. Applicants stated that understanding FDA's reasoning for requesting information enabled them to respond more comprehensively to an IR or to offer relevant data that FDA had not been aware of.

Contrary to ERG's assessment of FDA's use of Four-Part Harmony, applicants in interviews asserted that the IRs they received usually followed Four-Part Harmony and were complete. This suggests that FDA identifying "what was provided" or "what is the issue" in addition to "what is needed" might be sufficient for applicants to understand "why is it needed."

7. What practices enhance product quality IR communications, what challenges hinder communications, and what steps can FDA and applicants take to improve these processes moving forward?

FDA review teams and applicants provided feedback on good practices, challenges, and suggestions to improve product quality IR communications in group interviews. FDA staff noted that reducing the need for follow-up IRs, issuing IRs as early as possible, and training new staff in Four-Part Harmony enhances the efficiency of IR communications. Applicants stated that receiving clear and organized IRs is particularly important to achieve enhanced IR communications.

In identifying challenges with IR communications, FDA staff often pointed to the difficulty in including the "why is it needed" element of Four-Part Harmony. FDA staff also described Four-Part Harmony as redundant when elements are repeated throughout an IR letter and suggested that condensing elements could reduce the burden. Applicants often noted the unpredictability of receiving IRs during the review, especially near the end of application review timelines, where timely responses are challenging.

For additional details and feedback from interviews, please refer to Table 3-12 in *Section 3.4, FDA and Applicant Interview Feedback*.

8. What steps should FDA take to improve product quality information requests?

Please see Section 5, *Findings and Recommendations* for the answer to this assessment question.

9. What steps should applicants take to improve product quality information requests?

Please see Section 5, *Findings and Recommendations* for the answer to this assessment question.

5. Findings and Recommendations

Based on an integrated evaluation of all perspectives and data collected during this assessment of product quality IR communication practices, ERG developed a set of findings and recommendations based on two overarching themes:

1. FDA and applicant product quality IR communications are essentially clear, efficient, and effective.
2. Four-Part Harmony, as described in CDER MAPP 5016.8 Rev. 1 and CBER SOPP 8401.1, is rarely utilized to its full extent.

ERG presents findings and recommendations to enhance or address these themes in Table 5-1 below.

Table 5-1. Findings and recommendations on product quality IR communications

No.	Finding	Recommendation(s)
S1	Applicants note that tracking and organizing IRs is particularly important when multiple IRs are received at the same time or in quick succession.	**To FDA:** Consider applying a numbering system (e.g., CMC #1, CMC #2, CMC #3, etc.) when issuing product quality IRs to prevent misidentification of IRs with the same date. *Note: Some FDA project managers currently use numbers to identify IRs.*
S2	FDA reviewers appreciate well-organized responses to IRs, which allow them to efficiently locate and review the relevant information.	**To applicants:** If not already, consider including summary documents containing itemized responses to IRs in addition to the necessary detailed data.
S3	Despite IRs frequently lacking an explicit *"why is it needed"* Four-Part Harmony element, applicants find that IRs are clear and complete. Applicants often understand why an IR is needed from FDA's explanation of "*what is the issue/deficiency.*"	**To FDA and applicants:** If effective IR communications are possible with fewer Four-Part Harmony elements, consider modifying Four-Part Harmony to establish two tiers of elements for inclusion: • Expected elements: "*what was provided*," "*what is the issue/deficiency*," and "*what is needed.*" • As-needed elements (e.g., for less common deficiencies): "*why is it needed [impact]*," and "*why is it needed [reference]*." This could improve the efficiency of drafting FDA IRs, while maintaining the clarity of IRs to applicants.
S4	*"Why is it needed"* is commonly omitted from IRs written with Four-Part Harmony. FDA reviewers described difficulty in immediately identifying the correct references to cite, or the absence of a reference to cite.	**To FDA:** Consider creating an office-wide product quality IR reference repository based on product quality topic areas or categories for IR drafters. Assess the scale of data and support needed and determine its feasibility.

No.	Finding	Recommendation(s)
		This could allow reviewers who are drafting IRs to easily access relevant references and increase the efficiency and consistency of IRs.
S5	Training to use Four-Part Harmony in IRs encourages new FDA staff to effectively organize and communicate their thoughts on quality issues in a clear and logical format. This is beneficial to applicants, and it is also helpful to other FDA team members reviewing a new reviewer's drafted IRs.	**To FDA:** Continue to conduct Four-Part Harmony training with new reviewers. Continue to offer Four-Part Harmony training to all FDA reviewers. Discuss and share examples of what to include for the *"why is it needed"* element.

Appendix A. Acronyms, Abbreviations, and Glossary

Acronyms and Abbreviations

Acronym	Term
AP	Approval
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CMC	Chemistry, Manufacturing, and Controls
CR	Complete Response
ERG	Eastern Research Group, Inc.
FDA	Food and Drug Administration
FY	Fiscal Year
IR	Information Request
MAPP	Manual of Policies and Procedures
NDA	New Drug Application
PDUFA	Prescription Drug User Fee Act
SOPP	Standard Operating Procedures and Policies
OMB	Office of Management and Budget
RBPM	Regulatory Business Process Manager

Glossary

Amendment: Additional data or analysis submitted by an applicant after original submission of an application.

Applicant: For the purpose of this assessment, the applicant is the person or entity who takes responsibility for and initiates an NDA or BLA.

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

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

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

Center for Biologics Evaluation and Research (CBER): FDA organization that regulates a variety of biological products for human use (e.g., whole blood and blood-derived products, vaccines, allergenics, tissues, cellular and gene therapies) as well as selected devices and drugs, and ensures that these products are safe, effective, and available to those who need them.

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.

Complete Response (CR): FDA regulatory action on an application (in this case, an original BLA or NDA) which conveys FDA will not approve the application in its present form for one or more reasons, and that does not allow the applicant to commercially market the product; communicated in a CR action letter. To obtain marketing approval, the applicant must resubmit an application that addresses deficiencies cited.

Drug: An article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease (see 21 U.S.C. 321). When used broadly, this term includes biological products. When used more specifically (as in this report), the term refers to non-biological products.

Eastern Research Group, Inc. (ERG): Independent contractor enlisted to design and conduct the interim and final assessments of the Product Quality Information Request Communications Assessment.

Electronic Common Technical Document (eCTD): The standard format for submitting applications, amendments, supplements, and reports to FDA's CBER and CDER.

First-Cycle Action: Regulatory decision (Approval or Complete Response) on an application that concludes FDA's first cycle of review and closes the goal date.

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

Food and Drug Administration: 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.

Four-Part Harmony: A framework for IRs that encourage FDA reviewers to communicate: (1) what was provided, (2) what is the issue or deficiency, (3) what is needed, and (4) why it is needed in each information request sent to applicants.

Information Request (IR): FDA communication to an applicant to request data, analysis, or clarification needed to allow completion of a review.

Interview: For this assessment, virtual interviews that ERG conducted with applicant representatives or FDA reviewers. The purpose of the interview was to gather applicant and FDA review team opinions and experiences (including good practices, challenges, and suggestions) on product quality IR communications.

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.

Office of Management and Budget (OMB): Federal government agency that evaluates, formulates, and coordinates management procedures and program objectives within and among departments and agencies of the Executive Branch. It also controls the administration of the federal budget, while

providing the president with recommendations regarding budget proposals and relevant legislative enactments

Prescription Drug User Fee Act (PDUFA): Enacted in 1992, law that provided added funds through user fees that enabled FDA to hire additional reviewers and support staff and upgrade its information technology systems. In exchange, FDA agreed to review performance goals, such as completing application reviews for NME NDAs and original BLAs in a predictable timeframe.

Regulatory Action: The regulatory decision that FDA issues on an application. This includes an action that closes the PDUFA goal (Approval or Complete Response